CLINICAL PROTOCOL

An Open-Label Phase I/II Pilot Study to Assess the Safety/Tolerability and Efficacy of Ustekinumab for Symptomatic Gastrointestinal Inflammation Associated with Common Variable Immunodeficiency

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A1AT	Alpha-1 Antitrypsin
AE	Adverse event
AI	Associate Investigators
AR	Adverse Reaction
BTRIS	Biomedical Translational Research Information System of the NIH
CD	Crohn's disease
CD#	cluster of differentiation
CD40L	cluster of differentiation 40 ligand
CIs	confidence intervals
CRP	C-reactive protein
CRF	case report form
CT	computed tomography
CSO	Clinical Safety Office
CVID	common variable immunodeficiency
CXR	chest x-ray
EGD	esophagogastroduodenoscopy
ELISA	enzyme-linked immunosorbent assay
ESR	erythrocyte sedimentation rate
FDA	Federal Drug Administration
GI	gastrointestinal
GCP	Good Clinical Practice
HBeAg	hepatitis B e-antigen
HBsAg	Hepatitis B surface antigen
Hib	Haemophilus influenzae type B (vaccine)
HIV	human immunodeficiency virus
HRPP	Human Research Protection Program
IATA	International Air Transport Association
ICOS	inducible T-cell COStimulator
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
INR	International Normalized Ratio
IRB	Institutional Review Board
IUIS	International Union of Immunological Societies
IVIG	intravenous pooled immunoglobulin
IV	intravenous
LCIM	Laboratory of Clinical Immunology and Microbiology
LPMC	lamina propria mononuclear cells
LPS	Lipopolysaccharide
NIAID	National Institutes of Allergy and Infectious Diseases
NIH	National Institutes of Health
NLH	nodular lymphoid hyperplasia

OHRP	Office for Human Research Protections
PBMCs	peripheral blood mononuclear cells
OCRPRO	Office of Clinical Research Policy and Regulatory Operations
PCR	polymerase chain reaction
PI	Principal Investigator
PT/ PTT	Prothrombin Time, Partial Thromboplastin Time
SAE	Serious adverse event
SAC	Staphylococcus aureus Cowan
SAR	Suspected Adverse Reaction
SC	subcutaneous
SERF	Safety Expedited Report Form
SMC	Safety Monitoring Committee
SRCP	Safety Review and Communication Plan
SUSAR	Serious and Unexpected Suspected Adverse Reaction
$t_{1/2}$	half-life
TB	tuberculosis
TGF beta	transforming growth factor beta
Th1 / Th2	T-helper type 1 / type 2
TNF	tumor necrosis factor
ULN	upper limit of normal
UP	Unanticipated Problem
UPnonAE	Unanticipated Problem that is not an Adverse Event

PROTOCOL SUMMARY

Full Title: An Open-Label Phase I/II Pilot Study to Assess the Safety/Tolerability and Efficacy of Ustekinumab for Symptomatic Gastrointestinal Inflammation Associated with Common Variable Immunodeficiency

Short Title: Ustekinumab for CVID-GI

Clinical Phase: I/II

IND Sponsor: NIAID

Conducted by: NIAID / Laboratory of Clinical Immunology and Microbiology (LCIM)

Principal Investigator: Ivan J. Fuss, MD

Sample Size: 10 subjects

Accrual Ceiling: 10 subjects

Study Population: Subjects with Common Variable Immunodeficiency (CVID) or selective IgG subclass deficiency (functional agammaglobulinemia) and associated symptomatic gastrointestinal inflammation (enteropathy).

Accrual Period: July 2014 through December 2018

Study Design: This is an open-label study in CVID or selective IgG subclass deficiency (functional agammaglobulinemia) patients with active gastrointestinal symptoms (CVID enteropathy). Up to 10 eligible adult subjects will be enrolled at the NIH Clinical Center. This study consists of a Pre-Treatment Visit (Day -120 to -1), a Day 0 Treatment Visit, a Week 8 Treatment Visit, a Week 16 Treatment Visit, a Week 24 Treatment Visit, a Week 32 Treatment Visit, a Week 40 Treatment Visit and a Week 48 Endpoint Visit. A treatment dose of ustekinumab 270 mg (3 doses of 90 mg, either single-use prefilled syringe or single-use vial, depending on availability) will be injected subcutaneously in subjects by qualified nursing staff on Day 0. Subjects will then receive a follow up treatment dose of 90 mg (1 dose of 90 mg) at Week 8, Week 16, Week 24, Week 32, and Week 40. Patients will be seen at Week 8, Week 16, Week 24, Week 32, Week 40 and Week 48 for research visits and will be clinically followed for a total of 48 weeks.

Subjects who have already received a single 270 mg dose may be eligible for retreatment as follows: If they have had a reoccurrence of symptoms, meet study eligibility criteria and are at least 6 months or greater from receiving study agent subjects would receive a treatment dose of 270 mg (3 doses of 90 mg, either single-use prefilled syringe or single-use vial, depending on availability) will be injected subcutaneously in subjects by qualified nursing staff on the Day 0 study point. Subjects will then receive follow up treatment doses of 90 mg (1 dose of 90 mg) at the Week 8, Week 16, Week 24, Week 32, and Week 40 study points. These subjects will be classified as Cohort 1.

Newly enrolled subjects will be assigned into Cohort 2 and will receive ustekinumab doses as follows: A treatment dose of 270 mg (3 doses of 90 mg, either single-use prefilled syringe or single-use vial, depending on availability) will be injected subcutaneously in subjects by qualified nursing staff on the Day 0 study point. Subjects will then receive follow up treatment doses of 90 mg (1 dose of 90 mg) at the Week 8, Week 16, Week 24, Week 32, and Week 40 study points.

Study Duration: Individual subject participation will be 48 weeks from administration of study agent.

Study Agent: Stelara® (ustekinumab), Janssen Biotech, Inc.

Primary Objective: Assess the safety and tolerability of administration of ustekinumab in CVID enteropathy patients by measuring the rates of adverse events.

Secondary Objectives:
- To assess the efficacy of the study agent in alleviating symptoms of CVID enteropathy by comparing measurements of weight and stool frequency at the Week 8, Week 16, Week 24, Week 32, Week 40 and Week 48 study points with Day 0 baseline values.
- To assess changes in gut absorption and protein loss (D-xylose absorption, 48 hour stool fat collection, fecal alpha-1 antitrypsin (A1AT) clearance) at the Week 24 and Week 48 study points by comparison to baseline studies.
- To assess changes in mucosal histology score (modified D'haens scoring) at the Week 48 study point by comparison to baseline score.
- To measure changes in stimulated cytokine production and mRNA expression microarray by LPMCs at the Week 48 study point by comparison to baseline studies.
- To measure changes in gut microbiota and global gene expression of inducible interferon and metabolic genes at the Week 48 study point by comparison to baseline studies.
- To measure changes in laboratory surrogate efficacy markers of inflammatory bowel disease treatments (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], albumin, hemoglobin, platelets) at the Week 8 Week 16, Week 24, Week 32, Week 40 and Week 48 study points.

Primary Endpoint: The primary endpoint of the study is whether treatment with ustekinumab is safe and tolerated in the CVID enteropathy patients and does not cause a significant increase in infection or result in any serious adverse events (SAEs) that are determined to be definitely, probably or possibly related to administration of the study agent.

Secondary Endpoint: The secondary endpoint of the study is whether patients respond to the treatment with ustekinumab. Response will be defined as <1% decrease in weight or a decrease in the number of stools at the Week 8, Week 16, Week 24, Week 32 and Week 40 visit compared to Day 0 baseline values. We will also evaluate the change in immunologic laboratory parameters such as decreases in inflammatory cytokines and biomarkers that appear to play a role in disease pathogenesis at the Week 48 study point.

PRÉCIS

The purpose of this study is to assess the safety/tolerability and efficacy of using ustekinumab in subjects with common variable immunodeficiency CVID or selective IgG subclass deficiency (functional agammaglobulinemia) who have associated symptomatic gastrointestinal inflammation (CVID enteropathy). Ustekinumab (a Food and Drug Administration [FDA] approved drug) is a monoclonal antibody to interleukin (IL)-12/23p40. CVID is a clinically heterogeneous disorder characterized by decreased serum immunoglobulin IgG and IgA levels. In addition to chronic or recurrent pyogenic sino-pulmonary infections, many patients develop non-infectious gastrointestinal manifestations that can be disabling or fatal. Currently there is no standard therapy for the associated gastrointestinal disease outside of empiric nutritional intervention for weight loss, anti-diarrheal agents, and non-specific anti-inflammatory agents.

Recently, gut inflammation complicating functional hypogammaglobulinemia due to CVID and selective IgG subclass deficiency has been characterized as a T helper type 1 (Th1) inflammatory response, with excess IL-12 cytokine production associated with diarrhea and weight loss as well as reduced D-xylose absorption and steatorrhea. This protocol aims to test specific anti-IL-12 therapy in this patient group. It has been previously shown that therapy targeted to IL-12 successfully treated the Th1 gut inflammation of Crohn's disease (CD). Ustekinumab, a monoclonal antibody to the p40 subunit of IL-12 and IL-23, is FDA approved for the treatment of moderate to severe plaque psoriasis, active psoriatic arthritis, and more recently, moderately to severely active CD. This protocol is designed to measure the safety of ustekinumab in patients with functional hypogammaglobulinemia and CVID enteropathy, as well as measure effects on symptoms, gut function, expression of immune cell surface markers, production of cytokines and global gene expression from blood and gut mucosal mononuclear cells, and the gut microbiota.

Patients with CVID and selective IgG subclass deficiency with gastrointestinal symptoms of malabsorption, maldigestion, and chronic diarrhea will be enrolled into this study. Subjects (up to a total of 10 individuals) will receive a treatment dose of 270 mg (3 doses of 90 mg either single-use prefilled syringe or single-use vial, depending on availability) will be injected subcutaneously in subjects by qualified nursing staff on the Day 0 study visit. Subjects will then receive a follow up treatment dose of 90 mg at Week 8, Week 16, Week 24, Week 32 and Week 40 and be followed for a total of 48 weeks.

Subjects will have study procedures prior to treatment and 48 weeks post-treatment, these include upper and/or lower endoscopies, to measure changes in immune responses and studies to evaluate physiologic measures of gut function at 48 weeks, as well as routine safety monitoring throughout the study. Gut absorption tests will be performed at the Week 24 visit. Variables will include safety (adverse event rate), clinical (weight, stool frequency, results of gut absorption tests), and laboratory (lymphocyte and cytokine assays) parameters for descriptive summary statistical analysis (n, mean, median, standard deviation, minimum and maximum range).

1.0   INTRODUCTION

1.1   COMMON VARIABLE IMMUNODEFICIENCY (CVID)

Common variable immunodeficiency (CVID) is characterized by functional hypogammaglobulinemia due to a primary failure of B cell differentiation and impaired secretion of immunoglobulins. This is frequently accompanied by T cell abnormalities consisting of blunted proliferative responses to mitogenic and antigenic stimuli, a relative lack of mature (CD45RO) T cells, and reduced production of IL-2 and other cytokines. Well-defined genetic defects are just beginning to be identified, but most CVID is encountered as sporadic and not as inherited disease (Grimbacher et al., 2003; Salzer et al., 2005). The major manifestations of this disease include bacterial infections, autoimmune diseases (i.e., autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, and pernicious anemia), and an increased risk for lymphoproliferation and neoplasia. In addition, it has been described that patients with selective IgG subclass deficiency can also manifest similar infections and autoimmune disease (Martinot et al 2014; Quinti et al 2011; Geha 1988; Umetsu et al 1985). In addition, prior studies have indicated that selective deficiencies not only in IgG2 or IgG4, but also IgG3 can lead to decreased responses to capsular polysaccharide of Haemophilus influenza type B (Hib) and were associated with increased incidence of pneumonia in children (Umetsu et al. 1985). Finally, autoimmune cytopenias (i.e. neutropenia and idiopathic thrombocytopenia) which can commonly occur in CVID can also occur in selective IgG subclass deficiency (Sugita et al 1993).

Therapy for these conditions is aimed primarily at restoring immunoglobulin levels with the administration of intravenous pooled immunoglobulin (IVIG) (Quinti et al 2011). While this therapy clearly decreases the frequency and severity of infections, it has no effect on associated autoimmune disease or neoplasia risk. Furthermore, it is recognized that the GI tract is affected in CVID not only by infectious agents that respond to IVIG but also by idiopathic inflammation and lymphoproliferative lesions, which are unresponsive to IVIG therapy. For the purposes of this protocol, both CVID and selective IgG subclass deficiency will be termed CVID or functional hypogammaglobulinemia.

While the hallmark of CVID is the inability to make antibodies to specific antigens, this has been attributed to abnormalities in both B and T cell status and function. Low B cell (CD19+) numbers (in 5-10% of CVID patients) are associated with failure to produce antibodies *in vitro* (Farrant et al., 1994), and the majority of CVID patients with normal B cell numbers are lacking in mature class-switched B cells (i.e., CD27+IgM-IgD- memory B cells) (Warnatz et al., 2002; Jacquot et al., 2001). This latter observation is consistent with the lack of plasma cells (particularly those producing class-switched antibodies, as CD27 is known to promote interaction with T cells for differentiation into plasma cells) in the lamina propria (Herbst et al., 1994; Washington et al., 1996). Additionally, among those with normal B cell numbers, B cells may be induced *in vitro* to produce IgM alone, IgM and IgG, or remain unresponsive (Bryant et al., 1990) suggesting the mechanism for producing antibodies is not due to primary B cell defects in some patients. Furthermore, selective IgG subclass deficiency (i.e. IgG2 subclass deficiency) can also manifest associated poor antibody response to antigen challenge (polysaccharide antigen) similar to CVID patients (Geha et al. 1988). CVID patients with near normal numbers of mature class-switched B cells (CD27+IgM-IgD-) seem to be the ones who can produce IgM and IgG *in vitro* (those with

low numbers of mature class-switched B cells can be further defined by whether there is a concomitant excess of immature B cells (CD21-) (Warnatz et al., 2002). However, any such classification of B cell dysfunction does not seem to clearly predict the natural history or development of complications in CVID.

