PARTNERS HUMAN RESEARCH COMMITTEE

DETAILED PROTOCOL

Massachusetts General Hospital

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Study title

USTEKINUMAB FOR THE TREATMENT OF GIANT CELL ARTERITIS

Study Drug

Ustekinumab (Stelara)

Study Drug and Financial Support Provided By

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I. BACKGROUND AND SIGNIFICANCE

a. Clinical background and unmet need

Giant Cell Arteritis (GCA) is the most common form of primary vasculitis among adults in Western countries, with a prevalence ranging from 24 to 280 cases per 100,000 individuals older than 50. The incidence of GCA increases progressively with age and peaks during the eighth decade of life. The disease has a particular predilection for populations of northern European ancestry and is approximately twice as common in women than in men [1]

The main histopathologic feature of GCA comprises a chronic granulomatous inflammatory process that involves the aorta and its main branches, with a tendency to affect the extracranial carotid arteries and the ophthalmic circulation [1]. The clinical manifestations consist of constitutional symptoms (e.g., asthenia, fever), headaches, jaw pain, scalp tenderness, visual symptoms (e.g., blurry vision, amaurosis fugax, diplopia), shoulder and hip girdle pain and stiffness (i.e., polymyalgia rheumatica) and elevated acute-phase reactants. The most important complication of GCA is vision loss, which occurs in 15% of cases. Other possible complications include aortic aneurysm, limb claudication from large-artery stenosis (particularly the subclavian and axillary arteries), stroke, mesenteric ischemia, myocardial infarction and venous thromboembolism [1]

No curative treatment currently exists for GCA. However, glucocorticoids (prednisone) are able to control the clinical evidence of inflammation when administered in moderate to high doses . Unfortunately, 40-85% of the patients experience disease relapses upon glucocorticoid tapering or discontinuation [2-8]. Such patients require frequent re-treatment and most of them develop undesirable side effects form prolonged glucocorticoid exposure [9]. Long-term glucocorticoid therapy is associated with adverse events in approximately 86% of the patients, including osteoporotic fractures, diabetes mellitus, infection, cataracts, hypertension, femoral avascular necrosis, and gastrointestinal bleeding [9, 10]. In most cases, glucocorticoid-related toxicity becomes more problematic to patients than the disease itself.

No medication except glucocorticoids has been shown convincingly to be effective in suppressing the activity of GCA. The use of other immunosuppressive medications, including methotrexate, azathioprine, cyclophosphamide, and tumor necrosis factor (TNF) antagonists has been generally unsuccessful [7, 11-14]. Sudies using the interleukin (IL)-6 receptor inhibitor tocilizumab are ongoing [15]. There is currently a great unmet need for specific disease modifying agents to maintain disease remission in GCA, and therefore reduce the exposure to and the toxicity associated with glucocorticoids.

b. Pre-clinical and clinical studies leading up to and supporting the proposed research

Role of interleukin (IL)-12 and IL-23 in autoimmune diseases

IL-12 and IL-23 play important roles in regulating physiologic T-cell immune responses. IL-12 drives the differentiation of naïve T helper (Th) cells towards the Th1 cell phenotype [16], and IL-23 acts in concert with IL-6, IL-1β and transforming growth factor (TGF)-β to promote the generation and maintenance of Th17 cells [17, 18]. Once differentiated, Th1 and Th17 cells produce the effector cytokine interferon (IFN)-γ and IL-17, respectively

Although the activation of the Th1 and Th17 pathways is crucial for generating immunity against a variety of microorganisms, the deregulation of these mechanisms has been described in several immune-mediated diseases. IL-12 and IL-23 are important mediators in experimental models of psoriasis [19, 20], Crohn's disease [21], multiple sclerosis (MS) [22], rheumatoid arthritis [23], and thyroiditis [24]. In humans, IL-12 and IL-23 have been implicated in the pathogenesis of psoriasis [25], Crohn's disease [26, 27], MS [28], RA, and recently GCA [29-32] (see below).

Ustekinumab ameliorates Th1 and Th17 responses in vitro and in vivo

IL-12 and IL-23 are heterodimeric cytokines that have a common p40 subunit. A functional IL-12 molecule consists of a p40 and a p35 subunit, and a functional IL-23 molecule consists of a p40 and a p19 subunit. On the other hand, IL-12 and IL-23

receptors are also heterodimers that share the same IL-12Rβ1 chain. Whereas IL-12Rβ1 is responsible of binding to p40, the second receptor component, namely IL-12Rβ2 for IL-12 receptor and IL-23R for IL-23 receptor, is cytokine-specific, and mediates signal transduction upon binding to p35 and p19, respectively

Ustekinumab is a fully human IgG1-kappa monoclonal antibody that specifically binds with high affinity to the shared p40 subunit of the cytokines IL-12 and IL-23 (IL-12/23p40) and blocks the cytokine-cytokine receptor coupling, thereby preventing the initiation of the signaling cascade that leads to the generation and activation of Th1 and Th17 cells, and the production of IFN-γ and IL-17 [33, 34] (**Figure 1**. IL-12 and IL-17 pathways and ustekinumab mechanism of action).

By preventing IL-12/23p40 ligation to IL-12Rβ1, ustekinumab neutralizes the following IL-12 (Th1) and IL-23 (Th17) mediated in vitro cellular responses:

- Intracellular phosphorylation of STAT 4, STAT 6 and production of INF-γ (Th1)
- Intracellular phosphorylation of STAT 3 and production of IL-17A, IL-22, and IL-17F (Th17)

Ustekinumab was approved by the FDA in 2009 for the treatment of moderate to severe plaque psoriasis requiring systemic therapy based on 3 randomized controlled trials [35-37]. Besides the observed clinical response, serial skin biopsies in patients with psoriasis treated with ustekinumab showed decreased T-cell infiltrates and reduced gene expression of IL-12p40, IL-23p19, and IFN-γ [38].

Some evidence suggests that IL-12/IL-23p40 targeted treatment may also be beneficial in Crohn's disease [39], psoriatic arthritis [40, 41], and ankylosing spondylitis [42, 43]

Two distinct pathways driven by Th17 and Th1 cells contribute to the pathogenesis of GCA.

The etiology of GCA is not known. However, the mechanisms that perpetuate vascular inflammation in this disease are partially understood. In untreated patients, CD4-positive

T lymphocytes, mainly IFNγ-producing Th1 cells and IL-17-secreting Th17 cells, infiltrates large- and medium- sized arteries [29, 44-48]. Mirroring vascular inflammation, flow cytometry studies have demonstrated that Th1 and Th17 cell frequencies are also expanded in peripheral blood during periods of disease activity [29, 45, 46].

