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INDUCTION OPTIMIZATION WITH STELARA FOR CROHN'S DISEASE

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IND Number	155306
Study Product Provider:	Janssen Scientific Affairs, LLC (Janssen)

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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FFR	Federal Financial Report
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States

Protocol Summary

Title	Induction Optimization with Stelara for Crohn's Disease
Brief Summary	This is a 16-week randomized controlled trial comparing a second IV weight-based induction dose at week 8 to standard 90mg subcutaneous dose at week 8, with a primary endpoint of clinical remission at week 16.
Objectives	To evaluate the efficacy of a second IV dose of ustekinumab at week 8 in inducing remission in "high risk" moderate to severe Crohn's patients
Endpoint	Clinical remission at week 16: Defined as a CDAI <150
Study Duration	18 months
Participant Duration	Approximately 24 weeks
Population	Patients between the ages of 18 and 70 with Crohn's Disease
Study Sites	NYU Langone Medical Center University of Maryland
Number of participants	88 participants expected to be enrolled across two sites
Description of Study Agent/Procedure	This is a 16-week randomized controlled trial comparing a second IV weight-based induction dose at week 8 to standard 90mg subcutaneous dose at week 8, with a primary endpoint of clinical remission at week 16.

1 Key Roles

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2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

Inflammatory bowel diseases (IBD) are comprised of two diseases: Crohn's disease (CD) and ulcerative colitis (UC). Both CD and UC are driven by an aberrant immune response against intestinal flora and/or dietary antigens, but their pathophysiologies are quite different. The mainstay treatment of moderate to severe Crohn's disease is biologic and/or immunosuppressive agents. Despite the efficacy of anti-TNF agents in CD, about 30% of patients are primary non-responders, and up to 40% will lose response by the end of a year. Part of this loss of response is due to lack of optimization during induction therapy. Furthermore, dosing strategies for anti-TNF and anti-integrin therapies have evolved overtime. In patients with severe IBD (clinically and endoscopically), higher induction doses of anti-TNF are required to achieve remission. In the GEMINI 1 trial with vedolizumab, steroid refractory patients responded better to every 4 week dosing from the start compared to every 8 week dosing regimen. Therefore, optimizing our new medications with novel mechanisms of action is critical for the management of CD patients.

Ustekinumab was FDA approved in 2016 for moderate to severe Crohn's disease. The UNITI induction trials showed a significant higher clinical response at week 6 vs placebo, 33.7 percent in TNF exposed patients and 55.5% in TNF naïve patients. However, patients with elevated biomarkers, such as CRP or fecal calprotectin, had lower response rates compared to those with normal biomarkers. I postulate that these "high risk" patients will benefit from a higher induction dose.

2.2 Potential Risks & Benefits

2.2.1 Known Potential Risks

The following are risks associated with study drug:

Risk of Ustekinumab (Stelara)

The possible discomforts, side effects and risks related to Ustekinumab treatment are not all known. This section describes how frequently side effects occurred in subjects who were treated with Ustekinumab in the past.

Very Common (affects more than 1 user in 10):

- None

Common (affects 1 to 10 users in 100):

- Infection of the throat, airway or sinus
- Sore throat
- Feeling tired
- Redness and pain at drug injection site
- Back, joint or muscle pain
- Vomiting
- Headache
- Dizziness
- Diarrhea
- Nausea
- Itchiness

Uncommon (affects 1 to 10 users in 1,000):

- Swelling, itching, hardness, bleeding, bruising and irritation where the injection is given.
- Shingles (a painful rash)
- Depression
- Inflammation of tissue under the skin. Signs include warmth, swelling, redness and pain
- Nasal congestion
- A form of psoriasis with raised bumps on the skin that are filled with pus
- Allergic reactions including rash or raised, itchy bumps
- Tooth infections
- Acne
- Feeling weak
- Vaginal yeast infection
- Chest infection

Rare (affects 1 to 10 users in 10,000):

- Serious allergic reactions, which could be life-threatening (including low blood pressure, trouble breathing, swollen face, lips, mouth and/or throat)
- A form of psoriasis with redness and scaling of a much larger area of skin or entire body (erythrodermic psoriasis)
- In rare cases, symptoms such as cough, shortness of breath, and fever may also be a sign of an allergic lung reaction to Ustekinumab
- Inflammation of small blood vessels, which can lead to a skin rash with small red or purple bumps, fever or joint pain (vasculitis).

Infections

Ustekinumab is a drug that may change how the body fights infections. Serious infections requiring hospitalization for medical observation and /or treatment have been seen in Ustekinumab studies. Some of these infections have also been life threatening.

Patients will be instructed to notify the study team should they experience any of the following while in the study:

- Fever
- Chills
- Headache
- Coughing
- Congestion
- Chest tightness
- Shortness of breath
- Flu-like symptoms
- Night sweats
- Nausea
- Vomiting
- Diarrhea
- Increased frequency or burning while passing urine
- Redness warmth, tenderness or swelling of skin or joint
- Cold sores
- New or worsening of pain in any location
- Weight loss
- Tiredness

It is unknown if Ustekinumab may stop patients from developing a fever if you do have an infection, and therefore hide that you have one.

Fungal infections have been reported in subjects taking Ustekinumab. Some of these fungal infections can be serious and involve internal organs. Patients will be instructed to notify the study team of symptoms of such illnesses.

