PARTNERS HUMAN RESEARCH COMMITTEE
DETAILED PROTOCOL

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Study title
TOCILIZUMAB PLUS A SHORT PREDNISONE TAPER FOR GIANT CELL ARTERITIS

Study Drug
Tocilizumab (Roche / Genentech)

Study Drug and Financial Support Provided By
Roche / Genentech

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1. BACKGROUND AND SIGNIFICANCE

Giant cell arteritis (GCA), the most common form of primary vasculitis [1], is associated with severe morbidity [2], reduced quality-of-life [3, 4], and major treatment-related toxicities [5]. The disease is three times more common in women than in men [2] and its prevalence ranges from 24 to 280 cases per 100,000 individuals. It is estimated that more than 3 million people will be diagnosed with GCA in Europe, North America, and Oceania by 2050 [1]. The clinical manifestation of GCA include constitutional symptoms, headaches, jaw pain, visual symptoms (e.g., amaurosis fugax), and myoarthralgias (i.e., polymyalgia rheumatica [PMR]). The most serious complication of the disease is blindness [2]. Other possible complications include aortic aneurysm, limb ischemia from large-artery stenosis, stroke, mesenteric ischemia, and myocardial infarction [2] and venous thromboembolism [6].

The etiology of GCA remains unknown and the understanding of its pathogenesis is incomplete. Therefore, no curative treatment for this condition currently exists. Until recently, prolonged glucocorticoid tapering courses (e.g., 12-18 months) were the only treatment option available for disease control, and many patients remained on glucocorticoids for years. Nevertheless, up to 85% of patients treated with one full year of prednisone experience disease relapse when this medication is tapered [3]. Relapsing GCA leads to further glucocorticoid treatment and heightened glucocorticoid toxicity. More than 85% of the patients develop glucocorticoid-related side-effects (e.g., osteoporotic fractures, diabetes, infection, cataracts, hypertension, psychosis, dyslipidemia, and gastrointestinal bleeding) [5]. Studies of several potential "steroid-sparing" agents have failed or demonstrated only modest efficacy at best [7-10]. In contrast, a recent Phase III randomized controlled trial led by our group known as the GiACTA trial [3], demonstrated that 12 months of tocilizumab (TCZ), a monoclonal antibody directed against the interleukin (IL)-6 receptor (IL-6R), combined with a 6-month prednisone taper, is superior to the decades-old standard of care of prolonged prednisone taper alone.

In the GiACTA study [3], 251 patients were randomized in a 1:1:1:2 ratio to one of four groups:

- Placebo plus 26-week prednisone taper (PBO+26, N = 50)
- Placebo plus 52-week prednisone taper (PBO+52, N = 51)
- TCZ 162 mg every other week plus 26-week prednisone taper (TCZ Q2W, N = 50)
- TCZ 162 mg weekly plus 26-week prednisone taper (TCZ QW, N = 100).

The results of the study demonstrated that the addition of IL-6 signaling blockade therapy to a shorter glucocorticoid taper is more effective at achieving and maintaining disease remission, sparing the use of glucocorticoids, and improving the health-related quality-of-life of patients than the prior standard of care of glucocorticoid monotherapy [3, 4]. Based on the results of GiACTA [3], the subcutaneous TCZ formulation (the drug planned for this study) has been approved in the United States and Europe for use in patients with GCA.

Shorter prednisone tapers leading to reduced cumulative prednisone exposure are likely to result in fewer glucocorticoid-related adverse events. In this regard, prednisone tapers over 6 months (e.g., GiACTA trial [3]) represent an important step forward in the treatment of GCA. However, 6 months of prednisone are not exempted from causing significant toxicity. As an example, patients in the prednisone-only treatment groups in GiACTA were more likely to have serious adverse events compared to patients in the TCZ plus prednisone groups. Further, in the study of Hoffman et al [7], at least 1 serious adverse event occurred in 25% of patients

receiving prednisone only therapy for 6 months. In addition, 50% of the subjects in this group developed an infection requiring antibiotics [7]. In the study of Seror et al. [9], at least 1 serious adverse event was observed in up to 50% of patients allocated to ~ 6 months of prednisone plus placebo. Finally, in the study of Jover et al. [11], several adverse events developed in patients that received prednisone monotherapy for 29 weeks. Those included hypertension (60%), infection (40%), diabetes or glucose intolerance (25%), cataracts (20%), osteoporosis-related fragility fractures (20%), and neuropsychiatric symptoms (50%).