Doses of prednisone used in clinical practice significantly reduce the arterial infiltration of Th17 cells and normalize Th17 cell blood stream expansion [29, 45, 46]. Increased serum level of Th17-related cytokines (e.g., IL-6, IL-23, IL-1β, and IL-17) rapidly decline with glucocorticoid treatment [29, 49]. On the other hand, reports regarding the effects of glucocorticoids on the abnormalities of the Th1 axis are contradicting [29, 31, 32], with some reports describing persistance of the arterial Th1 infiltrates and the IL-12 and IFNγ serum and tissue up-regulation even after 3-9 months of therapy [29]

The pathogenesis of GCA supports the hypothesis that the down-regulation of the Th1 and Th17 pathways by blocking IL-12 and IL-23 signaling could allow patients to stay in remission off glucocorticoid therapy (See **figure 1**)

- **Pre-clinical safety of ustekinumab [50]**

In cynomolgus monkeys, ustekinumab was well-tolerated following IV doses up to 45 mg/kg/week for up to a month, and following twice weekly subcutaneous doses up to 45 mg/kg for 6 months. Except for one case of bacterial enteritis, no ustekinumab-related mortality or adverse events were reported, and there was no tumor, pre-neoplastic or other histological abnormality in necropsy studies**.** Immunotoxicity evaluations showed no alteration on lymphoid organ weight or histology; abnormalities on blood counts or lymphocyte subpopulations; nor adverse effects on immune response to neoantigen (KLH), delayed type hypersensitivity responses, or ex vivo lymphoproliferative responses to T cell mitogens**.** No adverse events were seen in an acute asthma model carried out given theoretical increased risk of exacerbation of Th2-driven pathologies with Th1 blocking agents**.** Ustekinumab did not show developmental toxicity, teratogenicity, or reproductive toxicity**.** The no observed adverse effect level (NOAEL)

for ustekinumab in general, developmental and reproductive toxicity studies was 45 mg/kg. The cumulative dose in the 6-month chronic toxicity study (45 mg/kg twice weekly for 26 weeks) was 2340 mg/kg. Based on the proposed dosing, a GCA participant who has 50 Kg of weight would receive ustekinumab doses of < 2 mg/kg (>22-fold lower than the NOAEL dose). In addition, based on the proposed dosing, upon completing the study a GCA patient who has 50 Kg of weight would receive 12.6 mg/kg (cumulative dose >180-fold lower than the dose given chronic toxicity studies)

- **Prior clinical experience with ustekinumab**

Summary of clinical efficacy [50]

Ustekinumab has shown efficacy with adequate safety profiles in psoriasis, and psoriatic arthritis (PsA)

Ustekinumab was approved by the FDA in 2009 for the treatment of adults with chronic moderate to severe plaque psoriasis. The psoriasis clinical development program consisted of 3 well-controlled Phase 2 and Phase 3 clinical trials that evaluated subcutaneous doses of 45 and 90 mg as monotherapy in a total of 2266 subjects [51-53]. In these studies, ustekinumab led to rapid, clinically significant, and sustained improvement of psoriatic skin lesions.

At week 28, over 90% of the subjects were Psoriasis Area and Severity Index (PASI) 50 responders in both the 45 mg and 90 mg groups, at least 70% of subjects achieved a PASI 75 response, and approximately 50% of subjects achieved a PASI 90 response. Clinical response was maintained with every 12 weeks administrations through 1 year in nearly 90% of long-term responders (PASI 75 response at 28 and 40 weeks).

Summary of clinical safety [50, 54]

Data pertaining to the safety of ustekinumab comes from 2266 exposed subjects during the psoriasis trials (1970 subjects received at least 6 months of ustekinumab, 1285 subjects were exposed for at least 1 year, and 373 underwent at least 18 months of treatment).

The rate of adverse events was similar in the placebo (50.4%), ustekinumab 45 mg (57.6%) and ustekinumab 90 mg (51.6%) groups. The risk of adverse events (AE) and serious adverse events (SAE) did not increase with the duration of exposure. Common AE tended to be mild and self-limited and included nasopharyngitis, upper respiratory infection, and headache. Dizziness, back pain, myalgia, injection-site erythema (1.3% ustekinumab, 0.4% placebo), ecchymosis, diarrhea, and pharyngolaryngeal pain were slightly more frequent in the ustekinumab group.

For all mortality causes, 8.11 deaths were expected through the data cutoff for the BLA, and only 1 death due to idiopathic dilated cardiomyopathy was reported. Three additional deaths were reported during phase 3 extension from causes unlikely related with the study drug (alcohol intoxication, post-operative bleeding, and metastatic renal cancer)

Serious adverse events were reported in 1.4%, 1.6%, and 1.4% of the patients in the placebo, 45 mg, and 90 mg groups, respectively, through week 12. Serious adverse event rate did not increase over time.

Serious infections were reported at a rate of 1.70 (95% CI, 0.35; 4.96) per hundred subject-years of follow up in the placebo group compared with 0.49 (95% CI, 0.01, 2.74) and 1.97 (95% CI, 0.54; 5.03) in subjects in the 45 mg and 90 mg ustekinumab groups, respectively.

Malignancies were reported in 3 placebo-treated subjects (2 of 3 were non melanoma skin cancer), and 4 ustekinumab-treated subjects (3 of 4 were non melanoma skin cancer). Overall rates of malignancies per hundred subject-years of follow up were comparable in both groups.

Through the data cutoff for the BLA, the rates of major adverse cardiovascular events (MACE) per hundred subject-years of follow up were comparable between groups. Rates of MACE were consistent with expected background rates. [55].

The overall incidence of antibodies to ustekinumab was 3.7% in the combined Phase 3 studies and did not differ across doses nor increase over time. There was no evidence of lymphocyte depletion; alteration on the proportion of naïve (CD45RA), memory (CD45RO), or activated T lymphocytes; or ex-vivo PBMC production of IFN-γ or IL-5. Ustekinumab did not impact in non-memory antibody response (pneumococcal vaccine) or antigen recall response (tetanus toxoid).

Safety of ustekinumab was consistent in all subpopulations including subjects >65 years of age.

The 120-day safety update did not show increase in the rates of adverse events, serious adverse events, serious infections, malignancies, and serious cardiovascular events.

Multiple subsequent studies have demonstrated similar safety profiles without unexpected adverse events. Some of these studies have used ustekinumab doses equivalent or higher to the dose proposed in this GCA study [41-43]

Clinical pharmacology

The SC bioavailability of the drug is 57.2% and after a single SC dose, ustekinumab reaches a maximum serum concentration in 7 to 14 days. The median volume of distribution ranged from 57 mL/kg to 83 mL/kg (intravascular space), and through the endogenous gammaglobulin metabolic pathway (reticuloendothelial system) ustekinumab is eliminated from the system with a median half-life of 3 weeks. In population PK analysis, only weight, diabetes and positive immune response status to ustekinumab affected the systemic exposure of the drug. No formal drug-drug interaction studies were conducted with ustekinumab.

c. Rationale behind the proposed research, and potential benefits to patients and society

Given its mechanism of action, ustekinumab will specifically target important pathogenic pathways of GCA, and consequently may help maintain the disease in clinical remission while reducing the requirements of glucocorticoids (steroid-sparing effect).

Remission maintenance and glucocorticoid-sparing effects may prevent or ameliorate the morbidity associated with GCA and the prolonged glucocorticoid exposure that this disease usually requires, improving the quality of life of the patients. In addition, if effective, the use of ustekinumab may reduce the costs of treating glucocorticoid-related side effects (e.g., osteoporotic fractures, diabetes mellitus, infections, cataracts, hypertension, femoral avascular necrosis, steroid induced myopathy, and gastrointestinal bleeding). Finally, ustekinumab may add to the limited therapeutic options currently available for GCA.