T cells in CVID patients have been variously reported to display reduced proliferation and activation by antigens and/or mitogens (Cunningham-Rundles and Bodian, 1999; Fischer et al., 1993; Fischer et al., 1994; North et al., 1991), have impaired IL-2 production, show lower expression of cell surface CD40L (Brugnoni et al., 1996; Farrington et al., 1994), fail to develop antigen-specific responses (Kondratenko et al., 1997; Stagg et al., 1994), and show excessive activity of CD8+ cells (Jaffe et al., 1993; North et al., 1998; Serrano et al., 2000; Wright et al., 1990; Waldmann et al., 1974). Although antigen-presentation appears to be intact for CVID monocytes and macrophages (Gupta and Damle, 1983; Thon et al., 1997), dendritic cells and monocytes may have altered cytokine production that could affect the function and differentiation of B cells (Cambronero et al., 2000; Cunningham-Rundles and Radigan, 2005). In sum, the variety of the altered cellular immune response observed in CVID lymphocytes supports the notion that failure to produce antibodies may be a primary B cell defect but more likely is contributed to by defective T cell signals and interactions.

1.1.1   Current Therapy for CVID

Current therapy for CVID is chronic replacement of immunoglobulins, and this has been a successful strategy for controlling the recurrent sino-pulmonary infections. However, this treatment does not generally affect other conditions that can complicate functional hypogammaglobulinemia including autoimmune diseases (cytopenias, hypothyroidism) (Cunningham-Rundles and Bodian, 1999), nodular lymphoid hyperplasia (NLH) of the intestinal mucosa, lymphoma, and an enteropathy presenting as chronic diarrhea and malabsorption.

Patients with CVID are more susceptible to protozoan and bacterial gastrointestinal pathogens. Infection with *Giardia lamblia* is frequently encountered and is characterized by clinical disease after lower levels of parasite exposure as well as increased resistance to eradication with conventional therapy. In addition, there is an increased incidence of infections with common gastrointestinal pathogens (e.g., *Salmonella*, *Shigella*, and *Campylobacter* species). Severe diarrhea has been associated with the fastidious gram-negative rod known as dysgonic fermenter-3 (DF-3) (Wagner et al., 1988). While the incidence of *Giardia* infection has decreased significantly in patients on chronic IVIG therapy (Teahon et al., 1994), the rate is still higher than seen in normal individuals.

In addition to protozoan and bacterial gastrointestinal pathogens CVID patient population can be at risk for viral pathogens. The most commonly reported being rhinovirus and norovirus. The former involving predominately the respiratory tract while the latter within the gastrointestinal tract and a reported rate of incidence of norovirus at 8% in a study population which included CVID and X-linked agammaglobulinemia patients (Duraisingham et al. 2015). Whether norovirus gastrointestinal infection impacts upon gastrointestinal malabsorption in this patient population is not apparent. Patients with immunodeficiency are observed to have prolonged clearance of this organism and can have chronic shedding of the virus. However, only patients with significant T cell impairment (status post bone marrow or cardiac transplant) have displayed prolonged

morbidity from norovirus. However, patients without significant T cell impairment with norovirus have received immunosuppression treatment without untoward outcomes despite prolonged viral shedding. Unfortunately in the care of patients with norovirus, measurement of viral load remains controversial, as viral load has not always correlated with degree of symptoms. Patients have been treated with oral preparations of immunoglobulin with small success in clearance of this organism (Duraisingham et al. 2015, Green 2014, Masclee et al. 2013, Nelson et al 2013, Kolho et al 2012 Florescu et al 2011, O' Connor et al 2009).

1.1.2   Gastrointestinal Manifestations of CVID

Gastrointestinal (GI) manifestations of CVID unrelated to infections occur in upwards of 20% of patients (Cunningham-Rundles and Bodian, 1999; Sneller et al., 1993, Mannon et al 2006). This is most likely an underestimate since patients without overt gastrointestinal symptoms are not routinely examined for gut abnormalities. Patients with this syndrome, termed CVID enteropathy, exhibit villous atrophy of the small bowel mucosa and a complex of associated symptoms including chronic diarrhea, malabsorption marked by increased excretion of fat, and protein-losing enteropathy leading to loss of albumin and other proteins into the fecal stream. These symptoms can lead to severe weight loss, hypoalbuminemia predisposing to edema, and the need for nutrient supplementation (Mannon et al 2006).

In one study, 51% (22/43) of patients with CVID had accompanying GI symptoms (i.e., chronic or bloody diarrhea, documented *Giardia* or other parasitic infection, pernicious anemia, pneumatosis coli, malabsorption, and perirectal abscess) and of those with gut tissue examined histologically (10/22), 100% had striking abnormalities (Washington et al., 1996). A wide range of histologic abnormalities are seen: in the stomach, morphologic changes consistent with acute graft-versus-host disease (apoptotic glandular epithelial cells, dense mononuclear inflammatory cell infiltrate with occasional crypt obliteration), increased intraepithelial lymphocytes, and varying degrees of gastritis (leading in some cases to atrophy and achlorhydria in the absence of *Helicobacter pylori* infection and anti-parietal cell and anti-intrinsic factor antibodies (Moriuchi et al., 1990; Twomy et al., 1970; Wright and Sears, 1987; Zullo et al., 1999)); in the small intestine histologic changes include mild to marked villous atrophy (differing from celiac sprue by the absence of lamina propria plasma cells, lack of significant basal crypt hyperplasia, and relatively normal enterocyte maturation with preserved brush border and Goblet cells), increased intraepithelial lymphocytes, nodular lymphoid hyperplasia (NLH), frank lymphomatous changes as well as the occurrence of non-granulomatous transmural inflammation with evidence of fibrosis and strictures (Teahon et al., 1994; Washington et al., 1996); finally in the colon there can be inflammation that resembles lymphocytic colitis (with increased lymphocytes in the surface epithelium), ulcerative colitis (with acute inflammatory cells in the crypt epithelium and lamina propria, and loss of crypts in severe disease, but lacking the plasma cell infiltrate seen in classical ulcerative colitis), or graft-versus-host disease. One study notes Crohn's disease, and ulcerative colitis/proctitis associated with CVID (Cunningham-Rundles and Bodian, 1999), but other more detailed studies of the accompanying enteropathy do not support its meeting the full histologic criteria for these diseases (Teahon et al., 1994; Washington et al., 1996).

The lesions of intestinal nodular lymphoid hyperplasia (NLH) are said to be virtually pathognomonic for CVID, but NLH does occur rarely in otherwise normal individuals. These macroscopic collections of lymphocytes are found primarily in the small bowel and sometimes in

the colon, appearing as submucosal nodules to the endoscopist. Histologic examination shows that the nodules consist of B cells bearing surface IgM surrounded by T cells, most of which are CD8+ (van den Brande et al., 1988) suggesting they are attempts to form productive B cell follicles that are not properly down-regulated by T cells. While not the source of symptoms themselves, they may be associated with an increased risk of intestinal lymphoma (Castellano et al., 1992; Ryan, 1996).

The gut inflammation and histologic changes accompanying CVID are not related to the presence of intestinal infections, although bacterial overgrowth and infection with pathogenic bacteria and parasites should be evaluated and treated as a cause of gastrointestinal symptoms. The enteropathy does not respond to antibiotic or IVIG therapy. Instead it has been suggested that the gut lesions could reflect autoimmune enteritis (Teahon et al., 1994; Washington et al., 1996). Although autoimmune enteritis occurs in young children and generally not adults, only one case report documents the characteristic anti-enterocyte antibodies (Catassi et al., 1988) in a boy with CVID, and another report notes that 58-67% of patients with CVID and gastrointestinal symptoms also have other possible autoimmune diseases (autoimmune hemolytic anemia, thrombocytopenia with antiplatelet antibodies, neutropenia, arthritis, thyroid dysfunction, pernicious anemia, vitiligo, episcleritis, and insulin-dependent diabetes mellitus) (Washington et al., 1996). A plausible immunologic mechanism for the enteropathy is the presence of a T cell dysfunction leading to autoimmune attack within the intestinal wall. Such a role for T cell dysfunction in CVID is consistent with the observation that the enteropathy does not occur in X-linked agammaglobulinemia, an immunodeficiency state with impaired B cell function equal or greater than CVID but with no accompanying T cell abnormality (Lederman and Winkelstein, 1985). Furthermore, CVID patients with related enteropathy are more likely to have T cell dysfunction than those without (Cunningham-Rundles and Bodian, 1999). Even the morphologic changes suggest a primary role for T cells in the enteropathy, with T cells predominating in the lamina propria infiltrate and the epithelial apoptosis so reminiscent of graft-versus-host disease that is mainly T cell-mediated.

Finally it should be stated that there is no standard treatment that ameliorates the gastrointestinal disease in CVID patients. Therapeutic interventions for weight loss are aimed at hyperalimentation, including total parenteral nutrition when indicated, and identifying any treatable causes of malabsorption such as small bowel bacterial overgrowth. The approach to chronic diarrhea is little different than in other immunodeficient patients, with an emphasis on ruling out treatable infectious etiologies. The gut inflammation can be treated with non-specific anti-inflammatory agents, but none have shown consistent efficacy in this patient population.

1.1.3   Current Immunology Research in CVID Patients

In recent years it has been shown that a significant subset of CVID patients demonstrates features of persistent immune activation characterized by a Th1-skewed cytokine profile. These patients may have an abnormally low CD4/CD8 ratio (<0.9), and an increased incidence of splenomegaly (71%) and anergy (42%) compared to CVID patients with normal CD4/CD8 ratios (29% and 7%, respectively) (Wright et al., 1990). The low CD4/CD8 ratio in this CVID group is due to an increase in CD8+ cells, which have impaired proliferation but secrete increased levels of IFNγ and IL-5 (but normal amounts of IL-4) when stimulated *in vitro* (Jaffe et al., 1993; Wright et al., 1990).

In these studies the CD4+ cells behaved normally, and in only the occasional patient could CD8+ effects potentially explain the hypogammaglobulinemia.

In another study of 24 CVID patients, low CD4+ cell counts and a low CD4/CD8 ratio < 0.9 was observed that could not be attributed to an expanded CD8+ population (Aukrust et al., 1996). In addition, this study group had significantly elevated serum TNF alpha levels which was particularly evident in the subset (11/24 patients) defined by splenomegaly, a CD4+ count < 400 x 10^6/L, and significantly elevated serum neopterin levels. Furthermore, another report showed that significantly more peripheral blood monocytes (CD14+, but not CD14- cells in a dendritic cell pool) from CVID patients expressed high IL-12 following lipopolysaccharide (LPS) stimulation than normal controls or patients with X-linked agammaglobulinemia (Cambronero et al., 2000); this was associated with significantly increased expression of IFNγ in CD4+ (and CD8+) T cells.

A more recent study confirmed the lack of IL-12 production in CVID dendritic cells (CD14-) compared to its induced production in normals, but other monocytes were not studied (Cunningham-Rundles and Radigan, 2005). Lastly, in CVID patients with granulomatous disease or reduced numbers of class-switched memory B cells, plasmacytoid dendritic cells (promoting Th2 responses) were disproportionately decreased compared to myeloid dendritic cells (promoting Th1 responses), suggesting a possible bias toward Th1 inflammatory responses (Viallard et al., 2005). While it is not known whether gastrointestinal disease is experienced at a higher rate in high-TNF or any of these other CVID subsets, given the role of TNF in gut granulomatous inflammation and its role in Crohn's disease, these data support the idea that immune activation, with a Th1 skewness, may be associated with gastrointestinal disease in CVID. Clearly excess TNFα can contribute to gastrointestinal inflammatory states as seen in transgenic animal models (Kontoyiannis et al., 1999) and in the beneficial response of human Crohn's disease to TNFα immunoneutralization.
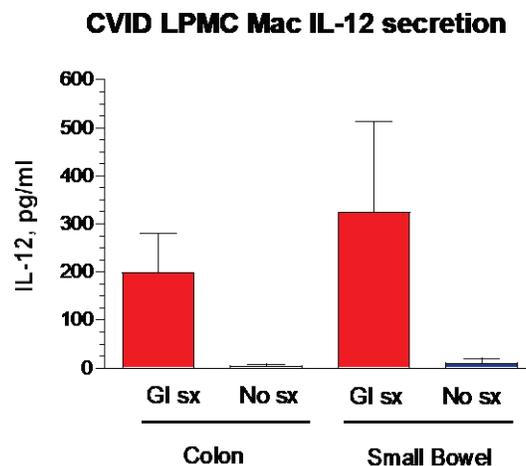
Figure 1: IL-12 secretion from LPMCs isolated from endoscopic biopsies of the duodenum and colon in CVID patients with or without chronic diarrhea or weight loss.

1.1.4   Preliminary Data in CVID Enteropathy

To evaluate the immunopathogenesis of CVID enteropathy we previously conducted an extensive comparison of the absorptive capacity and cytokine response of CVID patients with gastrointestinal symptoms and those with such symptoms. We observed that patients with gastrointestinal symptoms had evidence of metabolic dysfunction, which consisted of lower body mass index associated with an inability to absorb carbohydrates and proteins. Microscopic examination of tissue from symptomatic CVID patients exhibited diffuse histologic inflammatory changes in both the duodenal mucosa and sometimes the colonic mucosa as well. This included villus blunting, increased lamina propria and intraepithelial lymphocytes cell infiltrates (devoid of plasma cells), and epithelial cell apoptosis.

In addition, in immunologic studies, purified lamina propria mononuclear cells (LPMC) obtained from symptomatic CVID patients displayed a significantly higher IL-12-mediated T-helper (Th) 1 cytokine response (Figure 1) accompanied by greatly increased IFNγ secretion. However, compared with the cytokines produced by LPMCs from Crohn's disease (CD), cells from CVID patient cells did not produce excess amounts of the Th17 cytokines, interleukin-23, interleukin-17, or increased amounts of TNF-α. Thus, these studies indicated that CVID enteropathy was accompanied by excessive IL-12-mediated Th1 T cell cytokine production, distinct from that observed in Crohn's disease patients by its lack of concomitant Th17 response. Interestingly, only CVID patients with gastrointestinal symptoms of diarrhea and weight loss as well as the gut inflammatory changes had this excess cytokine production. CVID patients with similar histologic findings but no symptoms had no increased cytokine production (Mannon et al, 2006).