Subjects who receive Ustekinumab may also be at a greater risk for certain serious infections such as tuberculosis. Subjects will be instructed to tell their study doctor if they have ever had tuberculosis or anybody in their family has ever had tuberculosis or if they come in contact with someone who has tuberculosis.

Subjects will be instructed to notify the research team if they experience the following symptoms:

- A cough that does not go away
- Coughing up blood
- Shortness of breath
- Fever
- Night sweats
- Weight loss

Cancer

Cancers have been reported in subjects who have received Ustekinumab but it is unknown whether taking Ustekinumab has increased their risk for developing cancer. Because Ustekinumab may suppress the immune system, it is possible that it may increase risk of developing cancer, including skin cancers. Subjects who have been diagnosed with psoriasis have a higher chance of developing skin cancers. Subjects will be instructed to notify the research team if they have any new or changing skin lesions.

It is known that people who have had inflammatory diseases (such as, Crohn's disease, Rheumatoid Arthritis, Ulcerative Colitis etc.) for a long time and who have had long term use of immunosuppressive therapies (such as, azathioprine, methotrexate etc.) have a higher risk of developing cancer. These people get cancer of the lymph nodes or otherwise known as lymphoma more often than other people do.

Infusion Reactions, Injection Site Reactions and Allergic Reactions

Ustekinumab may cause an allergic reaction in some subjects. These reactions are usually mild to moderate. The body might have a reaction during or shortly following an infusion of Ustekinumab into the vein. This is called an infusion reaction and these reactions are usually mild to moderate. They are managed by slowing the infusion or by giving you medication. The following can be symptoms of an infusion reaction or an allergic reaction:

- Fever
- Chills
- Hives
- Rash
- Swelling
- Itching
- Headache
- Flushing
- Nausea
- Light-headedness
- Chest pain or tightness
- Wheezing
- Difficulty breathing or swallowing
- Decrease or increase in blood pressure
- Anaphylaxis (life threatening allergic reaction)

Serious allergic reactions have been reported in subjects taking Ustekinumab and can be life threatening. Signs of a serious allergic reaction include skin rash, swollen face, mouth, lips, and/or throat, and trouble breathing. If this happens during the infusion, the infusion will be stopped and necessary treatment will be provided immediately.

Delayed allergic reaction have occurred in some subjects 1-14 days after receiving some similar medications. Subjects will be instructed to inform the research team as soon as they experience any of the following reactions: fever, rash, muscle aches and joint pain

Cardiac and Vascular

Heart attacks and strokes have been reported in subjects who have received Ustekinumab. It is unknown whether taking Ustekinumab increases the risk for developing these events.

People who have psoriasis, and certain other inflammatory diseases, have a higher risk of having heart attacks. Subject will be informed to seek medical attention immediately upon experience any of the following:

- Chest pain or discomfort
- Trouble breathing
- Irregular heartbeats
- Dizziness
- Loss of balance
- New numbness or weakness
- Visual or speech changes

Allergy Immunotherapy (Allergy Injections)

Ustekinumab may affect response to allergy injections. Subjects will be asked to notify the research team of any scheduled allergy injections.

Other Risks

Two cases of a very rare disease of the brain, posterior reversible encephalopathy syndrome (PRES), also known as Reversible Posterior Leukoencephalopathy Syndrome (RPLS), were reported in clinical studies with Ustekinumab. PRES is generally reversible and is not caused by an infection. It is unknown whether taking Ustekinumab increases the risk of developing PRES/RPLS. The research team will follow subjects closely for the following signs and symptoms:

- Headache
- Seizures
- Confusion
- Loss of eyesight

3 Objectives and Purpose

The primary aim of this IIS is to evaluate whether a second IV weight-based induction dose at week 8 will improve clinical remission rates in “high risk” moderate to severe Crohn’s disease patient population at week 16.

A “high risk” patient is defined as a patient with moderate to severe CD with a CDAI between 220 and 450 and either a CRP > 8mg/L and/or a fecal calprotectin > 250ug/g, who at week 8, the CDAI does not drop by more than 100 points (clinical response), unless CDAI <150, (clinical remission), or at week 6 either the CRP does not drop below 5mg/L or fecal calprotectin does not decrease by 50%.

3.1 Primary Objective

To evaluate the efficacy of a second IV dose of ustekinumab at week 8 to induce remission in “high risk” moderate to severe Crohn’s patients.

3.2 Secondary Objectives

1. To evaluate the safety of a second IV dose of ustekinumab at week 8 in “high risk” moderate to severe Crohn’s patients.

2. To evaluate the efficacy of a second IV dose of ustekinumab at week 8 in clinical response in “high risk” moderate to severe Crohn’s patients.

3. To evaluate the efficacy of a second IV dose of ustekinumab at week 8 in health-related quality of life.

4. To evaluate the pharmacodynamics of a second IV dose of ustekinumab in moderate to severe Crohn’s disease patients, including C-reactive protein (CRP) and fecal calprotectin.

5. To evaluate the endoscopic response and endoscopic remission of a second IV dose of ustekinumab at week 8 in “high risk” moderate to severe Crohn’s patients.