II SPECIFIC AIMS

The objective of this study is to evaluate the efficacy and safety of ustekinumab, an IL-12/23 inhibitor, in patients with GCA

Hypothesis

IL-12/23 pathway blockade with ustekinumab maintains disease remission in patients with GCA

Specific Aims

- To evaluate the safety and tolerability of ustekinumab administration in 20 patients with GCA

- To evaluate the efficacy of ustekinumab for remission maintenance and glucocorticoid sparing in 20 patients with GCA

III. SUBJECT SELECTION

a. Inclusion Criteria (Subjects must meet the following criteria to be considered eligible for study entry):

1) Able and willing to provide written informed consent and to comply with the study protocol

2) Diagnosis of GCA classified according to the following criteria:

• Age 50 years or older

• History of ESR ≥ 50 mm/hour or CRP ≥ 10 mg/L

AND at least one of the following:

• Unequivocal cranial symptoms of GCA (new-onset localized headache, scalp tenderness, temporal artery tenderness or decreased pulsation, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain upon mastication)

• Symptoms of polymyalgia rheumatica (PMR), defined as shoulder and / or hip girdle pain associated with inflammatory morning stiffness

AND at least one of the following:

• Temporal artery biopsy revealing features of GCA (e.g., mononuclear cell infiltration or granulomatous inflammation).

• Evidence of large-vessel vasculitis by angiography or cross-sectional imaging study such as MRA, CTA, or PET-CT

3) New-onset or refractory active disease defined as follows:

• New onset: diagnosis of GCA within 6 weeks of Baseline visit

• Refractory: diagnosis of GCA > 6 weeks before Baseline visit and previous treatment with 40 mg/day prednisone (or equivalent) for at least 2 consecutive weeks at any time

AND

• Active GCA within 6 weeks of Baseline visit (active disease defined as the presence of clinical signs and symptoms [cranial or PMR] *and* ESR ≥ 30 mm/hour or CRP ≥ 10 mg/L)* #

*ESR ≥ 30 mm/hour or CRP ≥ 10 mg/L is not required if active GCA has been confirmed by a positive temporal artery biopsy within 6 weeks of the Baseline visit

Prior treatment with tocilizumab normalizes CRP and ESR values therefore these inflammatory markers cannot be used monitor disease activity. For patients who are failing treatment with tocilizumab due to flare, elevation of ESR and/or CRP is not required in the definition of active disease for eligibility purposes.

b. Exclusion Criteria

Patients who meet any of these criteria will not be enrolled in this study

- **Comorbidities**

- Allergies: Subjects who have history of previous severe allergic or anaphylactic reaction associated with the administration of monoclonal antibodies or antibody fragments or excipients to ustekinumab.

- Systemic infection: Subjects who have an active systemic infection.

- Serious infection: Subjects who have had serious infections (e.g., pneumonia, or pyelonephritis), or any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks of enrollment.

- Chronic or recurrent infection: Subjects who have chronic or recurrent bacterial, viral, fungal, mycobacterial (e.g., tuberculosis and other atypical mycobacterial disease), or protozoan infection.

- Opportunistic infection: Subjects who have, or have had, an opportunistic infection (e.g., cytomegalovirus, coccidioidomycosis, Pneumocystis carinii, aspergillosis, histoplasmosis, or mycobacterium) within 6 months prior to enrollment.

- Blood borne infection: Subjects who have active hepatitis B or active hepatitis C or a documented history of HIV, hepatitis B, or hepatitis C.

- Latent tuberculosis infection (LTBI): Subjects who have untreated LTBI are ineligible. Patients with LTBI are eligible for enrollment one month after initiating treatment for LTBI.

- Malignancy: Evidence of malignant disease or malignancies diagnosed within the previous 5 years (except basal and squamous cell carcinoma of the skin or carcinoma in situ of the cervix uteri that have been excised and cured)

- Uncontrolled disease: Subjects with evidence of serious uncontrolled concomitant cardiovascular, nervous system, pulmonary, renal, hepatic, endocrine, immunologic, psychiatric (incl. drug or alcohol abuse) or gastrointestinal disease that could interfere with participation in the trial according to the protocol.

- Transplanted organs: Subjects with transplanted organs (with the exception of a corneal transplant > 3 months prior to screening).

- Major surgery within 8 weeks prior to Screening or planned major surgery within 12 months after Baseline

- Pregnancy

- **Prohibited medications:**

- Subjects who received immunosuppressive agents [e.g., methotrexate (MTX) > 30 mg weekly, azathioprine, mycophenolate mofetil, cyclophosphamide, chlorambucil, tacrolimus, leflunomide]; IL-1 antagonists (e.g., anakinra, canakinumab); B-lymphocyte stimulator (BLyS) inhibitors (e.g., belimumab); co-stimulator blockers (e.g., abatacept); anti IL-6R monoclonal antibodies (e.g., tocilizumab); IL-17 antagonists (e.g., secukinumab); or any therapeutic agent targeted at reducing tumor necrosis factor (TNF) activity (e.g., infliximab, etanercept, adalimumab, golimumab, certolizumab) within the 3-month period prior to enrollment.

- Subjects who had treatment with any anti-CD20 agent (e.g., rituximab) within the 9-month period prior to enrolment

- Subjects who used any investigational drug within 1 month prior to enrollment or within 5 half-lives of the investigational agent, whichever is longer.

- Low dose MTX: Patients on < 30 mg of MTX weekly will be eligible for enrollment after a 2-week washout interval before receiving ustekinumab

- Vaccines: Prior to initiating therapy with ustekinumab, patients should be up to date with all immunizations appropriate for age as recommended by current immunization guidelines. Subjects who received any live virus or bacterial vaccinations other than BCG within the 3 months before the first administration of the study agent, or are expected to receive any live virus or live bacterial vaccinations during the study, or up to 3 month after the last administration of ustekinumab are not eligible. Subjects who received BCG vaccines within the 12 months before the first administration of the study agent, or are expected to receive BCG vaccines during the study, or up to 12 month after the last administration of ustekinumab are also not eligible. Caution is advised when administering live vaccines to household contacts of patients receiving ustekinumab because of the potential risk for shedding from the household contact and transmission to patient. Non-live vaccinations received during a course of ustekinumab may not elicit an immune response sufficient to prevent disease.

- **Baseline laboratory abnormalities**

- Hemoglobin < 8 gr/dL
- Platelets < 100/mm^3
- WBC < 3000/mm^3
- Absolute neutrophil count < 2.0 X 109/L (2000/mm3)
- Absolute lymphocyte count < 0.5 X 109/L (500/mm3)
- Serum creatinine > 1.4 mg/dL in female subjects and > 1.6 mg/dL in male subjects
- Total bilirubin > 2 mg/dL
- ALT or AST > 1.5 X ULN
- Positive hepatitis B surface antigen, hepatitis B core antibody or hepatitis C antibody

c. Source of subjects and recruitment methods

The source of patients will be the Massachusetts General Hospital Rheumatology clinic and the Massachusetts General Hospital Vasculitis and Glomerulonephritis Center, where staff physicians will be aware of this study protocol. Potential candidates will be initially approached by their primary provider (subjects' physician) at these two locations, who will review available treatment options, including this protocol. After this step, and if the

subject is interested in participating in this study, either Dr. Unizony or Dr. Stone will go over the informed consent process.