In summary, the era of IL6R blockade ushered in by the GiACTA trial offers the opportunity to reduce even further the glucocorticoid exposure in GCA. We therefore propose an open-label pilot study of TCZ 162 mg weekly for 52 weeks in combination with only 8-week of prednisone.

2. OBJECTIVES

The primary objective of this study is to evaluate the efficacy and safety of TCZ in combination with an 8-week prednisone taper in patients with GCA. The primary outcome measure will be the proportion of patients in sustained remission at week 52 following induction of remission and adherence to the protocol-defined prednisone taper.

Key trial definitions are shown below:

Remission: Defined as the absence of signs and symptoms attributable to active GCA.

Sustained remission: Absence of flare following induction of remission up to the 52-week time point.

Flare: Determined by the investigator based on recurrent signs or symptoms of GCA and/or ESR ≥ 30 mm/hr or CRP (≥ 10 mg/L) attributable to GCA. I order to fulfill the definition of disease flare; the investigator must make the clinical decision to increase the patient's prednisone dose or re-initiate prednisone treatment.

3. SUBJECT SELECTION

3.a. Inclusion Criteria

3.a.1. Ability and willingness to provide written or electronic informed consent and to comply with the study protocol

3.a.2. Diagnosis of GCA classified per the following criteria:

- Age 50 years or older

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:

- Cranial 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
- Ultrasound demonstration of features of GCA in a cranial artery.

3.a.3. New-onset or relapsing/refractory active disease defined as follows:

- New onset: diagnosis of GCA within 6 weeks of baseline visit

- Relapsing/refractory: diagnosis of GCA > 6 weeks before baseline visit

AND

- Active GCA within 6 weeks of baseline visit defined as the presence of clinical signs and symptoms [cranial or PMR]

3.b. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

3.b.1. General exclusion criteria

- Major surgery within 8 weeks prior to screening or planned major surgery within 12 months after randomization
- Transplanted organs (except corneal transplant performed more than 3 months prior to screening)
- Major ischemic event, unrelated to GCA, within 12 weeks of screening

3.b.2. Exclusions related to prior or concomitant therapy*

- Treatment with any investigational agent within 12 weeks (or 5 half-lives of the investigational drug, whichever is longer) of screening
- Previous treatment with cell-depleting therapies, including investigational agents, including but not limited to Campath (alemtuzumab), anti-CD4, anti-CD5, anti-CD3, anti-CD19, and anti-CD20
- Previous treatment with alkylating agents, such as chlorambucil, or with total lymphoid irradiation
- Immunization with a live/attenuated vaccine within ≤ 4 weeks prior to baseline
- Treatment with cyclosporine A, azathioprine, cyclophosphamide or MMF within 4 weeks of baseline. Patients on methotrexate at screening will require discontinuation of this agent prior to baseline visit.

- Treatment with etanercept within 2 weeks; infliximab, certolizumab, golimumab, abatacept, or adalimumab within 8 weeks; or anakinra within 1 week of baseline
- Patients requiring systemic glucocorticoid therapy for conditions other than GCA, which, in the opinion of the investigator, would interfere with adherence to the fixed glucocorticoid taper regimen and/or to assessment of efficacy in response to TCZ
- Inability, in the opinion of the investigator, to withdraw GC treatment through protocol-defined taper regimen due to suspected or established adrenal insufficiency

* Patients treated with TCZ before will be permitted to participate in the trial if they demonstrated treatment efficacy and they did not discontinue TCZ because of an adverse effect.

3.b.3. Exclusions related to general safety

- History of severe allergic or anaphylactic reactions to human, humanized, or murine monoclonal antibodies or to prednisone
- Evidence of serious uncontrolled concomitant cardiovascular, nervous system, pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine (including uncontrolled diabetes mellitus), psychiatric, osteoporosis/osteomalacia, glaucoma, corneal ulcers/injuries, or gastrointestinal (GI) disease
- Current liver disease, as determined by the investigator
- History of diverticulitis or active chronic ulcerative lower GI disease such as Crohn's disease, ulcerative colitis, or other symptomatic lower GI conditions that might predispose a patient to perforations
- Known active current or history of recurrent bacterial, viral, fungal, mycobacterial, or other infections (including but not limited to tuberculosis [TB] and atypical mycobacterial disease, hepatitis B and C, and herpes zoster, but excluding fungal infections of the nail beds)
- Any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks of screening or oral antibiotics within 2 weeks of screening
- Active TB requiring treatment within the previous 3 years. Patients treated for TB with no recurrence within 3 years are eligible
- Untreated latent TB infection (LTBI). Patients should be screened for latent TB and, if positive, treated according to local practice guidelines prior to initiating TCZ treatment. Patients treated for LTBI within 3 years are eligible. Patients with current LTBI are eligible for enrollment one month after initiating treatment for LTBI.
- Primary or secondary immunodeficiency (history of or currently active)
- 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)
- Females of childbearing potential and females who are breastfeeding