4 Study Design and Endpoints

4.1 Description of Study Design

This is a 16-week randomized, controlled trial comparing a second IV weight-based induction dose at week 8 to standard 90mg subcutaneous dose at week 8, with a primary endpoint of clinical remission at week 16.

A total of 88 patients are to be enrolled, 18 years or older, with moderate to severe Crohn's disease based on a CDAI between 220 and 450, and either a CRP > 8mg/L and/or a fecal calprotectin > 250ug/g.

All patients will receive IV ustekinumab weight-based dose at 260mg (55kg or less), 390mg (more than 55kg to 85kg), or 520mg (more than 85kg) at time point 0. At week 6, clinical and biochemical response will be assessed using CRP, and fecal calprotectin.

Patients will be randomized to a second weight based IV dose or standard 90mg subcutaneous dose at week 8 if:

- Week 8 CDAI (based on CDAI score calculated from previous 7 days) does not drop by more than 100 points from Week 0 (and is $\geq$150)
  OR
- Week 8 CDAI (based on CDAI score calculated from previous 7 days) does drop by 100 points from Week 0 (but is $\geq$150) but subject does not have a biomarker response.

Biomarker response at week 6 is defined as a CRP < 5mg/l, or a fecal calprotectin drops by at least 50%, or is less than 150 ug/g. Patients will be stratified based on lack of clinical response and lack of biomarker response. According to literature, a normal CRP is <5mg/L. For fecal calprotectin, based on the literature findings, over 250 ug/g suggests active inflammation. From 150-250 ug/g, it is less clear if there is still active inflammation. Less than 150 ug/g indicates the ability to rule out active inflammation.

All other subjects (e.g., attaining remission and those attaining biomarker response with clinical response) will not be randomized. These patients will continue to the standard 90 mg SC q8wk dosing and receive standard of care.

Outside of the randomization to IV vs SubQ dosing at week 8, the management will follow standards of care.

Given that this is an unblinded study, randomization will be done by study coordinators through the TrialMasters platform. Study coordinators will communicate the randomization assignment to the NYU Investigational Pharmacy via email.

The Investigators agree that CDAI is a subjective marker of disease. In an effort to mitigate the issue of subjectivity, randomized subjects will include those who do not have a drop in more objective biomarkers of disease including CRP and fecal calprotectin.

Steroid Taper:
Use of prednisone or budesonide and any tapering of these drugs will be at the discretion of the provider, consistent with standard of care.

If the provider assesses that the patient's disease has progressed based on CDAI or any other clinical or laboratory parameter, the provider may make any necessary medication changes as he or she sees fit. If prednisone is increased or another biologic/immunosuppressant is added, then the patient will be withdrawn from the study. Subjects withdrawn from the study will be called every three months for one year from the date of last intervention During this call, adverse events will be collected and reported to investigators.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

Clinical remission at week 16: Defined as a CDAI <150

4.2.2 Secondary Study Endpoints

Major Secondary Endpoints:

1. Clinical response at week 16: Defined as a drop in CDAI by at least 100 points between week 0 and week 16, or a CDAI < 150
2. Composite clinical and biomarker response at week 16: Defined as a drop in CDAI by at least 100 points from week 0 to week 16, or a CDAI < 150, and a biomarker response from week 0 to week 16
3. Composite clinical and biomarker remission at week 16: Defined as a CDAI < 150 and a CRP <5mg/l or a fecal calprotectin <150 ug/g
4. Change in CDAI from week 0 to week 16
5. Improvement in health-related quality of life at week 16: Increase in SIBDQ by at least 9 points between week 0 and week 16
6. Biomarker response:
   -Drop in CRP and fecal calprotectin at week 0 and week 16
   -Normalization of CRP defined as CRP < 5mg/L at week 0 and 16 (in patients with baseline elevation of CRP)
   -Normalization of fecal calprotectin defined as <150ug/g at week 0 and 16 (in patient with baseline elevation of fecal calprotectin)

7. Endoscopic response at month 6: Defined as a >/= 50% reduction from baseline in SES-CD score
8. Endoscopic remission at month 6: Defined as SES-CD score </=2 (The secondary endpoints of endoscopic response and endoscopic remission will be assessed in patients that had a colonoscopy within 3 months of the screening visit and a colonoscopy between 4-8 months after starting the study).

Other Secondary Endpoints Include:

9. Clinical response between week 8 and week 16: Defined as a drop in CDAI by at least 100 points between week 8 and week 16
10. Composite clinical and biomarker response between week 6/8 and week 16: Defined as a drop in CDAI by at least 100 points from week 8 to week 16 and a biomarker response from week 6 to week 16
11. Drop in CRP and/or fecal calprotectin between week 6 and week 16 in patients with baseline biomarker elevation
12. Steroid free clinical remission
13. Clinical remission based on past biologic failure status
14. Clinical response based on past biologic failure status

4.2.3 Exploratory Endpoints

PK testing will be done to look at the week 8 levels associated with subsequent response as well as possibly examine week 16 PK for subjects who have received the second IV dose. PK samples will be stored at NYU Langone for the time-being however they may be sent to Janssen at a future date (for which protocol will be amended). When/if PK samples are transferred to Janssen, they will be sent via courier designated by Janssen R&D to the Janssen R&D - Biologics Development Sciences labs located in Spring House, PA, U.S.A for analysis by Janssen researchers. PK samples will be labeled with a subject number to help protect the subject's privacy. The Janssen scientists doing the research will not know the identity of the study

subject. Once testing is complete and if any samples remain, they will be returned to NYU Langone Medical Center in New York, NY, U.S.A.