IV. SUBJECT ENROLLMENT

Procedures for obtaining informed consent

- Dr. Unizony or Dr. Stone will review the inform consent with the potential candidates

- The diagnosis of GCA will be confirmed through appropriate evaluations that will include comprehensive history, complete physical exam, and review of the medical records for prior temporal artery biopsy, inflammatory markers level, and cross sectional imaging (See Section III, inclusion criteria, diagnosis of GCA)

- Potential treatment approaches, including continued glucocorticoid monotherapy, conventional DMARDs (e.g., methotrexate), experimental biologics (e.g., tocilizumab), and this investigational protocol, will be discussed.

- Patients will be given at least twenty-four (24) hours to consider their potential treatment options. Adequate time will be permitted for patients to ask questions to Dr. Unizony or Dr Stone and to discuss treatment options further with family members, primary care providers, or referring physicians.

V. STUDY PROCEDURES

a. Study Overview

This is a single center, open label study that will assess the efficacy and safety of ustekinumab plus standard of care with a taper course of prednisone in 20 patients with active GCA. The study will enroll 20 subjects with a diagnosis of either new onset GCA or relapsing GCA. The study will consist of a screening phase (up to 6 weeks), a treatment phase (52 weeks) and a safety follow up phase (8 weeks). The primary efficacy

assessment will take place at week 52. The maximum duration of subject participation (including screening) is 66 weeks (See **table 1**. Schedule of events).

b. Study drugs

Treatment protocol

All subjects will receive ustekinumab and prednisone

1) Ustekinumab: 90 mg of ustekinumab will be administered at baseline, week 4, week 12, week 20, week 28, week 36 and week 44. Ustekinumab will be administered in a subcutaneous (SQ) injection in the rheumatology clinic by the physician investigator or other qualified study personnel. Ustekinumab interruption or withdrawal will be as per current US product insert (See attached ustekinumab package insert). **In case of ustekinumab-related toxicities that do not warrant the discontinuation of the medication, the dose of ustekinumab will be reduced to 45 mg keeping the same dosing intervals** (See section VII. Risks and discomforts, page 24).

2) Prednisone: All patients will receive standard of care therapy with prednisone tapered according to predefined schedules (See **table 2**, Prednisone tapers). There will be 3 possible initial prednisone doses (60 mg, 40 mg and 20 mg) to fully capture the different requirements of prednisone for induction of remission in GCA. The initial dose of prednisone will be chosen by the investigators following best clinical judgment. The duration of the prednisone taper will be 6 months in all cases. A 6 month prednisone taper will allow ustekinumab to fully reach steady state pharmacokinetics and pharmacodynamics while patients are still on prednisone. Patients who presents with vision-threatening manifestations (e.g., amaurosis fugax) will be treated with pulse methylprednisolone (1000 mg/day) for up to three doses at the discretion of the physician-investigator before starting the study prednisone taper at a dose deemed appropriate by the physician-investigator. Patients with severe clinical manifestations such as visual symptoms, jaw claudication or severe headaches will start the taper at a higher dose (e.g., 40

to 60 mg). Patients with less severe clinical manifestations such as PMR symptoms or mild headaches will start the taper at lower dose (e.g., 20 to 40 mg).

Please note that patients are required to have active disease (see inclusion criteria) within 6 weeks of baseline visit in order to be eligible for the study. Patients may or may not be on prednisone by the time of the screening visit and there is no timeframe for prior prednisone use as far as the criteria of disease activity within 6 weeks of baseline is met. Most of the relapsing patients and some of the new onset patients will be taking some prednisone by the time of the screening. For those who are already taking prednisone and demonstrate active disease at screening visit, the prednisone dose will be increased to one of the protocol initial doses (i.e., 20 mg, 40 mg or 60 mg) in order to control that activity. For those who are already taking prednisone and are in remission at screening (because the prednisone dose was recently modified to control disease activity), the dose will be kept if it is one of the protocol starting doses, and if it is not, modified in order to start the study on one of the protocol starting doses.

3) Escape therapy: Patients who do not achieve the status of clinical remission by week 12, can not follow the study prednisone taper, or develop a disease flare before week 52 will be deemed failures for the primary endpoint. Those subjects will stop ustekinumab and be offered treatment with an investigator-defined prednisone rescue regimen

Upon study completion, decisions on treatment options for individual subjects will be at the discretion of the investigator.

Concomitant medications:

- Anti-platelet therapy All the subjects will be treated with aspirin 81 mg daily unless contraindicated.

- Glucocorticoid induced osteopenia/osteoporosis prevention and treatment All the subjects will receive oral calcium and 25-hydroxy vitamin D supplementation (Ca 1200-1500 mg and vitamin D 800-1000 IU daily in divided doses). Bisphosphonate therapy (e.g., alendronate 70 mg weekly or zolendronate 5 mg annually) will also be employed at the discretion of the physician-investigator for the prevention of glucocorticoid-induced osteoporosis. Participants with documented osteoporosis will be treated with FDA-approved drugs for osteoporosis according to clinical guidelines [e.g., National Osteoporosis Foundation (NOF)].

- Gastric prophylaxis. Prophylaxis with proton pump inhibitors or H-2 blockers will be employed at the discretion of the physician-investigator for the prevention of glucocorticoid-induced gastrointestinal side effects

- PCP prophylaxis with an acceptable regimen which may include sulfamethoxazole and trimethoprim one single strength pill (80 mg / 400 mg) daily, sulfamethoxazole and trimethoprim one double strength pill (160 mg / 800 mg) three times a week or dapsone 50 to 100 mg daily

c. Study Visits (See **table 1**. Schedule of events).

- Screening visit (-42 to 0 days before Baseline). Complete medical history, physical examination and selective laboratory investigations will be obtained for the purpose of confirming the diagnosis of active GCA, determining study eligibility, and assessing baseline values for the outcomes of interest

During this visit the following procedures will be completed

- Written Informed Consent
- Subject Demography
- Medical and surgical history
- GCA history evaluation (date of disease diagnosis, date of temporal artery biopsy, duration of prednisone treatment, prednisone-related adverse events)
- Inclusion/Exclusion Criteria
- Concomitant Medications
- Assessment of signs and symptoms of GCA/PMR activity

- Vital signs and Physical exam
- Screening laboratory tests including complete blood count (CBC), creatinine, BUN, AST, ALT, total bilirrubin, alkaline phosphatarse, ESR, CRP level, urine analysis, HCV antibody, HBV superficial antigen, and HBV anti core antibodies.
- Chest x-ray (CXR)
- Electrocardiogram (ECG)
- Urine or serum pregnancy testing will be completed for female patients who report their last menstrual period within 12 months of the screening visit
- Evaluation for latent TB infection with interferon gamma releasing assay (e.g., quantiferon test or T spot).
- Blood samples for optional research studies (DNA/RNA/flow cytometry/serum biomarkers)

Following the Screening period, eligible subjects will proceed with a 52-week treatment phase

- Baseline-Week 52 visits

Subjects will start the treatment phase of the study only if all eligibility criteria are met. The treatment phase of the study will consist of a Baseline visit, and subsequent visits at week 4, week 12, week 20, week 28, week 36, week 44 and week 52.

Ustekinumab will be administered in site by the principal investigator or designated trained personnel at Baseline, and at visits week 4, week 12, week 20, week 28, week 36, and week 44. In addition, the patients will follow a pre-specified prednisone taper (See **table 2**. Prednisone taper protocol).