- Males of reproductive potential who are not willing to use an effective method of contraception, such as condom, sterilization, or true abstinence throughout study and for a minimum of 6 months after study drug therapy
- History of alcohol, drug, or chemical abuse within 1 year prior to screening

3.b.4. Laboratory exclusions (at screening)

- ALT or AST > 1.5 × upper limit of normal (ULN)
- Total bilirubin > ULN
- Platelet count < 100× 10^9/L (100,000/mm^3)
- Hemoglobin < 85 g/L (8.5 g/dL; 5.3 mmol/L)
- White blood cells < 3.0 × 10^9/L (3000/mm^3)
- Absolute neutrophil count < 1.0 × 10^9/L (1000/mm^3)
- Absolute lymphocyte count < 0.5 × 10^9/L (500/mm^3)

3.b4. Imaging Exclusions (please see imaging protocol for more details)

3.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 at these two locations by their primary provider (subjects' physician), who will review available treatment options, including this protocol. After this step, and if the subject is interested in participating in this study, either Drs. Unizony, Stone, Wallace, or Perugino will go over the informed consent process.

4. SUBJECT ENROLLMENT

Procedures for Obtaining Informed Consent

- Drs. Unizony, Stone, Wallace, or Perugino will review the inform consent with the potential candidates.
- Informed consent may be obtained in written form or through Electronic-Consent (e-Consent) in REDCap. REDCap implements consent forms through an online survey which can be accessed on a computer, mobile phone, or tablet. The e-Consent framework substitutes for a wet signature on a paper document. The e-Consent will include the consenting participants name (and date of birth in some cases) on the final consent form as extra documentation of their identity. The current e-Consent version and e-Consent type will be captured. The values for the fields below will be automatically inserted into the footer of the PDF consent form that the participant will review at the end of the survey, after which that PDF 'hard-copy' will be archived in the File Repository. Upon survey completion, a compact PDF copy of the survey response will be automatically stored in the project's File Repository, from which the archived PDFs can be downloaded at any time.

- The diagnosis of GCA will be confirmed through appropriate evaluations that will include comprehensive history, complete physical examination, and review of the medical records for information pertaining to prior temporal artery biopsy, inflammatory markers, and the results of ultrasound and cross-sectional imaging studies (See **Section 3. Inclusion Criteria**).

- Potential treatment options, including continued glucocorticoid monotherapy, conventional DMARDs (e.g., methotrexate), and TCZ in addition to prednisone tapers longer than 8 weeks, will be discussed.

- Adequate time will be permitted for patients to consider their potential treatment options and ask questions to Drs. Unizony, Stone, Wallace, or Perugino, and to discuss treatment options further with family members, primary care providers, or referring physicians.

5. STUDY PROCEDURES

5.a. Study Overview

This is a single center, open label study that will assess the efficacy and safety of 52 weeks of TCZ plus an 8-week prednisone taper in 30 patients with active GCA. The study will enroll subjects with new onset GCA and subjects with relapsing/refractory GCA because the unmet need for lower prednisone exposure exists in both patient subpopulations. The study will consist of a screening phase (up to 6 weeks), a treatment phase (52 weeks) and a safety follow up phase (4 weeks). The primary efficacy assessment will take place at week 52. The maximum duration of subject participation (including screening) is 62 weeks (See **Table 1**. **Schedule of Events**).

5.b. Study Drugs

5.b.1. Treatment Protocol

All subjects will receive TCZ and prednisone

- Tocilizumab: Prefilled syringes (PFS) containing 162 mg of TCZ (0.9 mL of a 180 mg/mL solution) will be administered by subcutaneous (SC) injection weekly by the patients or caregivers. Patients and caregivers will be trained on how to administer the medication by the study investigators or a designated study staff member during baseline and week 1 visits. TCZ interruptions or withdrawals will be as per the current U.S. product insert (See **Attached Investigator's Brochure**).

- Prednisone taper: Starting at baseline, all patients will receive concomitant prednisone therapy for 8 weeks per predefined taper regimens (See **Table 2**. **Prednisone Taper Regimens**). The initial dose of prednisone will be between 20 mg and 60 mg and will be chosen by the investigators according their best clinical judgment about a dose likely to control the patient's GCA initially, with due consideration given to the patient's disease severity and comorbidities.