The samples collected from patients entering into this IIS will be deidentified upon completion of this IIS. The only identifiers that will be kept includes, age, gender, disease and date of collection.

Subjects enrolled in this trial at NYU Langone will also be approached about participating in a separate biobanking protocol entitled, “Mucosal immune profiling in patients with inflammatory bowel disease” (s12-01137).- The purpose of this research study is to create a database of information from medical records of patients with and without Inflammatory Bowel Disease. However, co-enrollment in study s12-01137 is not a requirement for eligibility into this study (s19-01401). Should a patient choose to consent to this additional study, blood, stool, and biopsy samples will be collected in accordance with the timepoints under the s12-01137 protocol, which are in accordance with the subject’s standard of care visits.

The collection of biospecimens under the protocol, “Mucosal immune profiling in patients with inflammatory bowel disease” (s12-01137) will allow for post hoc analyses focusing on predictors of response (translational) and therapeutic drug monitoring in this study. Samples will be stored and analyzed at NYU Langone. Samples obtained under study s12-01337 will not be shared with Janssen R&D.

5 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

1. Males or females between the ages of 18 and 70
2. History of Crohn’s disease for at least 3 months confirmed by colonoscopy and/or cross sectional imaging reviewed by the PI
3. Moderate to Severe Crohn’s disease defined as a CDAI between 220 and 450 at Week 0.
4. Either a CRP >8mg/L or a fecal calprotectin > 250ug/g within 4 weeks of starting ustekinumab
5. Stable Concomitant medications (prior to first dose of ustekinumab)
    a. Stable dose of 6-MP, azathioprine, or methotrexate for at least 4 weeks
    b. Stable dose of oral mesalamine for at least 2 weeks
    c. Stable dose of prednisone of 20mg or less or budesonide 9mg daily for at least 2 weeks
6. If subject is a female, before randomization she must be:
    a. Postmenopausal, defined as
        a. ≥ 45 years of age with amenorrhea for at least 18 months,

        OR

        b. ≥ 45 years of age with amenorrhea for at least 6 months and a serum FSH level > 40 IU/mL

        OR

    b. Of childbearing potential, in which case she must satisfy at least one of the below:
        a. Surgically sterile (has had a hysterectomy or bilateral oophorectomy, tubal ligation, or otherwise be incapable of pregnancy), or
        b. If heterosexually active, practicing a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (eg, condoms, diaphragm, or cervical cap, with spermicidal foam, cream, film, gel or suppository), or male partner sterilization, consistent with local regulations regarding

use of birth control methods for subjects participating in clinical trials, for a period of 16 weeks after the last administration of study agent,

OR

c. Not heterosexually active.

Note: If a woman participant's childbearing potential changes after start of the study (e.g., a pre-menarchal woman experiences menarche) or if women of childbearing potential who are not heterosexually active at screening become heterosexually active, they must agree to utilize a highly effective method of birth control, as described above.

7. Female participants of childbearing potential (menstrual and not surgically sterile), must have a negative urine pregnancy test at Week 0 (prior to randomization) and agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of 16 weeks after the last administration of study agent.
8. Male participants who are not surgically sterilized and are heterosexually active with a woman of childbearing potential, must agree to use a barrier method of contraception (e.g., condom with spermicidal foam/gel/film/cream/suppository) and to not donate sperm during the study and for 16 weeks after last receiving study agent. Note that barrier methods must also be used in all male subjects sexually active with pregnant partners for at least 16 weeks after last study agent administration.

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Past Stelara or anti-IL 23 use.
2. Active infection.
3. Has any known malignancy or has a history of malignancy (except for basal cell carcinoma; squamous cell carcinoma in situ of the skin; or cervical carcinoma in situ that has been treated with no evidence of recurrence; or squamous cell carcinoma of the skin that has been treated with no evidence of recurrence within 5 years prior to screening).
4. Indeterminate colitis.
5. Active perianal fistula as the primary symptom.
6. Fibrostenotic disease with primarily obstructive symptoms.
7. Hospitalization within the past 2 weeks.
8. Bowel resection within the past 4 weeks.
9. Subtotal colectomy.
10. Permanent Ileostomy.
11. Known infection with human immunodeficiency virus (HIV).
12. Has a concomitant diagnosis or any history of congestive heart failure or demyelinating disease.
13. Has current signs or symptoms, or a history of severe, progressive, or uncontrolled renal, hepatic, hematologic, endocrine, pulmonary, cardiac, neurologic, systemic lupus erythematosus, or psychiatric diseases.
14. Has a transplanted organ (except for corneal transplant performed > 3 months prior to screening).
15. Has a history of lymphoproliferative disease including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy of unusual size or location (e.g., nodes in the posterior triangle of the neck, supraclavicular, epitrochlear, or paraaortic areas), or splenomegaly.
16. Has previously undergone allergy immunotherapy for prevention of anaphylactic reactions.
17. Is unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access to veins.
18. Has known allergies, hypersensitivity, or intolerance to ustekinumab or excipients (refer to the ustekinumab prescribing information).