During Baseline through week 52 visit the following procedures will be completed

- Vital signs and Physical exam
- Concomitant Medications
- Adverse Events Assessments
- Assessment of signs and symptoms of GCA/PMR activity
- Ability to adhere to the pre-specify prednisone taper
- Ustekinumab administration (baseline, w4, w12, w20, w28, w36, w44)

- Laboratories (CBC, creatinine, BUN, AST, ALT, total bilirrubin, alkaline phosphatarse, ESR, CRP level, and lipid profile)
- Blood samples for optional research studies (RNA/flow cytometry/serum biomarkers)

The main efficacy and safety endpoint will be measured at 52 weeks (See below **section IV**.)

- Safety follow up visit. The participants will undergo a safety follow up visit at week 60

During the safety follow up the following procedures will be completed

- Vital signs and Physical exam
- Concomitant Medications
- Adverse Events Assessments
- Assessment of signs and symptoms of GCA/PMR activity
- Laboratory assessments (CBC, creatinine, BUN, AST, ALT, total bilirrubin, alkaline phosphatarse, ESR, and CRP level)
- Blood samples for optional research studies (RNA/flow cytometry/serum biomarkers)

d. Toxicity Grading Scale

All adverse events will be recorded and classified according to the most recent version of the National Cancer Institute (NCI) *Common Terminology Criteria for Adverse Events* (CTCAE), published May 28, 2009 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf)

Adverse events will be recorded and graded 1 to 5 according to the CTCAE grades provided below:

Grade 1 = Mild adverse event

Grade 2 = Moderate adverse event

Grade 3 = Severe and undesirable adverse event

Grade 4 = Life-threatening or disabling adverse event

Grade 5 = Death

e. Optional research studies (DNA, RNA and flow cytometry analyses)

Optional research samples will be collected from patients who give specific consent to participate in this optional research. The Informed Consent Form will contain a separate section that addresses participation in the optional research studies

A blood sample will be collected for genetic analysis as follows: Blood (approximately 6 mL in K3 EDTA) for DNA isolation will be collected as shown **table 1** (Schedule of events). The sample may be processed using techniques such as array-based hybridization or PCR

Blood samples will be collected for RNA expression analysis as follows: Blood (1 × approximately 2.5 mL collected in PAXgene vacutainers) for RNA isolation will be obtained as shown in **table 1** (Schedule of events). The samples may be tested using techniques such as microarray profiling, RNA sequencing, and/or reverse transcriptase − polymerase chain reaction (RT-PCR)

Blood samples will be collected for serum assays for biomarkers as follows: Blood (one sample of approximately 6.0 mL) for serum isolation will be obtained at various time points as shown in **table 1**. (Schedule of events). The samples may be tested using techniques such as ELISA and Luminex. Biomarkers to be determined may include cytokines (e.g., IL-17, IFN gamma, IL-12, IL-6, etc), chemokines (e.g., CXCL-9, CXCL-10, etc), and other soluble molecules (e.g., VGEF)

Blood samples will be collected for determination of cell subpopulations as follows: Blood (approximately 15 mL) for peripheral blood mononuclear cell (PBMC) and lymphocyte purification and determination of cell subpopulations by flow cytometry will be collected as shown **table 1** (Schedule of events). Subpopulation of cells to be analyzed include T-helper (Th)1 cells, Th17 cells, and regulatory T cells.

Optional research samples will be destroyed no later than 15 years after the date of informed consent signature. These samples will be de-indentified and stored in the Division of Rheumatology, Allergy and Immunology (Dr Andrew Luster's Laboratory)

Optional research samples will be used to achieve the following objectives:

- To study genetic variants associated with GCA and treatment response to the study medication
- To study the association of biomarkers with efficacy, adverse events, or other disease-related outcomes
- To increase knowledge and understanding of disease biology

Patients will be told that they are free to refuse to participate in the optional research studies, and may withdraw their specimens at any time and for any reason during the storage period.

VI. BIOSTATISTICAL ANALYSIS

Signs and symptoms of GCA activity, compliance with the prednisone taper, specific laboratory parameters (e.g., ESR, CRP) and the occurrence of adverse events will be assessed over time for the analysis of the efficacy and safety endpoints.

Study endpoints

Primary efficacy endpoint:

1) Percentage of patients in glucocorticoid-free remission at 52 weeks

The definition of glucocorticoid-free remission contains 3 elements:
- Absence of clinical signs or symptoms of active GCA and PMR along with the normalization of the ESR (<40 mm/hour) and CRP (<10 mg/L)
- Completion of the pre-specified prednisone taper protocol
- Absence of disease flare (relapse) since the induction of remission

Definition of flare: Re-appearance of unequivocal signs or symptoms of active GCA or PMR (with or without elevation of ESR and CRP) that requires increase in the prednisone dose in order to be controlled

Secondary efficacy endpoint

1) Percentage of patients in clinical remission on prednisone ≤ 5 mg/day at 52 weeks

Clinical remission is defined as the absence of clinical signs or symptoms of active GCA and PMR along with the normalization of the ESR (<40 mm/hour) and CRP (<10 mg/L) regardless of the treatment being received

2) Time to disease flare
3) Number of disease flares at 6 and 12 months
4) Cumulative prednisone dose
5) ESR and CRP 6 and 12 months

Safety endpoints

1) The number, nature and severity of adverse events (AE) at week 52 and 60
2) The number, nature and severity of serious AE (SAE) at week 52 and 60
3) Number of glucocorticoid-related adverse events at week 52 and 60

Statistical Methods

Continuous data will be summarized using descriptive statistics (e.g., means, standard deviations, medians, interquartile ranges). Categorical data will be summarized as numbers and corresponding percentages. Descriptive statistics and two-sided 95% confidence intervals will be calculated to assist the interpretation of efficacy outcomes.

The remission rate of patients treated with Ustekinumab in this study will be compared to the remission rate by week 52 of historical controls treated with prednisone monotherapy in clinical trials (~15% in Jover et al. MTX trial 2001 [3]; 10% in Hoffman el al. MTX trial 2001 [4]; 50% in Hoffman el al. Infliximab trial 2007 [6] [early stop before 52 weeks due to inefficacy]; 22% in Martinez-Taboada et al. Etanercept trial [8]; 30% in

Seror et al. Adalimumab trial [7]) Setting up the probability of type I error at 0.05 and type II error at 0.2, and assuming a 40% remission rate by 52 week in historical controls, a sample size of 20 patients will provide more than 80% power to detect a difference in the proportion of patients in remission between the ustekinumab group and the historical controls of 30% if that difference actually exists.

We will complete an interim analysis after 5 patients from each stratum (i.e., new onset and relapsed disease) have completed 12 months of treatment. In case the flare rate within any of the strata is ≥ 60%, that strata will be terminated

VII. RISKS AND DISCOMFORTS

With the exception of ustekinumab administration, which is experimental, all the procedures performed in this study are consistent with the SOC for a patient with GCA.

a. Complications of Subcutaneous Medication Administration

The injection of subcutaneous medications is associated with a mild degree of discomfort at the injection site for a short period of time. Small degrees of bleeding or bruising may occur at the injection site. Skin irritation (erythema) and rarely cellulitis can result at the site of injection.