 IL-12 therefore is a notable contributor to inflammation, thus it is reasonable to believe that IL-12 blockade in CVID enteropathy patients should lead to a decrease in gut inflammation and subsequent improvement of gastrointestinal symptoms (Trinchieri G, 1998). Thus, CVID patients in Cohort 1 (n=3) have received a single subcutaneous dose administration (270 mg 3.9 mg/kg for a typical 70 kg patient) of ustekinumab. All patients have demonstrated improvement in stool pattern and 2 patients have had observable weight gain (range of 1.7 kg to 5 kg above baseline weight). No patient experienced any significant and/or unanticipated adverse events or infectious pathogen complications (see appendix G - Cohort 1 Single Dose Study Adverse Events).

1.2   STUDY AGENT

Usktekinumab (Stelara ®, Janssen Biotech, Inc) is a human IgG1kappa monoclonal antibody to the p40 subunit of IL-12 and IL-23. It has an approximate molecular weight of 148,600 daltons.

Figure 2: Usktekinumab
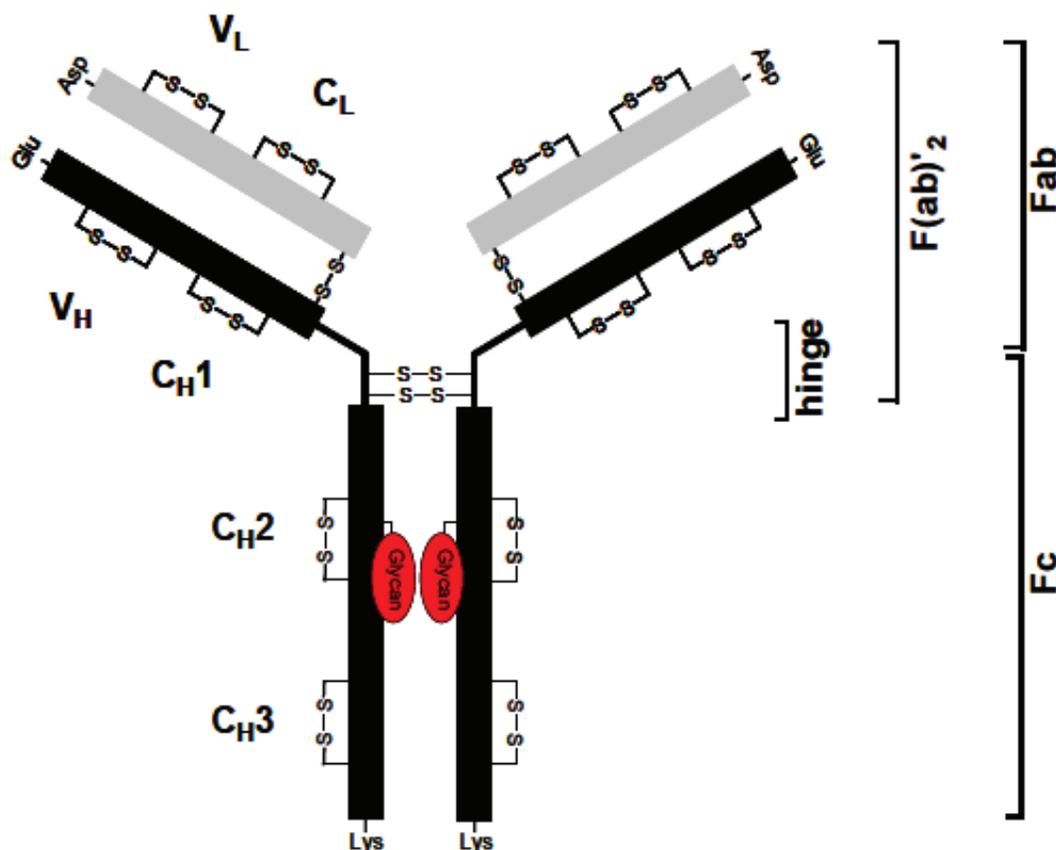
Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing these cytokines from binding to the IL-12Rbeta1 receptor protein expressed on the surface of immune cells. Ustekinumab has shown efficacy in trials for the treatment of moderate-to-severe plaque psoriasis, and was approved by the Federal Drug Administration (FDA) in 2009 for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. It is FDA approved for the treatment of adult patients with active psoriatic arthritis and more recently, in Sepetember 2016, ustekinumab has been approved for the treatment of patients with Crohn's disease. Ustekinumab is available for subcutaneous injection as either pre-filled syringes (45 mg/0.5 mL or 90 mg/1 mL), or a single-use vial (45 mg/0.5 mL dose, 90 mg/1 mL. Ustekinumab is also available as 130 mg/26 mL (5 mg/mL) for intravenous (IV Crohn's disease induction dosing. Dosing recommendations for plaque psoriasis are 45 mg administered at weeks 0 and 4, and then every 12 weeks; 90 mg can be used alternatively if the patient's body weight exceeds 100 kg (Stelara® Data Sheet, Appendix B). Dosing recommendations for Crohn's disease are 260 mg (patients less than 55 kg), 390 mg (patients 55 to 85 kg) and 520 mg (patients > 85 kg) IV administration at week 0 and then 90 mg subcutaneous every 8 weeks.

1.3   PHARMACOKINETICS

Pharmacokinetic data is available for the use of ustekinumab in the treatment of psoriasis. See attached Stelara® Data Sheet (drug insert), Appendix B.

1.4   CLINICAL EXPERIENCE IN CROHN'S DISEASE

Crohn's disease (CD) is thought to be a T-helper type 1 (Th1) mediated inflammation, with IL-12 and IL-23 playing major roles (Sandborn, 2008; Sandborn, 2012).   In addition, CD is characterized by a chronic inflammation of the gut mucosa leading to weight loss and diarrhea. CD patients with moderate to severe disease are also relatively immunosuppressed and more susceptible to infection than the general population due to the medications used to treat the disease. In both CD and CVID enteropathy patients an increased production of IL-12 is found in stimulated cytokine assays of LPMCs (Mannon et al, 2006). Therefore, CD serves as a comparable population to CVID enteropathy when assessing the potential benefits and risks of anti-IL-12 therapy.

The first published report of the use of a monoclonal antibody to IL-12/23p40 in CD described the results of a double-blinded randomized control trial. CD patients who received 3 mg/kg intravenous drug for 7 weeks had a 75% rate of response as compared to 25% in the placebo group (p=0.03) at the primary endpoint. In addition, patients who demonstrated clinical improvement from anti-IL-12/23p40 therapy had a decrease in the production of IL-12, IFNγ, and TNFα. There were no significant differences in the rate of adverse events between placebo and study drug groups other than local injection site reactions, which were mostly mild and transient (Mannon et al, 2004).

In previous phase II studies, ustekinumab has also been shown to be safe and effective in treating moderate-to-severe CD refractory to anti-tumor necrosis factor (anti-TNF) treatment.

In 2008, the results of a double-blind, cross-over trial comparing placebo, subcutaneous (SC), and intravenous (IV) dosing regimens of ustekinumab in patients with moderate-to-severe CD revealed that overall ustekinumab was more likely to induce response than placebo (53% vs 30%, p=0.02) at 4 and 6 weeks. Comparison between IV and SC dosing regimens showed that a single IV treatment dose had a trend towards higher rate of response versus multiple SC doses. There were no increased adverse events in the treatment group when compared to placebo (Sandborn et al, 2008). In a follow-up Phase IIb study of ustekinumab in CD patients who have failed anti-TNF therapy demonstrated that a 6 mg/kg IV treatment dose was significantly better than placebo in inducing clinical response (39.7% vs. 23.5%, p=0.005) at the 6 week endpoint. In addition, patients who did not respond to the placebo dose were given a SC treatment dose of 270 mg, with a clinical response rate of 35.3%. One patient who received 1 mg/kg of ustekinumab reported a basal-cell carcinoma that was resected. The relation of the basal-cell carcinoma to therapy was not commented on in the paper. Otherwise, there were no significant differences in rate of adverse events between groups (Sandborn et al, 2012).

Finally, in two phase 3 trials to evaluate the efficacy of ustekinumab in moderate to severe CD, patients, patients who could not tolerate or had an inadequate response to one or more TNF inhibitors (UNTI-1) were randomized to receive a single IV dose of 130 mg, a weight-based IV dose or placebo. For the weight based dosing, patients who weighed 55 kg or less received 260 mg

of ustekinumab; patients who weighed between 55 and 85 kg received 390 mg; and patients who weighed more than 85 kg received 520 mg. The primary endpoint was clinical response (decrease of CDAI of 70 points or greater) at week 6. The trial reached its primary endpoint yielding a clinical response rate at week 6 of 34% (P=0.03) in the 130 mg and weight based ustekinumab treated patient population as compared to placebo arm (21.5%). Clinical remission at week 8, defined by a CDAI score of less than 150, was a secondary endpoint. This endpoint was reached with remission rates of 16% and 20.9% (P<0.001) in the130 mg and weight based ustekinumab treated patients respectively as compared to the placebo arm (7.3%) (Lichtenstein G, 2016). In another randomized placebo controlled trial (UNTI-2) patients with moderate to severe CD who could not tolerate or had an inadequate response to corticosteroids, at least one immunomodulator, or both or had had never been treated with a TNF inhibitor were randomized to receive a single IV dose of 130 mg, a weight-based IV dose or placebo. The trial reached its primary endpoint yielding a clinical response rate at week 6 of 52% (P=0.03) in the 130 mg and 56% in the weight based ustekinumab treated patient population as compared to placebo arm (29%). Clinical remission at week 8, defined by a CDAI score of less than 150, was a secondary endpoint. This endpoint was reached with remission rates of 30% and 40% (P<0.001) in the 130 mg and weight based ustekinumab treated patients respectively as compared to the placebo arm (20%) (Lichtenstein G, 2016). Furthermore, in a maintenance trial (IM-UNTI), patients who had achieved a clinical response to ustekinumab after 8 weeks were randomized to receive maintenance treatment 90 mg SC every 8 or 12 weeks. After 52 weeks, 53% of patients who had received ustekinumab every 8 weeks and 49% of those patients that had received ustekinumab every 12 weeks were in remission, as compared to 36% of those that had received placebo (Lichtenstein G, 2016).

1.5   RATIONALE FOR DOSE SELECTION

Ustekinumab has been studied previously for the treatment of CD, which has a similar cytokine profile to CVID enteropathy. In those studies a treatment of 270 mg was given as a single intravenous (IV) dose and was found to be more effective than multiple subcutaneous (SC) doses in inducing a clinical response. On these studies, the highest dose tested, (6 mg/kg IV) had the highest rate of response. In addition, the single SC dose of 270 mg was also tested as a crossover treatment for those patients who did not respond to placebo treatment. Rate of response for the single 270 mg SC treatment was similar to the 6 mg/kg IV dose (35.3% vs. 39.7%, respectively). No increased rate of infection or other adverse events were found in any previous studies of CD patients at any of the studied dosages. A higher incidence of arthralgia, nausea, and dental infections was observed in STELARA®-treated patients when compared with placebo-treated patients (3% vs. 1% for arthralgia and 3% vs. 1% for nausea; 1% vs. 0.6% for dental infections) in the placebo controlled portions of clinical trials (Stelara® Data Sheet, Appendix B).

In this study, CVID patients in Cohort 1 (n=3) have received a single subcutaneous dose administration (270 mg 3.9 mg/kg for a typical 70 kg patient) of ustekinumab. All patients have demonstrated improvement in stool pattern and abdominal discomfort with 2 patients having observable weight gain (range 1.7 to 5 kg above baseline weight). No patient experienced any significant and/or unanticipated adverse events or infectious pathogen complications. Two patients have completed study (and one patient shortly in December 2016) at 6 months post induction subcutaneous dose of 270 mg with clinical response lasting for approximately 4-5 months duration.

More recently, dose administration recommendations for CD have been released (October 2016) as 260 mg (patients less than 55 kg), 390 mg (patients 55 to 85 kg) and 520 mg (patients > 85 kg) IV administration at week 0 and then 90 mg subcutaneous every 8 weeks.

Thus, based upon responses in CVID patient cohort 1 and recommended dose administration for CD patients CVID patients will receive a 270 mg subcutaneous loading dose and then receive 90 mg subcutaneous every 8 weeks (for a total of five 90 mg doses).

CVID patients enrolled in this study have existing cachexia and weight loss with body weight approximately 55-65 kg range. Therefore the initial dose of 270 mg previously used in CD patients and in Cohort 1 CVID patients represents a scientifically sound and reasonable balance between safety and efficacy and minimizing the risk of immunosuppression in an already immunocompromised population. Finally, IV dose vials (130 mg/26 mL) are to be released however, the 90 mg/mL concentration for subcutaneous administration is available and will be used for the continued study.

2.0 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

- Assess the safety and tolerability of administration of ustekinumab in CVID enteropathy patients by measuring the rates of adverse events.

2.2 SECONDARY OBJECTIVES

- To assess the efficacy of the study agent in alleviating symptoms of CVID enteropathy by comparing measurements of weight and stool frequency at Week 8, Week 16, Week 24, Week 32, Week 40, and Week 48 with Day 0 baseline values.
- To assess changes in gut absorption and protein loss (D-xylose absorption, 48 hour stool fat collection, fecal alpha-1 antitrypsin (A1AT) clearance) at Week 24 and Week 48 by comparison to baseline studies.
- To assess changes in mucosal histology score (modified D'haens scoring) at Week 48 by comparison to baseline score.
- To measure changes in stimulated cytokine production and mRNA expression microarray by LPMCs at Week 48 by comparison to baseline studies.
- To measure changes in gut microbiota and global gene expression of inducible interferon and metabolic genes in LPMCs at Week 48 by comparison to baseline studies.
- To measure changes in laboratory surrogate efficacy markers of inflammatory bowel disease treatments (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], albumin, hemoglobin, platelets) at Week 8, Week 16, Week 24, Week 32, Week 40 and Week 48.