19. Has a clinically significant substance abuse problem (eg, drugs or alcohol) at screening or during the previous 12 months prior to baseline.
20. Any biologic or small molecule therapy within 4 weeks of start of ustekinumab.
21. Known infection or symptoms of active tuberculosis including Positive quantiferon gold within the last 1 year that is not being treated and followed by Infectious Disease.
22. Known Hepatitis B infection or unknown Hepatitis B history including no documentation of immunity (vaccination history or positive HepB surface antibody test). Tests positive for HBV surface antigen (HBsAg), regardless of the results of other hepatitis B tests. Subjects who test positive only for core antibody (anti-HBc) must undergo further testing for hepatitis B DNA acid (HBV DNA test). If the HBV DNA test is positive, the subject is not eligible for this study. If the HBV DNA test is negative, the subject is eligible for this study. In the event the HBV DNA test cannot be performed, the subject is not eligible for this study.
23. Change in dose of 6-MP, methotrexate, or azathioprine within one month of the start of ustekinumab.
24. Change in prednisone or budesonide dose within 2 weeks of start of ustekinumab
25. Change in mesalamine dosage within 2 weeks of start of ustekinumab
26. Has a stool culture or other examination positive for an enteric pathogen, including Clostridium difficile toxin, in the last 4 months unless a repeat examination is negative and there are no signs of ongoing infection with that pathogen
27. Has received a Bacillus Calmette–Guérin (BCG) vaccination within 12 months or any other live bacterial or live viral vaccination within 2 weeks of baseline.
28. Have immune deficiency syndrome (e.g., severe combined immunodeficiency syndrome, T-cell deficiency syndromes, B-cell deficiency syndromes, and chronic granulomatous disease).
29. Known infection with Hepatitis C (HCV) without a history of clearance or successful treatment. Successful treatment is defined as being negative for HCV RNA at least 24 weeks after completing antiviral treatment.

5.3 Strategies for Recruitment and Retention

Patients will be enrolled by the study coordinator or investigators directly during routine office visits or prior to scheduled colonoscopy procedures. Patients will not be contacted outside of routine clinical interactions. No additional procedures will be performed specifically for the purposes of this study. Informed consent for participation in the study will be obtained in parallel with consent for the colonoscopy procedure.

5.4 Duration of Study Participation

Patients will be enrolled at both NYU and University of Maryland, under Dr. Raymond Cross. Each subject will be enrolled for approximately 32 weeks. We expect enrollment to be complete within 18 months.

5.5 Potential Benefits

Participants may or may not benefit directly from participating in this study. Those who do experience benefits from the study may see an improvement in symptoms related to Crohn's disease. Ultimately, the information gained from this study will help the scientific community's understand of Crohn's Disease. Total Number of Participants and Sites.

A total of 88 participants will be recruited at NYU Langone and University of Maryland sites.

5.6 Participant Withdrawal or Termination

5.6.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant fails to complete study
- Patients who experience disease progression and are in need of an addition or increase of prednisone or another biologic/immunosuppressant will be withdrawn from the study.

Subjects withdrawn from the study will be called every three months for one year from the date of the last dose of the study intervention. During this call, adverse events will be collected and reported to investigators.

5.7 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to Janssen Scientific Affairs LLC. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

6 Study Agent (Study drug, device, biologic, vaccine etc.) and/or Procedural Intervention

6.1.1 Preparation

The study drug will be provided by Janssen Scientific Affairs, LLC and prepared at the Investigational pharmacy located at:

160 East 34th Street, Room 610
New York, NY 10016

And

22. S. Greene St
Rm N9E14
Baltimore MD 21201

6.1.2 Administration of Intervention

Study drug will be administered by qualified individuals at respective study sites.

7 Study Procedures and Schedule

7.1 Study Procedures/Evaluations

Visit Schedule and Events: (All visits are standard of care except for week 8 randomization to IV or SQ ustekinumab. The only medication requested from Janssen will be the week 8 IV ustekinumab dose).

1. Screening (4 week window period)
    a. Informed consent will be obtained prior to any study procedures.
    b. Review of medical records – confirm diagnosis
    c. Inclusion and exclusion criteria to be reviewed.
    d. Routine labs and stool studies ordered including fecal calprotectin and CRP (about 1 teaspoon of blood). Fecal calprotectin and CRP results collected prior to consent may be used if the results are within 4 weeks of the scheduled Week 0 visit.
    e. Patients to be given CDAI worksheets to record data that will be used to calculate CDAI score at Week 0. A 3 day CDAI recall may also be calculated at Week 0.

    * **Please note**: If unable to approach patient prior to Week 0 Visit, patient may be consented at Week 0 and a 3 day CDAI recall worksheet may be used.