To minimize this risk, we have experienced infusion nurses who are experts in the administration of subcutaneous medications commonly used in the rheumatology practice (e.g., etanercept, adalimumab).

b. Potential Side-effects of Ustekinumab [56]

Ustekinumab has been approved by the FDA in 2009 for adults with chronic moderate to severe plaque psoriasis. Thus, there is substantial clinical experience with this drug and the adverse effect profile is well defined.

- **Common mild and self-limited side effects include**

- Dizziness
- Headache

- Back pain
- Myalgias
- Injection site erythema
- Diarrhea
- Upper airway infection

- **Potential serious side effects**

- Infections

Ustekinumab may increase the risk of infections and reactivation of latent infections. Serious bacterial, fungal, and viral infections were observed in subjects receiving ustekinumab.

As a risk mitigation strategy, patients will be screened for latent TB infection (LTBI), and undergo close monitoring for prompt diagnosis and treatment of any potential infection. Patients will be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. Ustekinumab will not be given to patients with any clinically important active infection. Ustekinumab will not be administered until any clinically important active infection resolves or is adequately treated. Should a patient have a serious or opportunistic infection, ustekinumab will be discontinued and the patient will not be re-challenged with the drug.

- Malignancy

Controlled trials have not shown increased risk of cancer associated with ustekinumab. However, given its immunosuppressive effects, surveillance for malignancy is required. Appropriate age and gender cancer screening will be recommended as per current national guidelines, and patients will be closely monitored during the study. Any sign or symptom suggestive of malignancy will be properly investigated. If a neoplastic condition were diagnosed, ustekinumab will be discontinued, and patients will be referred to oncology (or other pertinent specialist) for appropriate evaluation and treatment.

- Cardiovascular events

Phase 2 psoriasis studies showed an imbalance in the incidence of cardiovascular events, which were more frequent in the ustekinumab treated patients. Increased cardiovascular morbidity was not confirmed in phase 3 studies.

Sensitivity analysis showed an incidence of serious and non serious cardiovascular AE of 4.5%, 3.8% and 4.3% in the placebo, ustekinumab 45 mg and ustekinumab 90 mg, respectively. The rates of myocardial infarction and stroke seen in clinical trials were consistent with or lower than the rates expected in the general population.

The presence of cardiovascular risk factors will not exclude a subject from participating in this study. However, to minimize cardiovascular risks and following the standards of our practice, there will be communication with the subjects' primary care physician to have cardiovascular risk factors (e.g., hypertension, dylipidemia, smoking, diabetes) addressed according to national guidelines.

- Hypersensitivity reactions

No anaphylaxis or serum sickness events were reported in clinical trials, but serious allergic reactions (including angioedema, dyspnea and hypotension), and hypersensitivity reactions (including rash and urticaria) have been reported post-marketing.

Subjects will be monitored for hypersensitivity reactions and treated accordingly. If a serious hypersensitivity reaction occurs (e.g., analphylaxis), ustekinumab will be discontinued and subjects will not be re-challenged with the drug.

- Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

RPLS has been rarely reported in patients treated with ustekinumab. If RPLS is suspected in patients presentating with headache, seizures, confusion, or visual disturbances, ustekinumab will be discontinued, and patients will be properly evaluated and treated.

- Th-2 related disease exacerbation

No exacerbation of Th2 driven pathologies such as asthma or airway allergies were reported during clinical trials. Patients will be monitored for exacerbation of hypersensitivity conditions, and treated accordingly if indicated.

- Laboratory abnormalities

Markedly abnormal changes in hematology and chemistry laboratory values were infrequent during clinical trials, with comparable rates among ustekinumab and placebo treated patients. The ustekinumab manufacturer does not recommend any type of laboratory monitoring during ustekinumab treatment.

Selected labs will be checked at different times during the study (See **table 1**. Schedule of events). If a marked laboratory abnormality is detected (See below **section IX.b**. Criteria for dropping a subject from the study), the study drug will be discontinued and the patient will not be re-challenged.

Ustekinumab dose may be reduced to 45 mg for any of the following reasons:

1) Recurrent non-serious infections
2) Other non-serious adverse events deemed to be secondary to ustekinumab that justify a dose reduction

VIII POTENTIAL BENEFITS

a. Potential benefits to Subjects

The Subjects may benefit from having their disease controlled more effectively than with prednisone monotherapy or prior immunosuppressive regimens. They may also benefit from requiring less treatment with prednisone, and thereby incurring in fewer side effects associated with this treatment (e.g., hypertension, diabetes, osteoporosis, gastrointestinal bleeding, glaucoma, cataracts, other).

b. Potential benefits to Society

There is great unmet need for the treatment of GCA. Glucocorticoids are still the main agents used to control disease activity and prevent complications. However, glucocorticoid treatment is invariably associated with undesirable side effects that impair quality of life of patients and increase costs to society.

Ustekinumab may prove to be effective in controlling GCA activity and exerting glucocorticoid-sparing effects. Therefore, ustekinumab may increase the quality of life of the patients, and reduce the costs of treating glucocorticoid -related morbidity. On the other hand, ustekinumab may increase the options to treat GCA in patients refractory to or unable to take glucocorticoids due to contraindications (uncontrolled hypertension, uncontrolled diabetes, severe osteoporosis, cataracts, mood disorders, gastrointestinal bleeding), or toxicity.

In randomized controlled trials (mostly including *newly diagnosed GCA* subjects), the flare rate within 12 months in patients only receiving glucocorticoids has been between 50% and 85% [6-8, 19]. If $\geq$ 60% of the subjects in this cohort of GCA patients achieve the primary outcome (glucocorticoid-free remission) at 12 months, then this will be considered a successful pilot study, and an adequately powered randomized controlled trial would be indicated.

IX. MONITORING AND QUALITY ASSURANCE

Drs. Unizony and Stone will monitor study data to ensure the safety of patients.

a. Specific elements related to the safety of study subjects that will be examined include:

- Deaths
- Hospitalizations from any cause
- Infections
- Injection site reactions
- Other unexpected and serious adverse events

b. Criteria for dropping a subject from the study

- A disease flare while on ustekinumab (treatment failure) as defined by the principal investigator
- The occurrence of any malignancy,
- The occurrence of major cardiovascular event (e.g., stroke, acute coronary syndrome)

- The occurrence of reversible posterior leukoencephalopathy syndrome (RPLS)
- The occurrence of a severe hypersensitivity reaction, (e.g., anaphylaxis, bronchospasm, angioedema)
- The worsening of any Th2 related pathology (e.g., asthma)
- The occurrence of a serious, systemic, opportunistic, chronic/recurrent or blood-borne infection
- The occurrence of any marked laboratory abnormality including: Hemoglobin < 8 gr/dL, Platelets < 100/mm^3, WBC < 3000/mm^3, Absolute neutrophil count < 2.0 X 109/L (2000/mm3), Absolute lymphocyte count < 0.5 X 109/L (500/mm3), Serum creatinine > 1.4 mg/dL in female subjects and > 1.6 mg/dL in male subjects, Total bilirubin > 2 mg/dL, ALT or AST > 1.5 X ULN

c. Specific elements of efficacy that will be examined include:

- Improvement of active GCA symptoms, as judged by medical history, physical examination, and laboratory tests (ESR, CRP)
- Ability to followed the pre-specified glucocorticoid taper
- Ability of maintain remission off glucocorticoids
- Glucocorticoid-sparing effects by analyzing the incidence of glucocorticoid-related side effects

d. Adverse event reporting guidelines:

Adverse events and unanticipated problems involving risks to subjects or others will be reported to the PHRC in accordance with PHRC adverse event and unanticipated problems reporting guidelines.