- Escape prednisone therapy: Patients who do not achieve remission by week 8 or patients that after achieving remission at any time experience a GCA disease flare before week 52, will be deemed failures for the primary endpoint. These patients will receive a second predefined taper regimen over 8 weeks (See **Table 3**. **Prednisone Escape Therapy**). The initial dose of the prednisone escape therapy will be between 20 mg and 60 mg and will be chosen by the investigators following their best clinical judgment. The initial dose of the prednisone escape therapy may or may not be the same initial dose chosen at baseline. Patients requiring escape therapy will continue to receive TCZ up to week 52.

During the screening phase, prednisone will be used at the discretion of the investigators with the intention of ensuring GCA control.

Any disease flare that occurs after a subject has received prednisone escape therapy will be treated per best clinical judgment.

Short-term prednisone may be administered in addition to the protocol-defined prednisone taper regimen, if deemed necessary for the management of the patient when additional prednisone may be required to prevent or treat adrenal insufficiency or other problems unrelated to GCA (e.g., asthma exacerbation). This will be administered per the medical judgment of the investigator.

Upon trial completion, patients will be treated per best clinical judgment.

5.b.2. Concomitant Medications

Anti-platelet therapy. Subjects will be treated with aspirin 81 mg daily at the discretion of the investigators.

Glucocorticoid-induced osteopenia/osteoporosis prevention and treatment. All the subjects will receive oral calcium (1200-1500 mg daily), 25-hydroxy vitamin D supplementation (800-1000 IU daily) and bisphosphonate therapy (e.g., alendronate 70 mg weekly or zolendronate 5 mg annually) at the discretion of the investigators for the prevention and/or treatment of glucocorticoid-induced osteopenia/osteoporosis.

5.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 or electronic informed consent.
- ☐ Subject demography.
- ☐ Medical and surgical history.
- ☐ GCA history evaluation (date of disease diagnosis, date of temporal artery biopsy, date of vascular imaging, disease signs and symptoms, prior GCA treatments, etc).
- ☐ Inclusion/exclusion criteria.
- ☐ Concomitant medications.
- ☐ Assessment of signs and symptoms of GCA/PMR activity.
- ☐ Vital signs and physical exam.
- ☐ Screening laboratory tests including CBC, creatinine, BUN, AST, ALT, total bilirubin, alkaline phosphatase, ESR, CRP, urinalysis, HCV antibody, HBV surface antigen, and HBV anti core antibodies.
    - CBC, creatinine, BUN, AST, ALT, total bilirubin, alkaline phosphatase, ESR, CRP, urinalysis not required if completed within 10 days prior to screening. If abnormal, it will be repeated at screening visit)
    - HCV antibody, HBV surface antigen, and HBV anti core antibodies. Not required if completed within 30 days prior to screening
- ☐ Chest x-ray (Not required if completed within 30 days prior to screening. If abnormal, it will be repeated at screening visit)

- 12-lead electrocardiogram (ECG)
  - Not required if collected within 30 days prior to screening visit unless clinically indicated
- 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 quantiferon test, T spot test, or PPD test
  - (Not required if completed within 30 days prior to screening. If abnormal, it will be repeated at screening visit)
- Blood samples for mechanistic studies.

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

- **Baseline through 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 weeks 1, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52.

TCZ will be administered in site by the investigators or designated trained personnel at baseline and week 1 visits. During baseline and week 1 visits, the patients and/or caregivers will be trained on how to administer the TCZ injections after week 1. In addition, patients will follow a pre-specified prednisone taper (See **Table 2**. **Prednisone Taper Regimens**).

During Baseline through week 52 visit the following procedures/assessments 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.
- TCZ administration (baseline and week 1).
- Laboratories including CBC, creatinine, BUN, AST, ALT, total bilirubin, alkaline phosphatase, ESR, CRP, and lipid profile.
- Patient reported outcomes (PROs) (see below).
- Glucocorticoid toxicity index (GTI) [12].
- Blood samples for mechanistic studies.
- Skull base to mid-thigh positron emission tomography/magnetic resonance (PET/MR) (±4-week time window is allowed at baseline visit and week 52).
  - pregnant or breastfeeding (a quantitative serum hCG pregnancy test is required before the subject can participate)
- Bone density assessment by DXA (dual-energy x-ray absorptiometry) (±2-week time window is allowed at baseline visit and week 52). (Baseline and Week 52 only)
  - Bone density assessment is not required if already available within 30 days prior to screening visit.