3.0 STUDY DESIGN AND METHODS

This is an open-label study in CVID or selective IgG subclass deficiency (functional agammaglobulinemia) patients with active gastrointestinal symptoms (CVID enteropathy). Up to 10 eligible adult subjects will be enrolled at the NIH Clinical Center. This study consists of a Pre-

Treatment Visit (Day -120 to -1), a Treatment Visit (Day 0), a Week 8 Treatment Visit, a Week 16 Treatment Visit, Week 24 Treatment Visit, Week 32 Treatment Visit, Week 40 Treatment Visit and a Week 48 Endpoint Visit. A treatment dose of 270 mg (3 doses of 90 mg either single-use prefilled syringe or single-use vial, depending on availability) will be injected subcutaneously in subjects by qualified nursing staff on the Day 0 study visit. Subjects will then receive a follow up Treatment dose of 90 mg (1 dose of 90 mg) at Week 8, Week 16, Week 24, Week 32, and Week 40. Patients will be evaluated at Week 8, Week 16, Week 24, Week 32, Week 40, and Week 48 for research visits and will be clinically followed for a total of 48 weeks.

Subjects who have already received a single 270 mg dose may be eligible for retreatment as follows: A treatment dose of 270 mg (3 doses of 90 mg either single-use prefilled syringe or single-use vial, depending on availability) will be injected subcutaneously in subjects by qualified nursing staff on the Day 0 study visit. Subjects will then receive a follow up treatment dose of 90 mg (1 doses of 90 mg) at Week 8, Week 16, Week 24, Week 32, and Week 40. These subjects will be classified as Cohort 1 and when re-enrolled will be assigned a new subject number to prevent any confusion of the new data with the data previously collected from the single-dose study.

Newly enrolled subjects will be assigned into Cohort 2 and will receive ustekinumab doses as follows: A treatment dose of 270 mg (3 doses of 90 mg either single-use prefilled syringe or single-use vial, depending on availability) will be injected subcutaneously in subjects by qualified nursing staff on the Day 0 study visit. Subjects will then receive a follow up treatment dose of 90 mg (1 dose of 90 mg) at Week 8, Week 16, Week 24, Week 32, and Week 40.

3.1   STUDY ENDPOINTS

3.1.1   Primary Endpoint

The primary endpoint of the study is whether treatment with ustekinumab is safe and tolerated in CVID enteropathy patients and does not cause a significant increase in infection or result in any serious adverse events (SAEs) that are determined to be definitely, probably or possibly related to administration of the study agent.

3.1.2   Secondary Endpoint

The secondary endpoint of the study is whether patients respond to the treatment with ustekinumab. Response will be defined as <1% decrease in weight or a decrease in the number of stools at the Week 8, Week 16, Week 24, Week 32 and Week 40 visit compared to Day 0 baseline values. We will also evaluate the change in immunologic laboratory parameters such as decreases in inflammatory cytokines and biomarkers that appear to play a role in disease pathogenesis at the Week 48 visit.

4.0   INCLUSION AND EXCLUSION CRITERIA

4.1   DIAGNOSIS AND CRITERIA FOR INCLUSION:

A subject is eligible for the study if all of the following criteria are met:

- Has given written informed consent.
- Is male or female aged 18 through 75 years.
- Has CVID or selective IgG subclass deficiency of either one or concomitant IgG subclasses comprising IgG1, IgG2, IgG3 or IgG4 (functional hypogammaglobulinemia) diagnosed prior to screening as based on the International Union of Immunological Societies (IUIS) criteria. (Chapel et al., 2003; Martinot et al 2014; Quinti et al 2011; Geha 1988; Umetsu et al 1985; Sugita et al. 1993)
- Has a documented, unintended loss of >5% of their body weight over the last year or requires nutritional supplements to maintain his/her body weight and/or has chronic diarrhea defined as a complaint of at >/= 50% of stools are non-formed for at least 4 consecutive weeks per patient history. Alternately, must be dependent on a therapeutic dose of antidiarrheals (e.g., loperamide or diphenoxylate with atropine) for control of chronic diarrhea.
- If taking oral antibiotics chronically, must have used a stable dose of the antibiotic continuously for at least 2 weeks prior to start of screening period.
- Is willing to have samples stored.
- Be willing to consistently take appropriate measures to avoid pregnancy through the Week 48 study point. All subjects will be informed of the potential risks of ustekinumab during pregnancy and counseled on pregnancy avoidance appropriate to the subject's circumstances (e.g. fertility status, medical contraindications to hormonal birth control, and/or personal or religious beliefs regarding pregnancy avoidance). Subject to the judgment and discretion of the PI, some subjects may not need to take pregnancy avoidance measures (see Appendix F). Appendix F, patient handout on pregnancy avoidance will be provided to patients at the time of consent and discussion regarding pregnancy avoidance during the study.
- Subjects who have previously been treated with a single 270 mg dose of ustekinumab on this study must be > 6 months from their treatment dose and have had recurrence of enteropathy symptoms.

4.2   CRITERIA FOR EXCLUSION:

A subject is excluded from the study if any of the following criteria are met:

General Criteria

- Has any clinically significant disease or condition (e.g., renal, hepatic, neurological, cardiovascular, pulmonary, endocrinologic, psychiatric, hematologic, urologic, autoimmune or other acute or chronic illness) that in the opinion of the investigator would make the subject an unsuitable candidate for this trial, or put the subject at undue risk by participating in this study.
- Is a woman who has a positive pregnancy test or who is breast-feeding.

- Is a woman who does not agree to abide by the contraceptive measures required to prevent pregnancy during participation in the study, or meets exemption criteria for contraceptive measures, as outlined in Appendix F.
- Has any of the following clinical chemistry values:
  - AST >2.5 x upper limit of normal (ULN).
  - ALT >2.5 x ULN.
  - Serum bilirubin >1.5 x ULN.
  - Serum creatinine >1.5 x ULN.
  - Alkaline phosphatase >2.5 x ULN.
- Has a hemoglobin level <9 g/dL or hematocrit <30%.
- Has an International Normalized Ratio (INR) >1.3 or a Partial Thromboplastin Time (PTT) >3 sec of ULN.
- Has the following cell counts (cells/µL):
  - Platelet count <75,000 or >800,000.
  - White blood cell count <2,000.
  - Neutrophil count <1,000.
- Has a current infection requiring intravenous antibiotics, a serious local infection (e.g., cellulitis, abscess) or systemic infection (e.g., pneumonia, septicemia).
- Has a history of cancer within the past 5 years, with the exception of excised basal cell carcinoma, squamous cell carcinoma of the skin, or cervical carcinoma in situ.
- Had a dependency for any illicit drug, chemical, or alcohol within the past 5 years.
- Has a history of active tuberculosis (TB) (or a chest x-ray (CXR) with findings suggestive of old TB infection including calcified nodular lesions, apical fibrosis, or pleural scarring), acute or chronic hepatitis B, hepatitis C, human immunodeficiency virus (HIV) or opportunistic infections.

Gastrointestinal Criteria

- Has a stool sample determined positive for acute gastrointestinal infection with impact of occurrence on gastrointestinal inflammation as determined by principal investigator during screening. In addition, stool samples positive for GI pathogens will be discussed with an infectious disease physician to determine impact of occurrence on gastrointestinal inflammation. If organism thought to be pathogenic, the subject will be treated with appropriate therapy. This will be documented in the subject's medical record.

Prior Medication Criteria

- Received daily corticosteroids within 1 month prior to receiving study agent. The use of short-term or single-dose corticosteroids as a pretreatment regimen for IVIG is acceptable.
- Received any investigational drug within 3 months prior to receiving study agent.
- Received certolizumab or natalizumab within 3 months prior to receiving study agent.
- Received vedolizumab, infliximab, etanercept, or adalimumab within 2 months prior to receiving study agent.
- Received cyclosporine, tacrolimus, sirolimus, pimecrolimus, mycophenolate mofetil or any other systemic immunosuppressants within 1 month prior to receiving study agent.

4.3   SCREENING AND STUDY PROCEDURES

Subjects will be screened and may undergo baseline study procedures under NIH IRB approved protocol 89-I-0158 "Immune Regulation in Patients with Common Variable Immunodeficiency."

As patients with CVID are already pre-disposed to certain types of infections, all patients will be assessed for signs/symptoms of infection at each visit primarily by history (history of cough, fever, sinus congestion, etc.), physical (temperature, lung auscultation, etc.), and safety labs (CBC, chemistries, liver function tests). Further testing will be determined by the investigators of the study on an as needed basis (blood cultures, chest x-ray, etc.). Standard of care treatment and follow-up to resolution of infection will be provided to the patient, and/or coordinated through patient's home physician if required (in cases requiring close local management of therapy, such as intravenous antimicrobial therapy).

5.0   IMPLEMENTATION

5.1   STUDY POINT 1: PRE-TREATMENT VISIT - DAY -120 TO -1
The following screening studies/procedures may be done within 4 months prior to the administration of the study agent, either on this protocol or on the 89-I-0158 screening protocol.

- Review and sign the informed consent form for this protocol.

- History and physical, including review of medications, weight measurement, assessment of number and consistency of stools per day, detailed infection history over the past year, and assessment for any signs/symptoms of current infection.
- Blood Tests:
    - Complete blood count (CBC) with differential
    - PT (Prothrombin Time), PTT (Partial Thromboplastin Time), and INR (International Normalized Ratio)
    - Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP)
    - Chemistry (acute care panel, mineral panel, hepatic panel, creatine kinase, lactate dehydrogenase, total protein, uric acid)
    - Quantitative Immunoglobulins
    - IgG Subclasses
    - Anti-enterocyte Antibodies
    - HLA testing (to assess DQ2 and DQ8 frequency)
    - Ion Torrent (to assess for CVID-associated genomic polymorphisms, in particular *TNFRSF13B* and Inducible T-cell Co-stimulator (ICOS))
    - Assessment of mRNA production in suspected inflammatory pathways by microarray technology (research testing on GI biopsies)
    - Global gene expression microarray (research testing on GI biopsies)
    - Human immunodeficiency (HIV) antibody and viral load test
    - Hepatitis panel including Hepatitis B surface antigen (HBsAg), hepatitis B e-antigen (HBeAg), and Hepatitis C (RNA Quantitative)
    - Quantiferon Gold tuberculosis testing
- Urine and stool tests:
    - Urinalysis

- o Pregnancy test (for females of childbearing potential)
  - o Stool sample for GI pathogens (FilmArray GI Panel testing for 22 viral, bacterial and parasitic GI pathogens that cause infectious diarrhea)
  - o Stool collections for measurement of fat malabsorption (48 hour fecal fat) and protein loss (24 hour A1AT clearance)
  - o Stool sample for fecal calprotectin level
  - o Stool sample for microbiota research studies
- Clinical chest CT scan to assess for any clinically significant infection
- D-xylose absorption study
- An esophagogastroduodenoscopy (EGD) and/or colonoscopy to be done as an inpatient. Colonoscopy pending if evidence of malabsorption and occurrence of bright red blood per rectum, the latter associated with inflammatory disease in the colon.
  - o Assess extent and severity of inflammation via photography, biopsy for descriptive histopathology (4 to 6 biopsies) and histologic scoring (modified d'Haens score), and for collection of LPMCs (up to 30 biopsies)
  - o Biopsies from the gut may also be used to study gut microbiota
- May also include blood collection for the additional testing of the following (some or all) peripheral blood mononuclear cells (PBMCs) and LPMC collection from endoscopic biopsies:
  - o For CD4+ cells: Stimulated secretion/production of IL-4, IL-5, IL-6, IL-10, IL-13, IL-17, IFN gamma transforming growth factor (TGF) beta (ELISA/intracellular cytokine staining)
  - o For monocytes: CD40L- and Staphylococcus aureus Cowan (SAC)-stimulated secretion/production of IL-12 p70, and LPS-stimulated secretion of IL-10 (ELISA/intracellular cytokine staining)

Patients who do not fulfill the criteria on screening will be discharged back to the care of referring physicians.

5.2   STUDY POINT 2: TREATMENT #1 VISIT - DAY 0

On the day of treatment, the patient will have the following:

- History and physical, including review of medications, weight measurement, assessment of number and consistency of stools per day, assessment for any current infection and documentation of any infections since the last visit.
- Pregnancy test (for females of childbearing potential).
- Vital signs will be taken prior to administration of study agent.
- Administration of study agent by qualified Clinical Center nursing staff: A dose of ustekinumab 270 mg to be given by subcutaneous injection.
- Subject will be observed for 1 hour following administration of study agent, with another set of vital signs taken at the end of the observation period.

5.3   STUDY POINT 3: PHONE CALL - WITHIN 3 DAYS OF TREATMENT #1

Surveillance phone call with the subject to monitor for adverse effects or signs of infection and to review concomitant medications and compliance with pregnancy avoidance measures as applicable to the subject.

5.4   STUDY POINT 4: PHONE CALL - 2 WEEKS AFTER TREATMENT #1 (+/- 3 DAYS)

Surveillance phone call with the subject to monitor for adverse effects or signs of infection and to review concomitant medications and compliance with pregnancy avoidance measures as applicable to the subject.

5.5   STUDY POINT 5: TREATMENT #2 VISIT - WEEK 8 (+/- 4 DAYS)

At the Week 8 Follow-Up Visit, the patient will have the following:

- History and physical, including medication review, weight measurement, assessment of number and consistency of stools per day, assessment for any current infection and documentation of any infections since the last visit.
- Blood tests:
    o CBC with differential
    o Chemistry
    o ESR and CRP
    o PT/PTT/INR
    o Quantitative Immunoglobulins
- Urine and stool tests:
    o Urinalysis
    o Pregnancy test (for females of childbearing potential)
    o Stool sample for GI pathogens
    o Stool sample for fecal calprotectin level
    o Stool sample for microbiota research studies
- Vital signs will be taken prior to administration of study agent.
- Administration of study agent by qualified Clinical Center nursing staff: A dose of ustekinumab 90 mg to be given by subcutaneous injection.
- Subject will be observed for 1 hour following administration of study agent, with another set of vital signs taken at the end of the observation period.

5.6   STUDY POINT 6: PHONE CALL - WITHIN 3 DAYS OF TREATMENT #2

Surveillance phone call with the subject to monitor for adverse effects or signs of infection and to review concomitant medications and compliance with pregnancy avoidance measures as applicable to the subject.