Regarding safety data collection and reporting also refer to Addendum 1 (Interventional IIS Janssen Scientific Affairs Requirements for Safety Data Collection and Reporting)
The investigator may share coded safety information with Janssen Scientific Affairs, LLC so it may conduct additional reviews of the coded information in order to study the safety and effectiveness of the study drug, to develop a better understanding of disease, or to improve the efficiency of future clinical trials.

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Table 1. Schedule of events

EVALUATION	STUDY VISIT (week +/- 5 days)									
	Screen (-42 to 0 days)	**BL**	**4**	**12**	**20**	**28**	**36**	**44**	**52**	**60[8,9] Safety FU / EW**
Informed Consent	X									
I/E Criteria	X									
Demographics, medical and surgical history	X									
GCA history evaluation [1]	X									
AE Assessment		X	X	X	X	X	X	X	X	X
Con Meds	X	X	X	X	X	X	X	X	X	X
Physical Exam[2]	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X
Evaluation for LTBI[3]	X									
Ustekinumab Administration		X	X	X	X	X	X	X		
Signs and Symptoms of GCA/PMR activity[4]	X	X	X	X	X	X	X	X	X	X
ESR	X	X	X	X	X	X	X	X	X	X
CRP	X	X	X	X	X	X	X	X	X	X
Blood Chemistry[5]	X		X	X	X	X	X	X	X	X
CBC	X		X	X	X	X	X	X	X	X
Fasting lipid profile[6]		X		X		X			X	

HBsAg, anti-HBc Ab and anti-HCV Ab	X									
UA	X									
CXR	X									
ECG	X									
Pregnancy test[7]	X									
DNA	X									
Serum, RNA and Flow	X		X		X		X		X	

1. Date of diagnosis, date of temporal artery biopsy, duration of prednisone treatment, initial prednisone dose, prednisone-related adverse events.

2. Complete examination, including assessments of the skin, head, eyes, throat, neck, lungs, heart, abdomen, lymph nodes, and musculoskeletal (MSK) system

3. Tuberculin test (PPD) and/or interferon gamma releasing assay (IGRA)

4. Temporal artery or scalp tenderness with palpation; unequivocal jaw claudication; visual changes such us transient diplopia, transient blurry vision, amaurosis fugax, or new/worsening decrease visual acuity; or unequivocal evidence of active PMR as manifested by shoulder and/or pelvic girdle pain and stiffness (e.g. morning stiffness)

5. Creatinine, BUN, eGFR, AST, ALT, alkaline phosphatase, total bilirubin

6. Total cholesterol, LDL cholesterol, HDL cholesterol, triglicerides

7. If last menstrual period within 12 months of screening visit

8. Week 60 visit will be a safety follow up visit. During this visit, GCA treatment options moving forward will be discussed with the subjects. Treatment from this time point will be guided as per best clinical judgment.

9. In case of early withdrawal, an early withdrawal visit will take place 8 weeks after the last visit before the early withdrawal

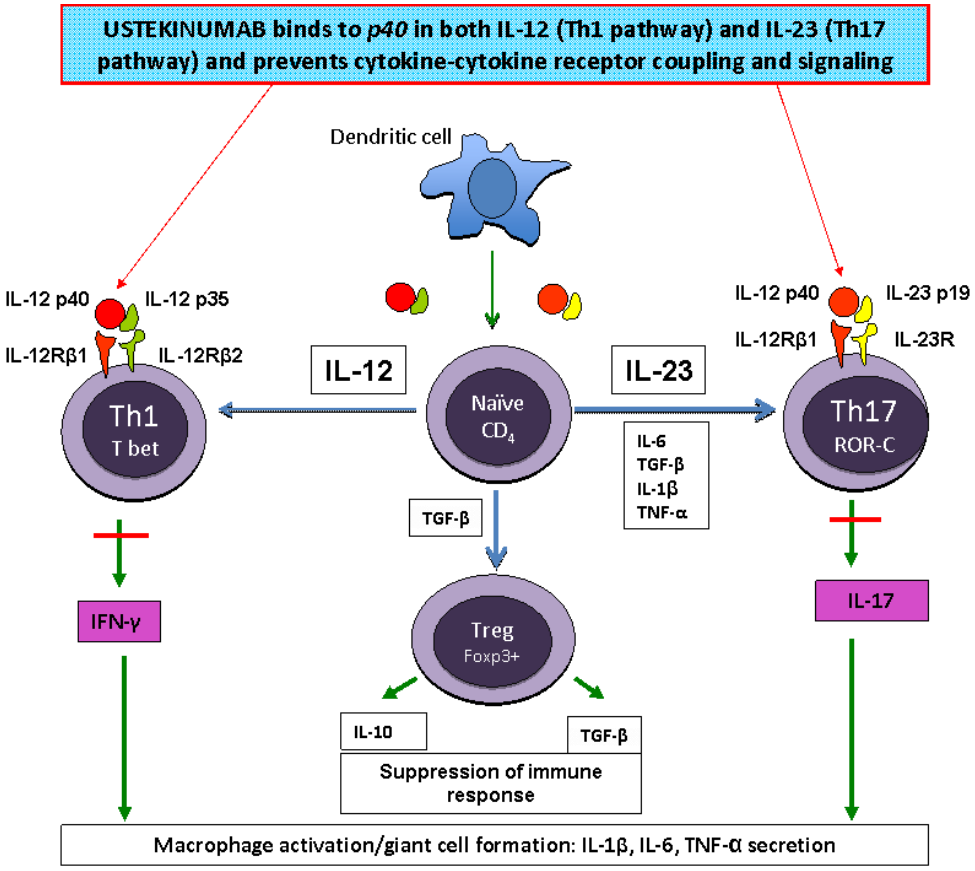
BL = baseline; EW = early withdrawal; I/E = inclusion/exclusion; AE = adverse events; Con Meds = concomitant medications; LTBI = latent tuberculosis infection; ESR = erythrocyte sedimentation rate, CRP = C-reactive protein; CBC = complete blood count; HBsAg = hepatitis B superficial antigen; anti-HBc Ab = anti Hepatitis B core antibody; anti-HCV Ab = anti Hepatitis C virus antibody; UA = urinalysis; CXR = chest x-ray; EKG = electrocardiogram

Table 2. Prednisone taper protocol

Week	Initial prednisone dose (*)					
	60 mg		40 mg		20 mg	
	Daily dose (mg/day)	Cumulative dose (mg)	Daily dose (mg/day)	Cumulative dose (mg)	Daily dose (mg/day)	Cumulative dose (mg)
1	60		40		20	
2	60		40		20	
3	50		30		17.5	
4	40	1470	25	945	15	507.5
5	30		20		12.5	
6	25		17.5		10	
7	20		17.5		10	
8	17.5	2117.5	15	1435	9	798
9	17.5		15		8	
10	15		12.5		7	
11	15		12.5		6	
12	12.5	2537.5	10	1785	6	987
13	12.5		10		5	
14	10		9		5	
15	10		8		4	
16	9	2828	7	2023	3	1106
17	8		6		3	
18	7		5		3	
19	6		4		2	
20	5		3		2	
21	4		2		2	
22	3		2		1	
23	2		1		1	
24	1	3080	1	2191	1	1211