2. Week 0 (5 day window period):
    a. Urine pregnancy testing for women of childbearing potential
    b. Standard of care history and physical exam
    c. Calculate CDAI measurement using the 7 day CDAI worksheet given to patient at Screening Visit. Alternatively, can also use a 3 day CDAI recall worksheet for those consented at Week 0.
    d. Inclusion and exclusion criteria to be reviewed.
    e. SIBDQ measurement
    f. Standard safety assessments*
    g. Standard labs – CRP (about 1 teaspoon of blood)
    h. Ustekinumab infusion
    i. Patients to be given CDAI worksheets to record data that will be used to calculate CDAI score at Week 6

3. Week 6: (5 day window period)
    a. Standard of care history and physical exam
    b. Calculate CDAI measurement
    c. SIBDQ measurement
    d. Standard safety assessment*
    e. Standard labs – CRP(about 1 teaspoon of blood)
    f. Fecal calprotectin
    g. Patients to be given CDAI worksheets to record data that will be used to calculate CDAI score at Week 8

4. Week 8: (within 5 day window period)
    a. Pregnancy testing for women of childbearing potential
    b. Standard safety assessment*
    c. Calculate CDAI measurement
    d. SIBDQ measurement
    e. Standard labs (about 1 teaspoon of blood)
    f. Serum samples for PK (less than 1 teaspoon of blood)

g. “High risk” patients randomized to weight based IV ustekinumab versus SQ ustekinumab (randomization to be done by investigational pharmacy, study is not blinded). Patients randomized to receive the second weight based IV dose of ustekinumab, will have their vital signs obtained 30 minutes after the start of the second infusion, and twice after the end of infusion at 30 minute intervals. In addition, patients are to be monitored for adverse events during and for at least 1 hour after the end of the second IV infusion.

5. Week 10: Follow-Up Call: A member of the research team will call patient to assess for any adverse events.

6. Week 16: (within 5 day period):
   a. Pregnancy testing for women of childbearing potentialPrimary endpoint – CDAI measurement
   b. Standard history and physical exam
   c. Standard safety assessment*
   d. SIBDQ measurement
   e. Standard labs including CRP (about 1 teaspoon of blood)
   f. Serum samples for PK (less than 1 teaspoon of blood)
   g. Fecal calprotectin
   h. SQ ustekinumab administration

7. Week 24: (Within 5 day period) – Long term follow up:
   a. Standard history and physical exam- **Standard of Care**
   b. CDAI measurement
   c. SIBDQ measurement
   d. Standard safety assessment*- **Standard of Care**
   e. Standard labs including CRP (about 1 teaspoon of blood)- **Standard of Care**

8. Week 24 Colonoscopy Visit (within 8 weeks): **Standard of Care**
   a. SES-CD measurement

* A Standard Safety Assessment will be conducting by an IRB approved member of the research team. This assessment is to collect information from the subject regarding any adverse events that may have occurred since last call/ visit.

Blood samples are collected at six time points (Screening, Week 0, 6, 8, 16, and 24). Over the course of the study, about 6.5 teaspoons of blood are drawn from each subject.

8 Assessment of Safety

8.1 Specification of Safety Parameters

8.1.1 Definition of Adverse Events (AE)

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 Harmonization [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.

Adverse Events of Special Interest (AESI)
Adverse events of special interest are events that the COMPANY is actively monitoring as a result of a previously identified signal (even if non-serious).

In addition to the usual expedited reporting of all "serious" adverse events (per ICH criteria), the following AEs of special interest must also be reported to Janssen in an expedited fashion, i.e., per SAE reporting timelines, even when not serious (AE does not meet any of the ICH serious AE criteria):

- All malignancies
- All cases of active tuberculosis (TB)
- Anaphylactic reactions
- Serum sickness-like reactions

Special consideration should be given to reporting adverse events that are opportunistic infections and clinically significant as serious adverse events based on the "otherwise medically significant" criteria for seriousness, when they do not meet other Serious AE ICH criteria (eg hospitalization).

8.1.2 Definition of Serious Adverse Events (SAE)

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.

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.]

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

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

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.

For Stelara (ustekinumab), the link to the package insert is:

http://www.stelarahcp.com/pdf/PrescribingInformation.pdf

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

The following guidelines will be used to describe severity of Adverse Event.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Agent

All AEs must have their relationship to study agent assessed. The following guidelines will be used:

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test

result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2.3 Expectedness

At NYU Langone, Dr. Hudesman will be responsible for determining whether an AE is expected or unexpected. Dr. Cross will determine whether an AE is expected or unexpected at the University of Maryland site. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At

each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4 Reporting Procedures – Notifying the IRB

Data Safety Monitoring Plan

The principal investigator (David Hudesman) will be responsible for systematic oversight of the study and will convene a data safety monitoring board (DSMB) comprised of Dr. Hudesman and the following investigators from NYULH and University of Maryland:
1.Raymond K. Cross, D, MS, AGAF, FACG is a professor of medicine, Division of Gastroenterology and Hepatology at the University of Maryland, Baltimore. He is also director of the Inflammatory Bowel Disease Program at the University of Maryland School of Medicine and is co-director of the Digestive Health Center at the University of Maryland Medical Center.
2. Shannon Chang, MD, MBA is Associate Professor at the Department of Medicine, Division of Gastroenterology at NYU Grossman School of Medicine. Dr. Chang specializes in Inflammatory Bowel Diseases and serves as the Clinical Director of the IBD Center, NYU Langone.

3. Jordan Axelrad, MD, MPH is and Assistant Professor at the Department of Medicine, Division of Gastroenterology at NYU Grossman School of Medicine. Dr. Axelrad specializes in Inflammatory Bowel Diseases at the IBD Center, NYU Langone.