5.7   STUDY POINT 7: PHONE CALL - 2 WEEKS AFTER TREATMENT #2 (+/- 3 DAYS)

Surveillance phone call with the subject to monitor for adverse effects or signs of infection and to review concomitant medications and compliance with pregnancy avoidance measures as applicable to the subject.

5.8   STUDY POINT 8: TREATMENT #3 VISIT - WEEK 16 (+/- 4 DAYS)

At the Week 16 Follow-Up Visit, the patient will have the following:

- History and physical, including medication review, weight measurement, assessment of number and consistency of stools per day, assessment for any current infection and documentation of any infections since the last visit.
- Blood tests:
    o CBC with differential
    o Chemistry
    o ESR and CRP
    o PT/PTT/INR
    o Quantitative Immunoglobulins
- Urine and stool tests:
    o Urinalysis
    o Pregnancy test (for females of childbearing potential)
    o Stool sample for GI pathogens
    o Stool sample for fecal calprotectin level
    o Stool sample for microbiota research studies
- Vital signs will be taken prior to administration of study agent.
- Administration of study agent by qualified Clinical Center nursing staff: A dose of ustekinumab 90 mg to be given by subcutaneous injection.
- Subject will be observed for 1 hour following administration of study agent, with another set of vital signs taken at the end of the observation period.

5.9   STUDY POINT 9: PHONE CALL - WITHIN 3 DAYS OF TREATMENT #3

Surveillance phone call with the subject to monitor for adverse effects or signs of infection and to review concomitant medications and compliance with pregnancy avoidance measures as applicable to the subject.

5.10   STUDY POINT 10: PHONE CALL - 2 WEEKS AFTER TREATMENT #3 (+/- 3 DAYS)

Surveillance phone call with the subject to monitor for adverse effects or signs of infection and to review concomitant medications and compliance with pregnancy avoidance measures as applicable to the subject.

5.11   STUDY POINT 11: TREATMENT #4 VISIT - WEEK 24 (+/- 4 DAYS)

At the Week 24 Treatment Visit, the patient will have the following:

- History and physical, including medication review, weight measurement, assessment of number and consistency of stools per day, assessment for any current infection and documentation of any infections since the last visit.
- Blood tests:
    o CBC with differential
    o Chemistry
    o ESR and CRP
    o PT/PTT/INR
    o Quantitative Immunoglobulins
- Urine and stool tests:

- o Urinalysis
- o Pregnancy test (for females of childbearing potential)
- o Stool sample for GI pathogens
- o Stool sample for fecal calprotectin level
- o Stool sample for microbiota research studies
- o Stool collections for measurement of fat malabsorption (48 hour fecal fat) and protein loss (24 hour A1AT clearance)
- D-xylose absorption study
- Vital signs will be taken prior to administration of study agent.
- Administration of study agent by qualified Clinical Center nursing staff: A dose of ustekinumab 90 mg to be given by subcutaneous injection.
- Subject will be observed for 1 hour following administration of study agent, with another set of vital signs taken at the end of the observation period.

5.12   STUDY POINT 12: PHONE CALL - WITHIN 3 DAYS OF TREATMENT #4

Surveillance phone call with the subject to monitor for adverse effects or signs of infection and to review concomitant medications and compliance with pregnancy avoidance measures as applicable to the subject.

5.13   STUDY POINT 13: PHONE CALL - 2 WEEKS AFTER TREATMENT #4 (+/- 3 DAYS)

Surveillance phone call with the subject to monitor for adverse effects or signs of infection and to review concomitant medications and compliance with pregnancy avoidance measures as applicable to the subject.

5.14   STUDY POINT 14: TREATMENT #5 VISIT - WEEK 32 (+/- 4 DAYS)

At the Week 32 Treatment Visit, the patient will have the following:

- History and physical, including medication review, weight measurement, assessment of number and consistency of stools per day, assessment for any current infection and documentation of any infections since the last visit.
- Blood tests:
    - o CBC with differential
    - o Chemistry
    - o ESR and CRP
    - o PT/PTT/INR
    - o Quantitative Immunoglobulins
- Urine and stool tests:
    - o Urinalysis
    - o Pregnancy test (for females of childbearing potential)
    - o Stool sample for GI pathogens
    - o Stool sample for fecal calprotectin level
    - o Stool sample for microbiota research studies
- Vital signs will be taken prior to administration of study agent.

- Administration of study agent by qualified Clinical Center nursing staff: A dose of ustekinumab 90 mg to be given by subcutaneous injection.
- Subject will be observed for 1 hour following administration of study agent, with another set of vital signs taken at the end of the observation period.

5.15   STUDY POINT 15: PHONE CALL - WITHIN 3 DAYS OF TREATMENT #5

Surveillance phone call with the subject to monitor for adverse effects or signs of infection and to review concomitant medications and compliance with pregnancy avoidance measures as applicable to the subject.

5.16   STUDY POINT 16: PHONE CALL - 2 WEEKS AFTER TREATMENT #5 (+/- 3 DAYS)

Surveillance phone call with the subject to monitor for adverse effects or signs of infection and to review concomitant medications and compliance with pregnancy avoidance measures as applicable to the subject.

5.17   STUDY POINT 17: TREATMENT #6 VISIT - WEEK 40 (+/- 4 DAYS)

At the Week 40 week Treatment Visit, the patient will have the following:

- History and physical, including medication review, weight measurement, assessment of number and consistency of stools per day, assessment for any current infection and documentation of any infections since the last visit.
- Blood tests:
    - CBC with differential
    - Chemistry
    - ESR and CRP
    - PT/PTT/INR
    - Quantitative Immunoglobulins
- Urine and stool tests:
    - Urinalysis
    - Pregnancy test (for females of childbearing potential)
    - Stool sample for GI pathogens
    - Stool sample for fecal calprotectin level
    - Stool sample for microbiota research studies
- Vital signs will be taken prior to administration of study agent.
- Administration of study agent by qualified Clinical Center nursing staff: A dose of ustekinumab 90 mg to be given by subcutaneous injection.
- Subject will be observed for 1 hour following administration of study agent, with another set of vital signs taken at the end of the observation period.

5.18   STUDY POINT 18: PHONE CALL - WITHIN 3 DAYS OF TREATMENT #6

Surveillance phone call with the subject to monitor for adverse effects or signs of infection and to review concomitant medications and compliance with pregnancy avoidance measures as applicable to the subject.

5.19   STUDY POINT 19: PHONE CALL - 2 WEEKS AFTER TREATMENT #6 (+/- 3 DAYS)

Surveillance phone call with the subject to monitor for adverse effects or signs of infection and to review concomitant medications and compliance with pregnancy avoidance measures as applicable to the subject.

5.20   STUDY POINT 20: ENDPOINT VISIT - WEEK 48 (+/- 5 DAYS)

At the Week 48 Endpoint Visit, the patient may be admitted as an inpatient at the NIH Clinical Center for approximately 5-7 days for the following:

- History and physical, including medication review, weight measurement, assessment of number and consistency of stools per day, assessment for any current infection and documentation of any infections since the last visit.
- Blood tests:
  - CBC with differential
  - Chemistry (acute care panel, mineral panel, hepatic panel, creatine kinase, lactate dehydrogenase, total protein, uric acid)
  - ESR and CRP
  - PT/PTT/INR
  - Quantitative immunoglobulins
- Urine and stool tests:
  - Urinalysis
  - Pregnancy test (for females of childbearing potential)
  - Stool collections for measurement of fat malabsorption (48 hour fecal fat) and protein loss (24 hour A1AT clearance).
  - Stool sample for GI pathogens
  - Stool sample for fecal calprotectin level
  - Stool sample for microbiota research studies
- EGD and/or colonoscopy to evaluate the extent and severity of inflammation via photography, biopsy for descriptive histopathology (4 to 6 biopsies) and histologic scoring (modified d'Haens score), and for collection of LPMCs (up to 30 biopsies). Biopsies from the gut may also be used to study gut microbiota. The EGD and/or colonoscopy performed during the pre-treatment phase will be repeated at this visit.
- D-xylose absorption test.
- Blood collection for the additional testing of the following (some or all) PBMCs and LPMCs from endoscopic biopsies:
  - For CD4+ cells: Stimulated secretion/production of IL-4, IL-5, IL-6, IL-10, IL-13, IL-17, IFN gamma TGF beta (ELISA/intracellular cytokine staining)
  - For monocytes: CD40L- and SAC-stimulated secretion/production of IL-12 p70, and LPS-stimulated secretion of IL-10 (ELISA/intracellular cytokine staining)
- Assessment of mRNA production in suspected inflammatory pathways by microarray technology (research testing on GI biopsies)
- Global gene expression microarray (research testing on GI biopsies)

5.21   UNSCHEDULED VISITS

Patients may be asked to return for an unscheduled visit to evaluate any adverse event or unanticipated problem that may be related to participation in the study.

6.0   ANALYSIS OF THE STUDY

6.1   SAMPLE SIZE JUSTIFICATION

The sample size is justified as follows: Previous studies have shown that ustekinumab is well tolerated. It is anticipated that the rate of SAE will be low. The chance of experiencing any serious adverse event is believed to be less than 5%. Table 1 shows the probability of observing at least one SAE for several assumed true event rates. With the planned sample size (10), the probability of observing at least one subject with a SAE is 40% if the rate of SAE is 5%.

Table 1: The probability of at least one subject for various SAE rate with the planned sample size (10)

True SAE rate	1%	5%	10%
Probability of observing at least 1 SAE	10%	40%	65%

Because of the small sample size of this study, the exact confidence interval associated with the estimated SAE rate will be reported by using the binomial distribution, where the width of the confidence interval indicates the degree of uncertainty about the estimated adverse event rate. Table 2 below presents the Clopper-Pearson binomial exact 95% confidence intervals (CIs) for various SAE rates with a sample size of 10. For example the 95% CI for the true SAE rate is (0.0025, 0.45) with a width of 0.45 if 1 of 10 subjects experience SAE during the study period.

Table 2: The binomial exact 95% for various AE rates with the planned sample size (10)

Number of patients with SAE	0	1	2	3	4	5
Observed SAE rate	0%	10%	20%	30%	40%	50%
95% CI for true SAE rate	(0%, 31%)	(0.25%, 45%)	(2.5%, 56%)	(6.7%, 65%)	(12%, 74%)	(18.7%, 81.3%)

6.2   STATISTICAL ANALYSIS PLAN

6.2.1   General Considerations

Statistical tests will be two-sided and carried out at the 0.05 level unless otherwise indicated. Continuous data will be summarized using the number of observations available: mean, standard deviation, minimum, median, and maximum. Categorical data will be summarized using counts

and percentages. Missing data will not be categorized in these summaries. Comparison on the continuous measurements between treatment or follow up time and baseline can be conducted by using the pairwise t-statistic. For categorical data such as frequency, the McNemar statistic can be employed.

6.2.2   Safety Analyses

The primary endpoint is the presence of any SAEs associated with ustekinumab treatment that is definitely, probably or possibly related to study agent. The proportion of subjects experiencing at least 1 associated SAE will be calculated, along with the 95% exact CIs. Statistical analysis for the primary safety endpoint will be performed on safety population, which consists of all subjects who received a dose. For interim safety reviews, this will be limited to data entered into the electronic database up to the cut-off date. To further describe the AE experience, rates will be presented for individual types of SAEs as well as for lower grade AEs.

6.2.3   Efficacy Analyses

As a secondary analysis, the analysis of efficacy endpoints will be performed on the intention-to-treat population, which will consist of all enrolled subjects comprising CVID and selective IgG subclass deficiency patients (regardless of the cumulative dose, and regardless of whether they receive treatment or not). Subjects who withdraw voluntarily or by design will be considered as failures in the efficacy analysis. The proportion of subjects with a clinical response will be reported, along with the 95% exact CIs. Response will be defined as <1% decrease in weight or a decrease in the number of stools at the Week 8, Week 16, Week 24, Week 32 and Week 40 visit compared to Day 0 baseline values. Based on initial three subjects' data, the observed standard error for the weight gain at months 6 is 6.2 pounds. The null hypothesis is that there is no weight gain at months 6 and the alternative hypothesis is that the weight gain at months 6 is at least 6.2 pounds. With 10 subjects, the power of detecting 6.2 pounds or more weight gain at months 6 is 80% (with type I error of 0.05). The same analysis will be performed for other binary secondary efficacy endpoints. The comparison between changes in responders and non-responders in terms of change in immunologic laboratory parameters will be grouped for all enrolled patient populations (e.g., stimulated proinflammatory cytokine levels) from baseline will be performed by using the nonparametric paired Wilcoxon rank-sum test at the Week 48 visit.

Data from the Week 24 visit will be used to make a mid-point determination as to whether a subject should continue with the study or be withdrawn. Subjects with a clinical response and an improvement in malabsorption parameters will continue with all scheduled study points and remaining study agent doses. Subjects with a lack of clinical response and no improvement in malabsorption testing parameters measured at the Week 24 visit will not receive any further study agent past the Week 24 dose, and will be followed for safety for 8 or more weeks from their last dose of ustekinumab.

7.0   HUMAN SUBJECTS PROTECTION

7.1   QUALIFICATIONS OF INVESTIGATORS

This clinical study will be conducted by a multidisciplinary team encompassing expertise in immunology and gastroenterology required for the care of participants on this study. The care teams also are knowledgeable in the conduct of Good Clinical Practice (GCP) principles of clinical research and the regulatory requirements for the protection of human subjects. All investigators collaborating in this study have met the training requirements of the Office of Human Subjects Research. Copies of the curricula vitae to demonstrate the experience and qualification of all of the investigators (Principal Investigator [PI] and Associate Investigators [AI]) will be kept updated and on file.

7.2   CONFLICT OF INTEREST

No reportable conflicts of interest have been identified at the present time for any of the investigators conducting this study. If such conflicts of interest should develop in the future, the PI will take immediate corrective action and the Institutional Review Board (IRB) will be notified.

7.3   CONDUCT OF THE STUDY

This study will be conducted in accordance with all applicable laws and regulations, policies of the National Institute of Allergy and Infectious Diseases (NIAID) IRB as well as the policies of NIAID and NIH. The PI will assure that no deviation from or changes to the protocol will take place without prior documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the study participants. The PI will promptly report to the IRB any changes in research activity and all unanticipated problems involving risk to human subjects or others.