The main efficacy and safety endpoints will be measured at 52 weeks (See **Section 6.a. Study Endpoints**)

Phone Call Assessments

Phone call assessments will be completed by the study investigator in case a subject cannot attend to a study visit due to unforeseen circumstances beyond the research team control (e.g., snow storm). During a phone call, the investigator will assess adverse events (AEs), concomitant medications, and symptoms of GCA disease activity (i.e., flare). In case of any concern (e.g., serious AE or GCA flare), recommendations on how to proceed will be given over the phone. In case there is suspicion for a serious AE or a GCA flare that require immediate attention, the patient will be instructed to seek that attention at the nearest hospital immediately. In case there is suspicion for an AE or a GCA flare that do not require immediate attention, the patient will be set up for an unscheduled study visit on a timely manner.

Phone call assessments will be completed if all the following conditions are met:
No more than 2 phone call assessments occur in each subject during the entire study period.
No phone call assessments may replace two consecutive visits.
No phone call assessment may replace baseline visit, week 1 visit, and week 52 visit.
If a phone call assessment should replace a visit that require safety labs including CBC and blood chemistry (i.e., weeks 4, 8, 16, 24, 32, 40, and 48), those safety labs will be completed locally within the timeframe required in the protocol (see Table 1. Schedule of events)
If a phone call assessment was to replace week 24, which requires patient reported outcome questionnaires, those questionnaires will be completed over the phone by the PI or the study coordinator within the timeframe required in the protocol (see Table 1. Schedule of events)

- **Safety follow-up visit**

The participants will undergo a safety follow up visit at week 56.

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.
- Laboratories including CBC, creatinine, BUN, AST, ALT, total bilirubin, alkaline phosphatase, ESR, and CRP.

5.d. Patient-Reported Outcomes

PRO data will be elicited from the patients at several time points. The PRO instruments will be provided as paper-based documents. They will be distributed by the investigator staff and completed by the patient. Patients will use visual analogue scale (VAS) to report the Patient Global Assessment of disease activity (PGA). Visually impaired

patients unable to complete the VAS will be asked to give the score verbally. Other PROs will include the 36-Item Short Form Health Survey (SF-36), the Euro QOL-5D-5L (EQ-5D-5L) health

questionnaire, and the Function Assessment of Chronic Illness Therapy (FACIT)-Fatigue score. The SF-36 is a multipurpose, short-form health survey with 36 questions. It yields 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. The EQ-5D-5L health questionnaire is a generic, preference-based health utility measure with questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression that are used to build a composite of the patient's health status. The FACIT-Fatigue score is a 13-item fatigue questionnaire with patients requested to score each on a 5-point scale.

5.e. 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). Please also refer to **Appendix 1. Mandatory Genentech Safety Language.**

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

Contingency Plan Related to the COVID-19 Pandemic.
In view of the COVID-19 pandemic we have modified the schedule of assessments in order to minimize the exposure of patients and study personnel to COVID-19 (see Table 1. Schedule of events). The modifications proposed take in consideration the potential morbidity associated with GCA and the study treatment and will unlikely impact the safety of patients.

Screening visit, baseline visit, week 24 visit and week 52 visit will require an in-person evaluation in the clinic for the subject to have a physical exam including vital signs. During baseline visit the patients and/or caregivers will be trained on how to administer the TCZ injections and will receive the first TCZ injection by the investigators or designated trained personnel. In order minimize the time of the subjects in the clinic, other procedures may be completed via telemedicine. These procedures may include inform consent, I/E criteria, demographics and medical history, GCA history evaluation, AE assessment, concomitant medications, and assessment of symptoms of GCA activity (i.e., flare).

All other visits will be done primarily via telemedicine until the medical and non-medical personnel schedules in the MGH Rheumatology Division return to baseline. During the telemedicine visits the study investigator will assess AEs, concomitant medications, and symptoms of GCA disease activity (i.e., flare). In case of any concern (e.g., serious AE or GCA flare), recommendations on how to proceed will be given. In case there is suspicion for a serious AE or a GCA flare that require immediate attention, the patient will be instructed to seek

that attention at the nearest hospital immediately. In case there is suspicion for an AE or a GCA flare that do not require immediate attention, the patient will be set up for an unscheduled study visit in-person at MGH on a timely manner.

Laboratories, CXR and EKG will continue to be done as per the original protocol regardless of whether the subject has an in-person or a telemedicine visit. The baseline and week 52 DEXA scans and PET/MRs will be done according to the availability and internal policies of the MGH bone density center (DEXA scan) and the Martinos Center (PET/MR).

All the assessments completed by the study coordinators (e.g., PROs, drug accountability) will be done remotely.

The study medication (TCZ) will be shipped to the patients.

The study procedures will be done completely in the clinic as the as the MGH Rheumatology Division returns to normal operations and full capacity.