The DSMB will conduct a quarterly review of accumulated data and safety information which includes adverse events and study deviations, to ensure proper conduct of protocol, compliance, data accuracy and integrity, and subject safety. Dr. Hudesman is the Medical Director for Inflammatory Bowel Disease Center at NYU Langone Health. He also has several years of experience conducting many clinical trials at his practice.

Adverse events will be reported by the patient throughout the study and recorded by the investigator.
The investigator and coordinator will review and train the University of Maryland investigators and coordinators on the protocol and follow up on a monthly basis. All safety data finding will be disseminated to the University of Maryland through secure email. An annual progress report will summarize the findings of these safety reviews and tabulate all AEs. This will be submitted to the IRB as part of the Annual/Continuing Review submission.

The PI will follow all rules and regulations listed in Janssen's Interventional IIS COMPANY Requirements for Safety Data Collection and Reporting.

8.4.1 Adverse Event Reporting

<u>Non-Serious AEs</u>

All adverse events that do not fit the criteria of Reportable New Information will be considered a non-serious adverse event. A list of adverse events will be maintained in each subject's binder and will be reported to the IRB with the annual continuing review.

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.

8.4.2 Serious Adverse Event Reporting

SAE's at NYU Langone Medical Center that meet the institution criteria for Reportable New Information will be reported to the IRB and Janssen Scientific Affairs, LLC within 24 hours of the PI or Sub-I becoming aware of the event.

Any SAEs at the University of Maryland will be reported to NYU within 24 hours and NYU will then report that SAE to the NYU IRB and Janssen Scientific Affairs, LLC immediately. If needed the investigator and coordinator will travel to the University of Maryland.

8.5 Reporting Procedures – Notifying the Study Sponsor

Overview

As the sponsor of the Study, INSTITUTION and 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 the COMPANY on adverse events, special situations including pregnancies and product quality complaints as defined within this EXHIBIT.

The INSTITUTION and the PRINCIPAL INVESTIGATOR) will transmit all SAEs, Adverse Events of Special Interest and special situations following exposure to a Janssen product under study in a form provided by the COMPANY in accordance with transmission methods listed in this exhibit, 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, Adverse Events of Special Interest 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 extraordinary (not including routine initial or follow-up ICSR submission) 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 listed in this exhibit within 24 hours of such report or correspondence being sent to applicable health authorities.

Management of Safety Data:

This Study has been designated as an interventional study. As such, all adverse events for Janssen Medicinal Products 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 after the last dose of study drug.

For the purposes of this study, the Janssen medicinal product is:
Stelara (ustekinumab)

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 in accordance with clinical practice.

SAEs, Adverse Events of Special Interest 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, Adverse Events of Special Interest and special situations following exposure to a Janssen product under study in a form provided by the COMPANY in accordance with transmission methods listed in this exhibit, 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, Adverse Events of Special Interest 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 extraordinary (not including routine initial or follow-up ICSR submission) 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 listed in this exhibit within **24 hours of such report or correspondence being sent to applicable health authorities.**

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.

Pregnancy

All initial reports of pregnancy must be reported to the COMPANY by the PRINCIPAL INVESTIGATOR within 24 hours of becoming aware 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 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 will be required.

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

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.

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.**

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.

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

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

- Electronically via Janssen SECURE Email service (preferred) IIS-BIO-VIRO-GCO@its.jnj.com
- For business continuity purposes, if SECURE Email is non-functional:

Facsimile (fax), receipt of which is evidenced in a successful fax transmission report to 1-866-451-0371

- Telephone (if fax is non-functional).

The contact information and process information provided by the COMPANY will be used.

Contacting COMPANY Regarding Safety
The names (and corresponding contact information) of the individuals who should be contacted regarding safety issues will be provided separately by the COMPANY.

SAEs Listing
At a minimum, on a quarterly basis and at the end of the Study, COMPANY will provide to the INSTITUTION and/or PRINCIPAL INVESTIGATOR, a listing of all SAEs reported to the COMPANY. SPONSOR and/or PRINCIPAL INVESTIGATOR will review this listing and will resolve any discrepancies with the data provided by the COMPANY

Dissemination of Safety Information from COMPANY to INSTITUTION/PRINCIPAL INVESTIGATORS
PRINCIPAL INVESTIGATOR will be responsible for submitting Serious Unexpected Serious Adverse Reaction (SUSAR) reports for the Study Product to INSTITUTION's IRB in accordance with Federal regulations 21 CFR 312.66. The PRINCIPAL INVESTIGATOR will provide a copy of each SUSAR report to sub-investigators where the study design is either a multi-center or cooperative study.

COMPANY agrees to provide to the PRINCIPAL INVESTIGATOR SUSAR reports for the Janssen Medicinal Product as they become available until all subjects in the Protocol have completed their last Study visit according to the Protocol (i.e. Last Subject Last Visit has occurred).

Suspected Unexpected Serious Adverse Reaction (SUSAR) – An adverse drug reaction (ADR) that is both serious and unexpected (per the reference safety information [RSI]) that based on the opinion of the investigator or sponsor, is felt to have a reasonable suspected causal relationship to a medicinal product.

Final Study Report
The INSTITUTION/PRINCIPAL INVESTIGATOR will prepare a final report including a complete and full summary of all adverse events, special situations and pregnancy reports according to the timeframe outlined in the agreement.