7.4   RECRUITMENT PLANS AND PROCEDURES

Adult subjects with CVID will be enrolled who have moderate to severe intestinal symptoms reflecting malabsorption. Recruitment will largely be from within the NIH population of CVID patients (>300 patients) as well as continued referral from the Office of Patient Recruitment. Print advertising in local newspapers, public access cable public service announcements, and print and internet notices through the NIH recruitment mechanism will be used. In addition, letters to clinicians who provide care for primary immunodeficiency diseases may be sent in order to solicit referrals. Any advertising and recruitment materials will be submitted to the NIAID IRB for approval prior to distribution.

7.5   JUSTIFICATION OF THE EXCLUSION OF WOMEN AND CHILDREN (SPECIAL POPULATIONS)

7.5.1   Exclusion of Children

Because there are insufficient data regarding dosing or adverse events in this specific patient population to judge the potential risk in children, children are excluded from this study.

7.5.2   Exclusion of Pregnancy

Pregnant women are excluded from this study because the effects of the study agent on the developing human fetus are unknown.

7.5.3   Breastfeeding

Because there is an unknown but potential risk for adverse effects in nursing infants secondary to treatment of the mother with the study agent, breastfeeding women are excluded from this study.

8.0   POTENTIAL RISKS AND BENEFITS

8.1   POTENTIAL BENEFITS

Patients with CVID enteropathy, exhibit villous atrophy of the small bowel mucosa and a complex of associated symptoms including chronic diarrhea, malabsorption marked by increased excretion of fat, and protein-losing enteropathy leading to loss of albumin and other proteins into the fecal stream. These symptoms can lead to severe weight loss, hypoalbuminemia predisposing to edema, and the need for nutrient supplementation (Mannon et al 2006). Additionally, many patients develop non-infectious gastrointestinal manifestations that can be disabling or fatal. Currently there is no standard therapy for the associated gastrointestinal disease outside of empiric nutritional intervention for weight loss, anti-diarrheal agents, and non-specific anti-inflammatory agents. The potential benefit of this study will be the generalizable knowledge about this disease and treatment options.

8.2   POTENTIAL HAZARDS AND DISCOMFORTS

8.2.1   Risks of Ustekinumab (Stelara®)

Further detailed information on adverse events can be found in the Stelara® Data Sheet (Appendix B) and the Stelara® Prescribing Information (Appendix C).

Stelara® is classified in Pregnancy Category B based on animal studies. There have been no adequate and well controlled studies in pregnant women, so risks to pregnant mothers and the developing fetus are unknown. Stelara is excreted in breast milk, and the extent to which it may be absorbed through breastmilk is unknown. Due to these risks, women cannot participate in this study if they are pregnant or breastfeeding. Subjects must either meet exclusion criteria for contraception as described in Section 4.1, Inclusion Criteria, or must agree to consistently use agreed upon contraceptive methods to prevent pregnancy during through the Week 48 visit.

Psoriasis Clinical Studies Experience

The safety data described below reflect exposure to Stelara® in 3 adequate and well-controlled studies of 2266 patients, including 1970 exposed for at least 6 months, 1285 exposed for at least 1 year and 373 for at least 18 months.

The following serious adverse reactions were reported:
- Serious Infections
- Malignancies

The most common adverse reactions (>10%) in controlled and uncontrolled portions of the psoriasis clinical studies with Stelara® were nasopharyngitis and upper respiratory tract infection. Most were considered to be mild and did not necessitate drug discontinuation.

The following table provides a summary of Adverse Drug Reactions from psoriasis clinical studies. The adverse drug reactions are ranked by frequency, using the following convention:

- Very common (>1/10)
- Common (frequent) (>1/100, <1/10)
- Uncommon (infrequent) (>1/1,000, <1/100)
- Rare (>1/10,000, <1/1,000)

Table 3: Summary of Adverse Drug Reactions

Infections and infestations	Common: Dental infections, upper respiratory tract infection, nasopharyngitis, Uncommon: Herpes zoster, cellulitis, viral upper respiratory tract infection.
Psychiatric disorders	Uncommon: Depression
Nervous system disorders	Common: Dizziness, headache
Respiratory, thoracic and mediastinal disorders	Common: Orthopharyngeal pain. Uncommon: Nasal congestion
Gastrointestinal disorders	Common: Diarrhoea, nausea
Skin and subcutaneous tissue disorders	Common: Pruritus
Musculoskeletal and connective tissue disorders	Common: Back pain, myalgia, arthralgia

Infections

In controlled studies of psoriasis patients, the rates of infection or serious infection were similar between Stelara®-treated patients and those treated with placebo. In the placebo-controlled period of clinical studies of psoriasis patients, the rate of infection was 1.39 per patient-year of follow-up in Stelara®-treated patients, and 1.21 per patient-year of follow-up in placebo-treated patients. Serious infections occurred in 0.01 per patient-year of follow-up in Stelara®-treated patients (5 serious infections in 407 patient-years of follow-up) and 0.02 per patient-year of follow-up in placebo-treated patients (3 serious infections in 177 patient-years of follow-up).

In the controlled and non-controlled portions of psoriasis clinical studies, the rate of infection was 1.24 per patient-year of follow-up in Stelara®-treated patients. The incidence of serious infections was 0.01 per patient-year of follow-up in Stelara®-treated patients (24 serious infections in 2251 patient-years of follow-up) and included cellulitis, diverticulitis, osteomyelitis, viral infections, gastroenteritis, pneumonia, and urinary tract infections.

Among 3117 patients treated in 4 psoriasis clinical trials of Stelara® (median follow up of 3.2 years) representing 8998 patient-years of exposure (1569 patients treated for at least 3 years, 1482 patients for at least 4 years and 838 patients for at least 5 years), the rates of infection or serious infection were similar to those described above. In clinical studies, patients with latent tuberculosis who were concurrently treated with isoniazid did not develop tuberculosis.

In psoriasis patients, the infection rate did not increase significantly, however as patients with CVID are already pre-disposed to certain types of infections, treatment with ustekinumab could further weaken the immune system, potentially placing the patient at a higher risk of infection.

Malignancies

In the controlled period of the 3 placebo-controlled psoriasis clinical studies, the incidence of malignancies excluding non-melanoma skin cancer was 0.25 per 100 patient-years of follow-up for Stelara®-treated patients (1 patient in 406 patient-years of follow-up) compared with 0.57 per 100 patient-years of follow-up for placebo-treated patients (1 patient in 177 patient-years of follow-up).

The incidence of non-melanoma skin cancer was 0.74 per 100 patient-years of follow-up for Stelara® -treated patients (3 patients in 406 patient-years of follow-up) compared with 1.13 per 100 patient-years of follow-up for placebo-treated patients (2 patients in 176 patient-years of follow-up).

Among 3117 patients treated in 4 psoriasis clinical trials (median follow up of 3.2 years) of Stelara® (1569 patients treated for at least 3 years, 1482 patients for at least 4 years and 838 patients for at least 5 years), malignancies excluding non-melanoma skin cancers were reported in 54 patients in 8980 patient-years of follow-up (incidence of 0.60 per 100 patient-years of follow-up for Stelara®-treated patients). This rate of malignancies reported in Stelara®-treated patients was comparable to the rate expected in the general population (standardized incidence ratio = 0.98 [95% confidence interval: 0.74, 1.29], adjusted for age, gender and race). The most frequently observed malignancies, other than non-melanoma skin cancer, were prostate, melanoma, colorectal and breast. The incidence of non-melanoma skin cancer was 0.52 per 100 patient-years of follow-up for Stelara®-treated patients (47 patients in 8965 patient-years of follow-up).

Hypersensitivity Reactions

In clinical studies of Stelara®, rash and urticaria have each been observed in <2% of patients.

Immunogenicity

Approximately 5% of patients treated with Stelara® developed antibodies to ustekinumab, which were generally low-titre. No apparent correlation of antibody development to injection site reactions was seen. The majority of patients who were positive for antibodies to ustekinumab had neutralizing antibodies. Patients positive for antibodies to Stelara® tended to have lower efficacy, however, antibody positivity does not preclude a clinical response.

Adverse Events

The following adverse events have been reported in patients treated with Stelara®. A causal relationship to Stelara® is uncertain.

In psoriasis clinical trials of Stelara®, serious cardiovascular events, including cardiovascular death, myocardial infarction, and stroke, were reported in 0.3% of patients who received Stelara® compared with 0% of patients treated with placebo, during the placebo-controlled period.

Individuals with chronic inflammatory diseases, such as psoriasis, have higher rates of cardiovascular risk factors and cardiovascular events. Rates of myocardial infarction and stroke reported in Stelara®-treated patients were comparable to rates expected in the general population.

Adverse events of depression were reported in some patients who received Stelara® in psoriasis clinical trials, including rare events of suicidality. Individuals with psoriasis have higher rates of depression, and it is not known if Stelara® may have contributed to these events since Stelara® also resulted in improvements of the Hospital Anxiety and Depression Scale.

Crohn's Disease Clinical Studies Experience

Of note, there was no significant increase in rate of serious infections or any other serious adverse events in the ustekinumab treatment versus placebo groups in either of the 2 published phase II studies in CD (Sandborn et al, 2008, Sandborn et al 2012).

8.2.2 Risks and Discomforts of Phlebotomy

Blood draws may cause pain and bruising and, rarely, infection. Sometimes drawing blood causes people to feel lightheaded or even faint. The amount of blood drawn will be within the limits allowed for adult subjects by the NIH Clinical Center (Medical Administrative Policy 95-9: Guidelines for Limits of Blood Drawn for Research Purposes in the Clinical Center: http://cc-internal.cc.nih.gov/policies/PDF/M95-9.pdf

8.2.3 Risks and Discomforts of EGD and/or Colonoscopy with Biopsies

Diagnostic esophagogastroduodenoscopy (EGD) and colonoscopy are generally safe and well tolerated, even in high-risk subject groups (Cappell, 1996 and Terheggen, 2008). The majority of morbidity and mortality from these diagnostic procedures is related to cardiopulmonary complications of conscious sedation (aspiration or gastric contents, arrhythmia, hypoxemia) (Hart and Classen, 1990) with rates of attributable adverse outcomes and fatality of 0.54% and 0.03%, respectively.

As a general practice, this risk is minimized by monitoring pulse, blood pressure, and oxygen saturation throughout the procedure. The procedure-related complications of EGD include perforation (0.8-4/10,000 procedures), bleeding (2-6/10,000 procedures), and bacteremia (about 4% incidence rate usually associated with therapeutic maneuvers such as dilation, mucosal injection, or electrocautery) that rarely has attributable sequelae (Froehlich et al., 1999). The overall estimates of total morbidity and mortality from diagnostic EGD are 14-20/10,000 procedures and 0-7/10,000 respectively. At the Clinical Center, patients undergoing EGD are informed that the cardiopulmonary complication rate is 6/10,000 procedures, esophageal perforation is 3/10,000, and death 7/10,000.

For colonoscopy the reported mortality rates are 2-6 deaths/10,000 colonoscopies (Froehlich et al., 1999); subjects at the Clinical Center are informed that the complication rates with colonoscopy are 2-4 perforations/1,000 colonoscopies, 10 perforations/1,000 colonoscopic polypectomies, 25 clinically significant bleeding episodes/1,000 colonoscopic polypectomies, 1 death/10,000 colonoscopies, and 2 deaths/1,000 colonoscopic polypectomies. Colonic perforation during lower endoscopy is almost exclusively associated with excess tension due to scope movement,

inadvertent passage of an instrument (e.g., biopsy forceps) through the wall, or over-insufflation of a segment of bowel and is reported to range from 0.03% to 0.65% for diagnostic colonoscopy and 0.073% to 2.14% in therapeutic procedure (Damore et al., 1996). While colonoscopy in the setting of active colitis may carry an increased risk of perforation due to these mechanisms, there are no data available on this risk in populations of subjects with inflammatory bowel disease (Irvine *and* Hunt, 1997). On the other hand, it is generally accepted that endoscopic biopsy-related perforation of the colon is a rare event overall, though it has been recognized to occur anecdotally in particular settings including in an area of atrophic mucosa over thinned bowel musculature (Eckardt et al., 1997) and in the ceca of elderly subjects with bowel walls thinned by distension with air and (likely ischemia-related) mucosal ulceration and inflammation (Foliente et al., 1996).

Similarly, clinically significant bleeding after colonoscopic mucosal biopsy is "exceedingly rare" (Raijman et al., 1992) with no episodes of significant bleeding (requiring post-procedural evaluation or treatment) after cold biopsy in 2 series (Macrae et al., 1983; Shiffman et al., 1994) and an estimate of minor bleeding (asymptomatic, self-limited, spotting on toilet paper or coloring toilet water) of 2.2% (Shiffman et al., 1994). There was no data found relating specifically to the risk of bleeding to the number of biopsies taken per procedure. Only one published report of a single episode of major bleeding following a single cold biopsy of the cecum could be found (Raijman et al., 1992).

However, research endoscopies with multiple biopsies have been shown to be safe and well tolerated. In a recent large scale study of 253 research endoscopies (169 colonoscopies, 64 sigmoidoscopies, and 24 upper endoscopies) performed at the NIH Clinical Center, where a total of 9661 biopsy specimens were taken for research and histopathology purposes, no major complications occurred. There were 5 episodes of pain, 4 episodes of minor bleeding, and 4 episodes of both pain and bleeding in the 253 procedures, all of which were self-limiting. There was no statistical significance between the number of biopsies, type of procedure, location of biopsies and the risk of complications (Yao et al, 2009).

Because of the large number of biopsies planned per endoscopy, the subjects will be informed of the potential for an increased risk of bleeding and perforation. In order to prevent complications and minimize their impact, study investigators will avoid biopsies within ulcerated regions (where relative thinning of the gut wall may be present), avoid over-insufflation during biopsies, and provide post procedure instructions for subjects to recognize early warning signs of significant complications (abdominal pain, fever, persistent hematochezia) while providing mechanisms for early evaluation and treatment at the Clinical Center (being available 24 hours a day by page, having emergency radiology, surgical consultation, and endoscopy available).