6. BIOSTATISTICAL ANALYSIS

Signs and symptoms of GCA activity, compliance with the prednisone taper, cumulative prednisone dosing, 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.

6.a. Study Endpoints

- **Primary efficacy endpoint:**

1) Proportion of patients in sustained remission at 52 weeks.

The definition of sustained 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 (See **Table 2**. **Prednisone Taper Regimens**).

- Absence of disease flare (relapse) since the induction of remission by week 8.

Definition of flare: Re-appearance of unequivocal signs or symptoms of active GCA or PMR (with or without elevation of ESR and/or CRP) or the elevation of the ESR and/or CRP that is thought to be due to active GCA and that requires increase in the prednisone dose or re-initiation of prednisone treatment.

- **Secondary efficacy endpoints**

1) Proportion of patients in remission at 24 weeks.
2) Time to GCA disease flare after remission.
3) Number of disease flares at 24 and 52 weeks.
4) Annualized flare rate.
5) Cumulative prednisone dose at 52 weeks.
6) Cumulative glucocorticoid toxicity index (GTI).
7) HRQoL based on PROs including SF-36, PGA, FACIT-Fatigue, and EQ-5D-5L scores.

- **Safety endpoints**

1) The number, nature and severity of adverse events (AE) at 24 and 52 weeks.
2) The number, nature and severity of serious AE (SAE) at 24 and 52 weeks.

- **Exploratory endpoints**

1) To assess the effects of TCZ in combination with an 8-week prednisone taper in the aorta and main aortic branches measured by PET/MR imaging at baseline and week 52.
2) To complete mechanistic studies to gain insight into the pathogenesis of GCA and discover biomarkers of disease activity and risk of disease relapse.

6.b. Statistical Methods

Descriptive statistics and two-sided 95% confidence intervals will be calculated to assist the interpretation of efficacy and safety outcomes. Continuous data will be summarized using means, medians, standard deviations, ranges and interquartile ranges, where appropriate. Categorical data will be summarized as numbers and corresponding percentages. We expect missing data to be minimal because patients will be closely followed. However, in case that missingness is non-ignorable, we will use appropriate statistical methods (e.g., multiple imputation).

6.b.1. Analysis of the Primary, Secondary and Safety Endpoints

For the analysis of the primary endpoint, key secondary endpoints (e.g., cumulative prednisone dose, time to flare, and HRQoL), and safety endpoints, we will utilize as historical controls, the group of patients assigned to

TCZ in the GiACTA trial. Of note, GiACTA [3] used eligibility criteria and definitions of disease remission and relapse (flare) equivalent to the proposed study. In GiACTA [3], the remission rates in patients receiving TCZ weekly and every other week were 56% and 53%, respectively, and the cumulative prednisone dose by week 52 associated with these two arms was 1862 mg.

The analysis of the proportion of patients experiencing at least 1 flare by week 52 (primary endpoint) will be done using multivariable logistic regression adjusted for relevant covariates. The cumulative prednisone dose by week 52 will be compared with multivariable linear regression. Time to flare will be compared using multivariable-adjusted Cox proportional hazards models. To compare HRQoL data we will use multivariable mixed effects models. The number of total adverse events and adverse events of grade 3 or higher will be compared with multivariable-adjusted Poisson regression.

We will determine the relationships between the moving average of the GTI score and different HRQoL PROs using mixed effects regression where the PRO measure score is the outcome and the GTI score is the exposure. We will also assess for an association between the cumulative glucocorticoid dose and the PRO scores using mixed effects regression.

6.b.2. Analysis of the Exploratory Endpoints

Positron emission tomography/magnetic resonance

The arterial uptake of ^{18}fluorine-2-deoxy-D-glucose (FDG) will be determined via a skull base to mid-thigh PET/MR at baseline and week 52. The ascending aorta, aortic arch, descending aorta, abdominal aorta, carotid artery and subclavian artery territories will be assessed by maximum standardized uptake values (mSUV) measurement. For each territory, we will calculate average, most diseased segment (MDS) and most diseased slice (hottest spot) mSUVs. In addition, for each territory we will calculate target background ratios (TBR) using as background the vena cava (aortic measures) and the jugular veins (supra-aortic measures) (**Figure 1**). Changes in FDG between baseline and week 52 will be assessed using univariable (e.g., Wilcoxon signed rank test or paired Student's t-test) and multivariable (e.g., multilevel models) methods as appropriate