(*) Rational for allowing patients to enter the prednisone taper at different initial doses. New onset patients usually require doses of prednisone between 40 to 60 mg for induction of remission. In contrast, the prednisone dose required for induction of remission in patients with relapsed disease is variable. Relapses characterized by cranial symptoms (e.g., headaches, jaw claudication, visual manifestations) usually require higher prednisone doses (40 to 60 mg). In contrast, a relapse characterized by polymyalgia rheumatica (PMR) symptoms, typically responds to lower prednisone doses (e.g., 20 mg). In addition, other patient's comorbidities (e.g., diabetes, hypertension, etc) may influence the prednisone dose selection as lower prednisone doses are associated with lower prednisone-induced toxicity

Figure 1. IL-12 and IL-17 pathways and proposed mechanism of action of ustekinumab in GCA



Addendum 1. **Interventional IIS Janssen Scientific Affairs Requirements for Safety Data Collection and Reporting**

1. OVERVIEW

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

The INSTITUTION and PRINCIPAL INVESTIGATOR will provide safety information to Janssen Scientific Affairs on adverse events, special situations including pregnancies and product quality complaints as defined within this EXHIBIT.

2. Management of Safety Data

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

3. Definitions

3.1. Adverse Event (AE)

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse

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

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

3.2. Adverse Events of Special Interest

Adverse events of special interest are events that Janssen Scientific Affairs is actively monitoring as a result of a previously identified signal (even if non-serious). The adverse events of special interest for ustekinumab are:

- Malignancies
- Tuberculosis (TB)
- Serious infections including Opportunistic infections
- Severe Hypersensitivity reactions (including anaphylactic reactions and angioedema)
- Neurologic events (eg, demyelination, progressive multifocal leukoencephalopathy (PML), facial palsy, reversible leukoencephalopathy syndrome (RPLS))
- MACE events (Non fatal Stroke, Non fatal MI, CV death)
- Erythrodermic psoriasis
- Pustular psoriasis

Adverse Events of Special Interest will be reported on a Serious Adverse Event Report Form and be reported to Janssen Scientific Affairs **within 24 hours of becoming aware of the event.**

3.3. Individual Case Safety Report (ICSR)

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

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- an identifiable reporter (investigational site)
- a Janssen medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

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

3.4. Product Quality Complaint (PQC)

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

Examples of PQC include but not limited to:

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

3.5. Serious Adverse Event (SAE)

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

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

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

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

3.5.1. Hospitalization

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

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

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

3.5.2. Life-Threatening Conditions

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

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

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

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

For Stelara (ustekinumab), the link to the package insert is:
http://www.stelarainfo.com/pdf/PrescribingInformation.pdf

5. Special Reporting Situations

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

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Janssen medicinal product
- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- Failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product
- Unexpected therapeutic or clinical benefit from use of a Janssen medicinal product

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

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

6. Pregnancy

The effect of ustekinumab on human sperm, pregnant women, and women making breast milk, unborn babies or breast feeding infants is not known. Pregnant women and women making breast milk to feed infants cannot participate in this study. Urine and/or blood pregnancy tests will be conducted for female participants who are capable of getting pregnant. It is very important that men taking part in this study do not get a woman pregnant while taking part in this study.

Contraceptive recommendation will be given to all women participants who could become pregnant and all men participants who may father a child as follows:

- During this study and for 4 months after the last dose of study drug, you must use proven birth control methods.
- If you are using a hormone birth control method (such as oral contraception ["the pill"], a patch, injections, etc.), you must also use a second method of birth control, such as a condom or diaphragm. It is not known if ustekinumab affects the effectiveness of hormonal birth control methods. However, ustekinumab may lower the concentration/amount of active ingredients of the hormonal birth control methods.
- If you are planning to donate eggs (ova, oocytes) during the study and for 4 months after your last dose of study drug, you must notify your study doctor or healthcare team and discuss the associated risks.

Pregnancies in women participants and pregnancies in partners of male subjects exposed to ustekinumab will be reported by the PRINCIPAL INVESTIGATOR **within 24 hours of their knowledge of the event** using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner. Follow-up information

regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

7. Maintenance of Safety Information

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

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

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

All (serious and non-serious) adverse events reported for a Janssen medicinal product should be followed-up in accordance with clinical practice.

8.1. SAEs and Special Reporting Situations

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

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct

- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The INSTITUTION and the PRINCIPAL INVESTIGATOR) will transmit all SAEs and special situations following exposure to a Janssen product under study in a form provided by Janssen Scientific Affairs in English **within 24-hours of becoming aware of the event(s).**

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

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

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

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

- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Janssen Product under study, are to be provided to

Janssen Scientific Affairs within **24 hours of such report or correspondence being sent to applicable health authorities.**

8.2. Non-Serious AEs

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

8.3. PQC Reporting

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen Scientific Affairs, and are mandated by regulatory agencies worldwide. Janssen Scientific Affairs has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

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

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

9. Reporting Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Non-Janssen Medicinal Products

For SAEs, special reporting situations and PQCs following exposure to a non-Janssen medicinal product under study, the PRINCIPAL INVESTIGATOR should notify the appropriate regulatory/competent authority or the manufacturer of that medicinal product (in the absence of appropriate local legislation) as soon as possible.

10. Transmission Methods

The following methods are acceptable for transmission of safety information to the Janssen Scientific Affairs:

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

Please use the contact information and process information provided by Janssen Scientific Affairs

11. Reconciliation of SAEs

At a minimum, on a quarterly basis and at the end of the Study, Janssen Scientific Affairs will provide to the INSTITUTION and/or PRINCIPAL INVESTIGATOR, a listing of all SAEs reported to the Janssen Scientific Affairs. SPONSOR and/or PRINCIPAL INVESTIGATOR will review this listing and provide any discrepancies to Janssen Scientific Affairs.

Upon request, INSTITUTION and PRINCIPAL INVESTIGATOR shall provide Janssen Scientific Affairs with a summary list of all SAEs, and AEs of Special Interest and Special Reporting Situation reports to date, for reconciliation purposes.

12. Dissemination of Safety Information from COMPANY to INSTITUTION/PRINCIPAL INVESTIGATORS

PRINCIPAL INVESTIGATOR will be responsible for submitting IND safety reports for the Study Product to INSTITUTION's IRB in accordance with Federal regulations 21 CFR 312.66. The PRINCIPAL INVESTIGATOR will provide a copy of each IND safety report to sub-investigators where the study design is either a multi-center or cooperative study.

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

13. Contacting Janssen Scientific Affairs **Regarding Safety**

The names (and corresponding contact information) of the individuals who should be contacted regarding safety issues will be provided separately by Janssen Scientific Affairs.

14. Final Study Report

The INSTITUTION/PRINCIPAL INVESTIGATOR will prepare a final report including a complete and full summary of all adverse events, special situations and pregnancy reports according to the timeframe outlined in the pertinent Research Funding Agreement section.