8.6 Reporting Procedures – Notifying the FDA

The following describes the IND safety reporting requirements by timeline for reporting and associated type of event:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division of Gastroenterology, Office of Immunology and Inflammation at the Center for Drug Evaluation and Research no later than 7 calendar days after initial receipt of the information.

- All 7-day reports will be submitted electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG).

- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division Gastroenterology, Office of Immunology and Inflammation at the Center for Drug Evaluation and Research and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting. Given the IND is in eCTD format, submissions of 15-day reports to FDA will be made electronically in eCTD format via the ESG.

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND became active (the date clinical studies were permitted to begin).

SUBMISSION REQUIREMENTS

The IND number will be listed above at the top of the first page of any communications concerning this application.

Electronic submissions:

Future amendments, that are in eCTD format, will be submitted electronically via the FDA CDER NextGen Portal.

Paper submissions:

If submitting in paper, each submission to this IND will be provided in triplicate (original plus two copies). Include three originals of all illustrations that do not reproduce well. FDA will also accept submissions on certain physical media (e.g. CDs, DVDs (up to 6 pieces), external hard drives); a printed copy of the cover letter will be included with submissions on electronic media. All submissions, electronic or paper, including those sent by overnight mail or courier, will be sent to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper will be three-hole punched on the left side of the page and bound. The left margin will be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) will be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages will be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved.

Future amendments to the IND will be sent electronically through the FDA Electronic Submissions Gateway (ESG) which is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review.

9 Statistical Considerations

We expect a 20% clinical remission rate in the subcutaneous group and a 50% clinical remission rate in the IV group. Based on supplementary appendix from the UNITI trials and post hoc analysis, we expect

that 75 percent of the patients starting ustekinumab therapy will get randomized (CDAI will not drop by 100 points or CRP will not drop below 5mg/l or calprotectin will not drop by 50% at week 6). This yields an estimated enrollment ratio of 0.6 (IV group to subcutaneous group). Under these assumptions a sample size of 80 total participants is needed to achieve a power of 1- β=0.80 for a two-sided statistical level of α=0.05. Given an estimated 10% drop out rate, we plan to enroll **88 patients** into the study.

Descriptive statistics (eg, mean, median, standard deviation) will be used to summarize continuous variables. Frequencies and percentages will be used to summarize categorical variables. The primary efficacy endpoint, clinical remission at week 16, and other binary secondary outcomes will be analyzed using a two-sided, Cochran-Mantel-Haenszel chi-squared test. The Fisher exact test will be used for treatment comparisons in rare events. Secondary continuous response parameters will be compared using an analysis of variance (ANOVA) or covariance (ANCOVA). All statistical testing will be performed at the α=0.05 (2-sided) level. Nominal p-values will be displayed for all treatment comparisons.

9.1 Statistical Hypotheses

A second IV dose of ustekinumab at week 8 is superior to standard 90mg sq dosing at week 8 to induce clinical remission at week 16 in “high risk” moderate to severe Crohn’s disease patients.

10 Ethics/Protection of Human Subjects

10.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

10.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

10.3 Informed Consent Process

Consent and Other Informational Documents Provided to Participants. This study will first be introduced to eligible subjects by the PI or Sub-I. PI/Sub-I and an available coordinator will review the consent form with the patient. Patients will be given ample time to review the consent form, and the coordinator or investigator will be available to answer any questions the patient may have. Consenting may occur in office during the patient’s regularly scheduled clinic visit, with additional time given to patients if required. An IRB approved personnel will sign consent with the subject. The consent process will be documented and signed by the PI/Sub-I, and the documentation will be kept in the patient’s study binder.

A copy of the signed informed consent document will be stored in the subject’s research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject’s research record. Any alteration to the standard consent process (e.g. use of a translator, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

11 Data Handling and Record Keeping

11.1 Data Collection and Management Responsibilities

NYU Langone Medical Center will serve as the Data Coordinating Site for this trial. Pertinent data collected at the University of Maryland will be de-identified and sent to NYU Langone Medical Center for analyses via TrialMaster.

Careful data monitoring and quality control will be maintained with all possible precautions taken to protect the confidentiality of study subjects. All study staff delegated to enter data into the selected electronic database will have their own login information and passwords. All information with patient identifiers will be coded using study IDs. Data will be collected and stored in an encrypted database such as TrialMaster. Patient information with identifiers will be under lock-and-key with access only to the PI and study co-coordinator at each respective site. No participant will be identified from published reports and correspondence between investigators will not include patient names. All information will be reviewed in a private location and only by study staff delegated to review records.

12 Study Finances

12.1 Funding Source

Janssen Scientific Affairs, LLC will provide Stelara for patients randomized to the second IV arm at no additional cost to patients.

12.2 Costs to the Participant

Participants will not be reimbursed for taking part in this study.

13 Study Administration

Dr. Hudesman is the Principal Investigator of this study. NYU Langone Medical Center will serve as the Primary and the Data Coordinating Site for this study. All interim data findings and study related modifications will be relayed to other site(s) via email detailing the changes that need to be made. These changes will need to be approved by each site(s) respective IRB(s).

Dr. Cross will be the lead Investigator at the University of Maryland. The University of Maryland IRB will provide approval of study before any study related procedures take place.

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