8.2.4   Risks and Discomforts of HIV Testing

In addition to the usual risks and discomforts of phlebotomy, there is a psychological risk in the event of a positive HIV test result. A positive HIV test result could potentially result in discrimination, stigmatization or difficulties with insurability. The attendant responsibilities of reporting, notification of partners, and limits of confidentiality will be fully discussed.

8.2.5   Risks and Discomforts of Tests of Gut Function

These tests require no instrumentation while blood and stool are collected. Substances are taken orally (e.g., D-xylose) and have no significant toxicities outside of a potential for transient nausea.

8.2.6   Risks and Discomforts of Chest CT

Patients will undergo a single chest CT prior to administration of study agent to assess for any clinically significant infection. Patients will be exposed to a small amount of radiation. The amount of radiation the subject will receive from this single chest CT is a total of 0.2 to 1.6 rem (which is well below the guideline of 5 rem per year allowed for research subjects by the NIH Radiation Safety Committee.

8.3   INFORMED CONSENT PROCESS

Informed consent is a process where information is presented to enable persons to voluntarily decide whether or not to participate as a research subject. It is an ongoing conversation between the human research subject and the researchers, which begins before consent is given and continues until the end of the subject's involvement in the research. Discussions about the research will provide essential information about the study and include: purpose, duration, experimental procedures, alternatives, risks and benefits. Subjects will be given the opportunity to ask questions and have them answered.

The subjects will sign the informed consent document prior to undergoing any research procedures. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The researcher will document the signing of the consent form in the subject's medical record. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

8.4   SUBJECT CONFIDENTIALITY

All records will be kept confidential to the extent provided by federal, state, and local law. The study monitors and other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records. Records will be kept locked and all computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the IRB, FDA, NIAID, Office for Human Research Protections (OHRP), or sponsor's designee.

9.0   ASSESSMENT OF SAFETY

9.1   DOCUMENTING, RECORDING, AND REPORTING ADVERSE EVENTS

At each contact with the subject, information regarding adverse events will be elicited by appropriate questioning and examinations and will be:
- Immediately documented in the subject's medical record/source document,
- Recorded in the electronic database, and
- Reported as outlined below (e.g., IND Sponsor, IRB, and FDA).

9.2   DEFINITIONS

Adverse Event (AE)
An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the research.

Adverse Reaction (AR)
An adverse event that is caused by an investigational agent (drug or biologic).

Suspected Adverse Reaction (SAR)
An adverse event for which there is a reasonable possibility that the investigational agent caused the adverse event. 'Reasonable possibility' means that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction which implies a high degree of certainty.

Serious Adverse Event (SAE)
A Serious Adverse Event is an AE that results in one or more of the following outcomes:
• Death
• A life threatening (i.e., an immediate threat to life) event
• An inpatient hospitalization or prolongation of an existing hospitalization
• A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
• A congenital anomaly/birth defect
• A medically important event*

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

Unexpected Adverse Event
An AE is unexpected if it is not listed in the Investigator's Brochure or Package Insert (for marketed products) or is not listed at the specificity or severity that has been observed. It is the responsibility of the IND Sponsor to make this determination.

Serious and Unexpected Suspected Adverse Reaction (SUSAR)
A SUSAR is a Suspected Adverse Reaction that is both Serious and Unexpected.

Unanticipated Problem (UP)
An Unanticipated Problem is any event, incident, experience, or outcome that is:
1.   Unexpected in terms of nature, severity, or frequency in relation to
   a.   The research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents; and
   b.   The characteristics of the subject population being studied; and

2. Possibly, probably, or definitely related to participation in the research; and
3. Places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. (Per the IND Sponsor, an AE with a serious outcome will be considered increased risk.)

Serious Unanticipated Problem (UP): A UP that meets the definition of a Serious Adverse Event or compromises the safety, welfare or rights of subjects or others.

Unanticipated Problem that is not an Adverse Event (UPnonAE)
Unanticipated problem that is not an Adverse Event (UPnonAE): An unanticipated problem that does not fit the definition of an adverse event, but which may, in the opinion of the investigator, involve risk to the subject, affect others in the research study, or significantly impact the integrity of research data. Such events would be considered a non-serious UP. For example, we will report occurrences of breaches of confidentiality, accidental destruction of study records, or unaccounted-for study drug.

Protocol Deviation: Any change, divergence, or departure from the IRB approved study procedures in a research protocol. Protocol deviations are designated as serious or non-serious and further characterized as:
1. Those that occur because a member of the research team deviates from the protocol
2. Those that are identified before they occur, but cannot be prevented
3. Those that are discovered after they occur.

Serious Protocol Deviation: A deviation that meets the definition of a Serious Adverse Event or compromises the safety, welfare or rights of subjects or others.

Non-compliance: The failure to comply with applicable NIH Human Research Protection Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human subjects. Non-compliance is further characterized as:

1. Serious: Non-compliance that:
    a. Increases risks, or causes harm, to participants
    b. Decreases potential benefits to participants
    c. Compromises the integrity of the NIH-HRPP
    d. Invalidates the study data.
2. Continuing: Non-compliance that is recurring
3. Minor: Non-compliance that, is neither serious nor continuing.

9.3 **INVESTIGATOR ASSESSMENT OF ADVERSE EVENTS**

All AEs occurring from the time the informed consent is signed through the day prior to dosing (through day -1) will EITHER be recorded and reported as a baseline condition (if unrelated to study procedures), OR will be reported as required for AEs or SAEs (if possibly, probably or definitely related to study procedures.)

From the time the informed consent is signed through the 48 week visit, all AEs will be documented, recorded, and reported as required for AEs and SAEs.

After the 48 week visit, SAEs (including AEs requiring hospitalization) will be reported in an expedited manner (i.e., as required for SAEs) if possibly, probably, or definitely related to the study drug, and will otherwise be reported to Sponsor and IRB annually. Therefore, after week 48 post-dosing, in-patient admission to the NIH or other hospital for infection or other inflammatory process that is possibly, probably or definitely related to the disease process under study AND that is unlikely or definitely NOT related to study drug, will not be reported in expedited manner.

Inpatient hospitalization as required and outlined in the protocol, i.e., for the purpose of protocol participation alone, will not be considered an AE or SAE. Emergency room and day or night survey visits are not considered serious until one of the above criteria is met. Any elective hospitalization for a baseline condition (i.e. a condition that is documented as to its precise nature and severity) that has been documented to exist at the time of baseline evaluation, AND that has not worsened, does not constitute a serious adverse event.

Recurrence of an infection that was documented as having been present within 30 days of baseline, will not be recorded as an AE unless it:
- is a new diagnosis based on greater specificity, and/or
- has worsened as to severity, nature, or frequency

Infections typically seen in CVID patients may include infections such as: 1) sinopulmonary infections secondary to streptococcus pneumonia, hemophilus influenzae, or mycoplasma; 2) gastrointestinal infections secondary to giardia, campylobacter, or salmonella. Many CVID patients also have abnormal lab values at baseline, so any abnormal lab values reported while on this study will only be assessed as an AE if it is a new diagnosis and/or worsening, requiring clinical treatment.

If a diagnosis is clinically evident (or subsequently determined), the diagnosis rather than the individual signs and symptoms or lab abnormalities will be recorded as the AE.

A laboratory abnormality should be reported as an adverse event if it requires an intervention. Interventions include, but are not limited to, discontinuation of treatment, dose reduction/delay, additional assessments, or concomitant treatment. In addition, any medically important laboratory abnormality may be reported as an adverse event at the discretion of the investigator. This could include a laboratory result for which there is no intervention but the abnormal value suggests a disease or organ toxicity.

The Investigator will evaluate all AEs with respect to **Seriousness** (criteria listed above), **Severity** (intensity or grade), and **Causality** (relationship to study agent and relationship to research) according to the following guidelines.

9.3.1   Severity

The most current version of the Common Terminology Criteria for Adverse Events (CTCAE) will be used for grading adverse events from any of the research procedures:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm will be used
Severity grading for clinical events not found in the Toxicity Table will be graded according to the following grading scale:
- Grade 1 (Mild): Events causing no or minimal interference with usual social and functional activities.
- Grade 2 (Moderate): Events causing greater than minimal interference with usual social and functional activities.
- Grade 3 (Severe): Events causing inability to perform usual social and functional activities.
- Grade 4 (Potentially Life-Threatening)*: Events causing inability to perform basic self-care functions OR medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death.
- Grade 5 (Death)

* Note: A severity assessment of "potentially life-threatening" is not necessarily the same as life-threatening when used as an "SAE" criterion. The latter means that the event is an immediate threat to life as opposed to a potential threat to life.

9.3.2   Causality

Causality (likelihood that the event is related to the study agent) will be assessed considering the factors listed under the following categories:

Definitely Related
- Reasonable temporal relationship
- Follows a known response pattern
- Clear evidence to suggest a causal relationship
- There is no alternative etiology

Probably Related
- Reasonable temporal relationship
- Follows a suspected response pattern (based on similar agents)
- No evidence of a more likely alternative etiology

Possibly Related
- Reasonable temporal relationship
- Little evidence for a more likely alternative etiology

Unlikely Related
- Does not have a reasonable temporal relationship
                            OR
- Good evidence for a more likely alternative etiology

Not Related
- Does not have a temporal relationship
                            OR
- Definitely due to an alternative etiology

Note: Other factors (e.g., dechallenge, rechallenge) should also be considered for each causality category when appropriate. Causality assessment is based on available information at the time of the assessment of the AE. The investigator may revise the causality assessment as additional information becomes available.

9.4   INVESTIGATOR REPORTING RESPONSIBILITIES TO THE SPONSOR

9.4.1   Adverse Events

Line listings, frequency tables, and other summary AE data will be submitted to the IND Sponsor when needed for periodic safety assessments, review of IND annual reports, review of IND safety reports, and preparation of final study reports.

9.4.2   Serious Adverse Events

All SAEs (regardless of relationship and whether or not they are also UPs) must be reported on the Safety Expedited Report Form (SERF) and sent to the Sponsor Clinical Safety Office (CSO) by fax or e-mail attachment. Deaths and immediately life threatening SAEs must be reported to the CSO within 1 business day after the site becomes aware of the event. All other SAEs must be reported within 3 business days of site awareness.

SPONSOR CLINICAL SAFETY OFFICE CONTACT INFORMATION:

    Clinical Safety Office
    5705 Industry Lane
    Frederick, MD 21704

    Phone 301-846-5301
    Fax 301-846-6224
    E-mail: rchspsafety@mail.nih.gov

9.4.3   Unanticipated Problems

Unanticipated Problems that are also adverse events must be reported to the CSO and sent by fax or e-mail attachment no later than 7 calendar days of site awareness of the event. UPs that are not AEs are not reported to the Sponsor CSO.

Report all UPs that are also adverse events to the CSO on the NIH Problem Report Form.

9.4.4   Pregnancy

Pregnancy itself is not an AE. However, complications of pregnancies are AEs and may be SAEs. Pertinent obstetrical information for all pregnancies will be reported to the CSO via fax or email within 3 business days from site awareness of the pregnancy.

Pregnancy outcome data (e.g., delivery outcome, spontaneous or elective termination of the pregnancy) will be reported to the CSO within 3 business days of the site's awareness on a protocol-specified form.

In the event of a pregnancy, the following steps will be taken:
- Discontinuation of the study agent
- Withdraw from the study but continue in follow up for safety
- Report to IRB, sponsor and SMC
- Advise research subject to notify the obstetrician of study agent exposure

9.5   REPORTING PROCEDURES TO THE NIAID IRB

9.5.1   Expedited Reporting to the NIAID IRB

Serious and non-serious Unanticipated Problems, deaths, serious deviations, and serious or continuing non-compliance will be reported within 7 calendar days of investigator awareness. Serious Adverse Events that are possibly, probably, or definitely related to the research will be reported to the NIAID IRB within 7 calendar days of investigator's awareness, regardless of expectedness.

9.5.2   Waiver of Reporting Anticipated Protocol Deviations, Expected UPnonAEs and Deaths to the NIAID IRB

Anticipated deviations in the conduct of the protocol will not be reported to the IRB unless they occur at a rate greater than anticipated by the study team. Expected adverse events will not be reported to the IRB unless they occur at a rate greater than that known to occur in patients with CVID and/or CVID enteropathy. If the rate of these events exceeds the rate expected by the study team, the events will be classified and reported as though they are unanticipated problems. Deaths related to the natural history of CVID and/or CVID enteropathy will be reported at the time of continuing review.

9.5.3   Annual Reporting to the NIAID IRB

The following items will be reported to the NIAID IRB in summary at the time of Continuing Review:
- Serious and non-serious unanticipated problems

- Expected serious adverse events that are possibly, probably, or definitely related to the research
- Serious adverse events that are not related to the research
- All adverse events, except expected AEs and deaths granted a waiver of reporting.
- Serious and Non-Serious Protocol deviations
- Serious, continuing, and minor non-compliance
- Any trends or events which in the opinion of the investigator should be reported

9.6   FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

AEs that occur following enrollment of the subject are followed until the final outcome is known or until the end of the study follow-up period of six months.

SAEs that have not resolved by the end of the follow-up period are followed until final outcome is known. If it is not possible to obtain a final outcome for an SAE (e.g., the subject is lost to follow-up), the reason a final outcome could not be obtained will be recorded by the investigator in CRIMSON and on the SERF.

SAEs that occur after the study follow-up period of six months that are reported to and are assessed by the Investigator to be possibly, probably, or definitely related must be reported to the CSO, as described above.

9.7   SPONSOR'S REPORTING RESPONSIBILITIES

Serious and unexpected suspected adverse reactions (SUSARs) as defined in 21 Code of Federal Regulations (CFR) 312.32 and determined by the IND Sponsor will be reported to FDA and all participating Investigators as IND Safety Reports.

The IND Sponsor will also submit an IND Annual Report of the progress of the investigation to the FDA as defined in 21 CFR 312.33.

9.8   HALTING CRITERIA FOR THE PROTOCOL

Halting the study requires immediate discontinuation of study agent administered for all subjects and suspension of enrollment until a decision is made whether or not to continue study agent administration.