Mass spectrometry

We will quantitatively map the plasma proteins of patients at baseline and either (**1**) during the first disease flare or (**2**) at week 52 for the patients who do not develop a disease relapse. We will use tandem mass tag (TMT) technology for multiplexed proteomics of the PLASMA samples [13, 14]. The measurements will be done on an Orbitrap Lumos mass spectrometer using the SPS-MS3 method. Samples will be fractionated off-line using high pH reversed-phase (HPRP) chromatography, and twelve fractions will be analyzed on the mass spectrometer. Commonly about 1000 proteins can be quantified from one sample using this approach. A global comparison of the proteome changes will be done using hierarchical clustering and principal component

analysis. The Student's t-test followed by multiple-hypothesis testing using the Benjamini-Hochberg procedure will be applied to identify plasma proteins with significant concentration differences between the status of active disease and disease remission. Similar methodology will be used to identify proteins with significant concentration differences at baseline between the group of patients with and without disease relapse by week 52. Univariable comparisons will be followed by multivariable analyses to include confounders of interest.

7. RISKS AND DISCOMFORTS

Except for a shorter prednisone taper, which is experimental, all the procedures performed in this study are consistent with the standard of care for patients with GCA.

7.a. Complications of Subcutaneous Medication Administration

The injection of SC medications is associated with a mild degree of discomfort at the injection site for a short period. 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.

7.b. Risks Associated with TCZ Use

- **Infection.** Patients treated with TCZ are at increased risk for developing serious infections that may lead to hospitalization or death, including tuberculosis (TB), bacterial, invasive fungal, viral, or other opportunistic infections. The overall safety profile of TCZ in GCA patients (defined in the GiACTA trial) was comparable to the one observed in rheumatoid arthritis (RA) patients, except that there was an overall higher incidence of infections in GCA patients relative to RA patients. The rate of infections was 200.2 per 100 patient-years in the TCZ QW group and 160.2 per 100 patient-years in the TCZ Q2W group, as compared to 156.0 per 100 patient-years in the PBO+26 and 210.2 per 100 patient-years in the PBO+52 groups. The rate of serious infections was 9.7 per 100 patient-years in the TCZ QW group and 4.4 per 100 patient-years in the TCZ Q2W group, as compared to 4.2 per 100 patient-years in the PBO+26 and 12.5 per 100 patient-years in the PBO+52 groups.

- **Hypersensitivity reactions.** Hypersensitivity reactions, including anaphylaxis, have been reported in association with TCZ and anaphylactic events with a fatal outcome have been reported with intravenous (IV) infusion of TCZ. Anaphylaxis and other hypersensitivity reactions that required treatment discontinuation were reported in 0.1% (3 out of 2644) of patients in the 6-month controlled trials of IV TCZ, 0.2% (8 out of 4009) of patients in the IV all-exposure RA population, 0.7% (8 out of 1068) in the SC 6-month controlled RA trials, and in 0.7% (10 out of 1465) of patients in the SC all-exposure population. In the systemic juvenile inflammatory arthritis (JIA) controlled trial with IV TCZ, 1 out of 112 patients (0.9%) experienced hypersensitivity reactions that required treatment discontinuation. In the polyarticular JIA controlled trial with IV TCZ, 0 out of 188 patients (0%) in the TCZ all-exposure population experienced hypersensitivity reactions that required treatment discontinuation.

- **Neutropenia.** Decreases in neutrophil counts have been observed following treatment with TCZ.

- **Thrombocytopenia.** Decreases in platelet counts have been observed following treatment with TCZ.

- **Elevated liver enzymes.** Transaminase elevations have been observed following treatment with TCZ. These elevations did not result in apparent permanent or clinically evident hepatic injury in clinical trials.

- **Lipid abnormalities.** Increases in lipid parameters such as total cholesterol, triglycerides, LDL cholesterols, and/or HDL cholesterol has been observed following treatment with TCZ.

- **Gastrointestinal (GI) perforations.** Events of GI perforation have been reported in clinical trials, primarily as complications of diverticulitis in RA patients. No GI perforations were reported in GCA clinical trials.

- **Immunosuppression and potential risk of malignancy.** Although no imbalance of malignancies was observed in controlled clinical trials of TCZ, malignancies have been identified as a concern for other immunosuppressive agents.

- **Demyelinating disorders.** The impact of treatment with TCZ on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies.

- **Live vaccines.** Vaccination with live vaccines may lead to infection in patients under immunosuppressive therapy including TCZ.

- **Pregnancy.** The limited available data with TCZ in pregnant women are not sufficient to determine whether there is a drug-associated risk for major birth defects and miscarriage.

Additional information on TCZ safety can be found in the attached **Investigator's Brochure**.