The halting criteria (as determined by the PI) for an individual site include:
- Two or more subjects experience the same or similar SAEs that are unexpected and are possibly, probably, or definitely related to the study agent
<div align="center">OR</div>

- Any safety issue that the site investigators determine should halt the study

The halting criteria (as determined by the study PI and IND Sponsor secondary to aggregate data review) for this study include:

- Two or more of the same or similar AE in different subjects that are grade 3 or above and are unexpected and possibly, probably, or definitely related to the study agent

OR

- Any safety issue that the study PI or IND Sponsor determines should halt the study

The IRB, the IND Sponsor, or the FDA may halt the study at any time following review of any safety concerns. In addition, the SMC may recommend a study halt.

9.8.1   Reporting of Study Halting

If a halting requirement is met, a description of the event(s) or safety issue must be reported by the PI within one business day to the Sponsor CSO by fax or email. The PI must inform the IRB and SMC that a halting rule has been met.

9.8.2   Resumption of a Halted Study

The IND Sponsor, in collaboration with the PI and SMC will determine if it is safe to resume the study. The IND Sponsor will notify the Site Investigators of this decision. The conditions for resumption of the study will be defined in this notification. The PI will notify their local IRB of the decision to resume the study.

9.9   PAUSING CRITERIA FOR A SUBJECT OR GROUP

The decision to suspend administration of the study agent(s) for a single subject or for all subjects in a specific group requires discontinuation of study agent administrated for the study subject(s) or group until a decision is made whether or not to continue study agent administration.

The pausing criteria for a single subject or for the subjects in a specific group in this study include:
- A subject experiences an SAE or Grade 3 or greater AE that is unexpected (as determined by the IND Sponsor) and is possibly, probably, or definitely related to the study agent;

OR

- Any safety issue that the PI determines should pause administration of the study agent to a single subject or to all subjects in a specific group.

OR

- If any subject develops any concomitant illness that requires administration of immunosuppressive agents that will impact this study.

The IND Sponsor, in collaboration with the PI, may also pause for an individual subject or entire group if a safety concern is identified during routine aggregate data analysis.

9.9.1   Reporting of Pausing for a Subject or Group

If a pausing requirement is met, a description of the adverse event(s) or safety issue must be reported by the Site Investigator by fax or email within one business day to the Sponsor CSO, PI, the IRB and the SMC. The PI must inform the IRB that a pausing rule has been met.

9.9.2   Resumption of a Paused Study

The IND Sponsor in collaboration with the PI and SMC will determine if it is safe to resume administration of the study agent to the subject/group. The IND Sponsor will notify the Site Investigators of this decision. The Site Investigators will notify their local IRB of the decision to resume administration of the study agent prior to resumption.

If a subject has been paused for less than or equal to 5 half lives ($t_{1/2} \sim 21$ days, thus 5 half lives are 105 days) of ustekinumab and it is deemed safe to resume administration of study drug, the subject will not require re-induction (270 mg induction dose) and will complete remaining study visits, testing and treatments.

If a subject has been paused for greater than 5 half lives ($t_{1/2} \sim 21$ days, thus 5 half lives are 105 days) of ustekinumab and it is deemed to be safe to resume administration of study drug, the subject will require re-induction (270 mg induction dose) and will repeat all study visits, testing and treatments from Day 0 through Week 48. Pre-treatment eligibility studies (including malabsorption studies and endoscopy with biopsies) do not need to be repeated. The subject will not need to be re-consented, unless there has been an amendment to the study.

9.10   WITHDRAWAL CRITERIA FOR AN INDIVIDUAL SUBJECT

An individual subject will be withdrawn for any of the following:

- An individual subject's decision. Subjects will be allowed to withdraw at any time, even after receiving the study agents, although withdrawal at these stages would be highly discouraged. Withdrawn subjects who received the study agent will be asked to return approximately 8 weeks following the last dose of study agent for a history and physical and safety labs and any clinically indicated testing such as CBC, chemistry, esr, crp, pregnancy test, blood culture, and/or chest CT. Investigator should attempt to determine the reason for the subject's decision to withdraw.
- Any clinical AE, laboratory abnormality or other medical condition or situation such that continued participation in the study would not be in the best interest of the subject. Subjects will be followed for the duration of the study for indicated safety assessments.
- Non-compliance with study procedures to the extent that it is potentially harmful to the subject or to the integrity of the study data.
- A change in the subject's baseline condition after enrollment so that the subject no longer meets any of the following inclusion/exclusion criteria. In particular, if any subject develops any concomitant illness that requires administration of immunosuppressive agents study agent will be suspended.
- If an individual subject has shown no clinical response with no improvement in malabsorption testing parameters at Week 24, no further study agent will be administered after the Week 24 study agent dose.
- The investigator deems a subject to be no longer fit to participate in the study.

9.11   REPLACEMENT FOR WITHDRAWN SUBJECTS

Any subject who is removed or drops out of the study before the Week 24 study point may be replaced.

9.12   SAFETY OVERSIGHT

9.12.1   Safety Review and Communications Plan (SRCP)

A Safety Review and Communication Plan (SRCP) has been developed for the protocol. The SRCP is an internal communications document between the Principal Investigator and the IND Sponsor Clinical Safety Office (CSO), which delineates the safety oversight responsibilities of the PI, the CSO, and other stakeholders. The SRCP also includes the overall plan for conducting periodic safety surveillance assessments.

9.12.2   Sponsor Medical Monitor (SMM)

A Medical Monitor, representing the IND Sponsor (OCRPRO), has been appointed for oversight of safety in this clinical study. The Sponsor Medical Monitor will be responsible for performing safety assessments as outlined in a Safety Review and Communications Plan (SRCP).

9.12.3   Safety Monitoring Committee (SMC)

An independent SMC, including 3 experts in the fields of inflammatory bowel disease and biologics, will meet to assess subject safety and study integrity. The SMC will review the study prior to initiation and will meet twice yearly thereafter, or more frequently as needed. The independent experts do not have direct involvement in the conduct of the study and do not have other interests with any of the collaborating or competing pharmaceutical firms involved in the study.

Prior to each SMC review, the PI will submit individual and cumulative subject data on safety, enrollment and drop-out data as well as all study results that are available. The SMC will review all SAEs and will also review safety data as needed in response to AEs considered medically significant by the PI. After each SMC review, a recommendation as to whether the study is to continue, be modified, or be terminated will be provided in a summary report. All serious adverse events, all unanticipated problems and all IND Safety Reports will be reported by the PI to the SMC at the same time they are submitted to the IRB or IND Sponsor. The SMC will be notified immediately if pausing or halting rules are met and the SMC will provide a recommendation for continuation, modification, or termination of the study. The PI will submit the written SMC summary reports with recommendations to their IRB. All privacy and confidentiality of all participants will be maintained as per NIH guidelines and policy.

10.0   DATA MANAGEMENT AND PROTOCOL MONITORING PLAN

As per International Conference on Harmonization (ICH) GCP 5.18 and FDA 21 CFR 312.50, clinical protocols are required to be adequately monitored by the study sponsor. This study monitoring will be conducted according to the "NIAID Intramural Clinical Monitoring Guidelines." Monitors under contract to the NIAID Office of Clinical Research Policy and Regulatory Operations (OCRPRO) will visit the clinical research site to monitor aspects of the study in accordance with the appropriate regulations and the approved protocol. The objectives of a monitoring visit will be:

- To verify the existence of signed informed consent documents and documentation of the informed consent process for each monitored subject;
- To verify the prompt and accurate recording of all monitored data points and prompt reporting of all SAEs;
- To compare CRIMSON data abstracts with individual subjects' records and source documents (subjects' charts, laboratory analyses and test results, physicians' progress notes, nurses' notes, and any other relevant original subject information); and
- To help ensure investigators are in compliance with the protocol. The monitors also will inspect the clinical site regulatory files to ensure that regulatory requirements OHRP, FDA, and applicable guidelines (ICH-GCP) are being followed. During the monitoring visits, the investigator (and/or designee) and other study personnel will be available to discuss the study progress and monitoring visit.

The investigator (and/or designee) will make study documents (e.g., consent forms and CRIMSON data abstracts) and pertinent hospital or clinical records readily available for inspection by the local IRB, the FDA, the site monitors, and the NIAID staff for confirmation of the study data.

A specific protocol monitoring plan will be discussed with the PI and study staff prior to enrollment. The plan will outline the frequency of monitoring visits based on such factors as study enrollment, data collection status, and regulatory obligations.

10.1   DATA HANDLING AND RECORD KEEPING

10.1.1 Data Management Responsibilities

The Investigator is responsible for assuring that the data collected are complete, accurate, and recorded in a timely manner. Source documentation (the point of initial recording of information) should support the data collected in the electronic data system and must be signed and dated by the person recording and/or reviewing the data. All data should be reviewed by the Investigator and signed as required with electronic signature.

The data collected under prior version of protocol for Cohort 1 subjects (n=3) will be analyzed separately from data collected under revised protocol (n=10). This later analysis will include prior treated subjects if they meet eligibility criteria.

10.1.2 Data Capture Methods

Study data will be collected at the study site and maintained in CRIMSON. This system will be completed on an ongoing basis during the study. Data entry into CRIMSON will be performed by authorized individuals. Corrections will be tracked electronically (password protected or through an audit trail) with time, date, individual making the correction, and what was changed.

10.1.3 Types of Data

Source documents include, but are not limited to, the subject's medical records, laboratory reports, ECG tracings, subject's diaries, biopsy reports, progress notes, pharmacy records, and any other similar reports or records of procedures performed during the subject's participation in the study.

10.1.4 Source Documents and Access to Source Data/Documents

Source documents include all recordings of observations or notations of clinical activities, and all reports and records necessary for the evaluation and reconstruction of the clinical trial. Data from CRIMSON will be collected directly from subjects during study visits and telephone calls, or will be abstracted from the subjects' medical records. The subject's medical record must record his/her participation in the clinical trial and study treatment (with doses and frequency) or other medical interventions or treatments administered, as well as any AEs experienced during the trial.

10.1.5 Record Retention

The investigator is responsible for retaining all essential documents listed in the ICH-GCP Guideline. All essential documentation for all study subjects will be maintained by the investigators in a secure storage facility for a minimum of 3 years per NIAID policies. The FDA requires study records to be retained for up to 2 years after marketing approval or disapproval (21 CFR 312.62), or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational agent for a specific indication. These records will also be maintained in compliance with IRB, state, and federal medical records retention requirements, whichever is longest. All stored records will be kept confidential to the extent required by federal, state, and local law.

Should the investigator wish to assign the study records to another party and/or move them to another location, the investigator will provide written notification of such intent to OCRPRO/NIAID with the name of the person who will accept responsibility for the transferred records and/or their new location. NIAID will be notified in writing. Destruction or relocation of research records will not proceed without written permission from OCRPRO/NIAID.

10.2 DATA SHARING

Human data generated in this study for future research will be shared as follows:
- Identified data in the Biomedical Translational Research Information System of the NIH (BTRIS).
- De-identified or identified data with approved outside collaborators under appropriate agreements.

Data will be shared through:

- BTRIS.
- Approved outside collaborators under appropriate individual agreements.
- Publication and/or public presentations.

Data will be shared before publication and/or at the time of publication or shortly thereafter.

11.0   SPECIMEN COLLECTION AND STORAGE

Specimens of serum, blood cells, and biopsy tissue may be stored. These specimens will be labeled with a code and not by subject name. A separate file will be maintained that will include the key for coupling the code to a specific subject. Both the specimens and the file will be stored in locked storage units within a locked room for the purpose of maintaining confidentiality. These specimens may be used in collaborative research, but the specimens will not be able to be linked with specific subjects. The future research use of these stored specimens will be conducted in accordance with policy set by the NIH Office of Human Patients Research and only with appropriate IRB approval where applicable. Any transport of blood specimens to the study sponsor will be provided by the sponsor according to regulations specified by International Air Transport Association (IATA) and the Department of Transportation for shipment of biologically hazardous materials. Any unanticipated loss or destruction of samples or data will be reported to the IRB. Upon termination of this protocol all patient samples and data will be destroyed or with IRB approval transferred to another existing protocol or repository.

12.0   REMUNERATION

Subjects will not be paid for their participation in this protocol. Travel expenses may be paid on a case-by-case basis.

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APPENDIX A - PROTOCOL FOR TESTS OF GASTROINTESTINAL FUNCTION

1. _D_-xylose Absorption Test: Twenty-five g _D_-xylose PO will be given after an overnight fast. At one hour a blood sample will be drawn; the lower limit of is 20 mg/dl. Adjustment for the interpretation of results will be made in the presence of moderately impaired renal function (creatinine clearance >30 mL/min) (Craig and Atkinson, 1988).

2. Quantitative Stool Fat: Subjects will be placed on a defined fat diet (e.g. 60-100 g/day) during the 48 hr fecal fat collection, and for the 8 hours prior to start of collection. Stool will be collected into pre-weighed containers prior to homogenization and fat content determination. Excretion of >6% of the estimated daily fat intake will be considered abnormal.

3. Alpha-1 Antitrypsin (A1AT) Fecal Clearance: Subjects will collect stool output for a defined 24 hour period for measurement of stool volume and A1AT concentration. A simultaneous blood sample for serum A1AT will be drawn in order to calculate the A1AT fecal clearance. Values >50 mg/24hr will be considered abnormal.

4. Fecal Calprotectin: Calprotectin is a protein that can be excreted intact in the stool in cases of malabsorption or diseases causing inflammation of the bowel. It is a stool (fecal) test that therefore, is used to detect inflammation or malbsorption in the intestines. The calprotectin test however, is not diagnostic but can follow indirectly a patients degree of malabsorption and/or intestinal inflammation.

APPENDIX B - STELARA® FORMULARY DOSSIER (DATA SHEET)

APPENDIX C - STELARA® PRESCRIBING INFORMATION

APPENDIX D - STELARA® PATIENT INFORMATION SHEET

APPENDIX E - SCHEDULE OF EVENTS

APPENDIX F - PREGNANCY AVOIDANCE PATIENT HANDOUT

APPENDIX G - COHORT 1 SINGLE DOSE STUDY ADVERSE EVENTS