7.c. Risks Associated with GCA Relapse

Patients enrolled in this study may be at risk of disease relapse. Disease relapses are frequent in GCA patients. Patients treated with prednisone monotherapy relapse within 24-48 months in 60-85% of the cases depending on the duration of prednisone use [3, 15]. Patients treated with TCZ and 6 months of prednisone relapse in approximately 20% of the cases within 1 year [3]. Of note, the incidence of permanent vision loss is

significantly low in GCA patients that have received treatment [2] and no cases of permanent vision loss occurred in the GiACTA study [3].

7.d. Loss of Confidentiality

Risks to subjects include loss of confidentiality resulting from access to electronic health record data**.**

8. POTENTIAL BENEFITS

8.a. Potential Benefits to Subjects

The subjects may benefit from using less amounts of prednisone and therefore having less risk of prednisone related toxicity (e.g., hypertension, diabetes, osteoporosis, gastrointestinal bleeding, glaucoma, cataracts, other).

8.b. Potential Benefits to Society

TCZ plus a short course of prednisone may prove to be effective in controlling GCA activity. If this is the case, this protocol may increase the quality of life of the patients and reduce the costs of treating glucocorticoid- related morbidity. Positive results in this pilot study will support the conduction of a larger clinical study.

9. MONITORING AND QUALITY ASSURANCE

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

9.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.

9.b. Criteria for Dropping a Subject from the Study

- The occurrence of any malignancy.
- The occurrence of major cardiovascular events (e.g., stroke, acute coronary syndrome).
- The occurrence of a severe hypersensitivity reaction, (e.g., anaphylaxis, bronchospasm, angioedema).
- The occurrence of a serious, systemic, opportunistic, chronic/recurrent or blood-borne infection.
- Pregnancy.
- The occurrence of any marked laboratory abnormality including hemoglobin < 8 gr/dL, platelets < 50/mm^3, absolute neutrophil count < 0.5 X 10^9/L (500/mm^3), absolute lymphocyte count < 0.5 X 10^9/L (500/mm^3), serum creatinine > 2 mg/dL, ALT or AST elevation > 5 x ULN, and ALT or AST elevation > 3 x ULN and at least one of the following: total bilirubin > 2 x ULN, international normalized ratio (INR) > 1.5, liver

alkaline phosphatase > 2 x ULN or presence of worsening fatigue, nausea, vomiting, fever, rash, or eosinophilia.

9.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 follow the pre-specified prednisone taper.
- Ability of maintain disease remission off prednisone.
- Glucocorticoid-sparing effects by analyzing the cumulative prednisone dose and the incidence of glucocorticoid-related side effects.

9.d. Adverse Event Reporting Guidelines:

Adverse events and unanticipated problems involving risks to subjects or others will be reported to the Partners Human Research Committee (PHRC) in accordance with PHRC adverse event and unanticipated problems reporting guidelines. Adverse events and unanticipated problems involving risks to subjects or others will also be reported to Genentech following the guidelines described in **Appendix 1. Mandatory Genentech Safety Language.** Genentech as the Marketing Authorization Holder will be responsible for the reporting of individual case safety reports from the study to the regulatory authority in compliance with applicable regulations.

9.e. Management of Specific Adverse Events

- **Complications of subcutaneous medication administration.** To minimize this risk, we have experienced nurses who are experts in the administration of subcutaneous medications commonly used in the rheumatology practice.

- **Opportunistic infections and serious infections.** Investigators will exercise caution when considering the use of TCZ in patients with a history of recurring infections or with underlying conditions (e.g., diabetes mellitus), which may predispose patients to infections. Infection including LTBI will be ruled out during the screening process. During the study, TCZ will not be administered to patients with active infection. The effects of TCZ on CRP, neutrophils, and the signs and symptoms of infection will be considered when evaluating a patient for potential infection. Although rarely reported within the TCZ clinical trial programs in RA and GCA based on the exclusion criteria at study entry, reactivation of viral and other serious infections (e.g., TB) has been observed with biologic therapies for RA and GCA, including TCZ. Vigilance for timely detection of serious infection will be exercised for patients receiving TCZ as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reaction. Patients will be instructed to contact the investigators immediately when any symptoms suggesting infection appear, to ensure rapid evaluation and appropriate treatment. If a patient develops a serious infection, TCZ will be interrupted until the infection is controlled. The investigator will consider the benefits and risks to the patient before resuming treatment.

- **Gastrointestinal perforations.** Diverticulitis, or chronic ulcerative lower GI disease such as Crohn's disease, ulcerative colitis, or other chronic lower GI conditions might predispose patients to perforations. Therefore, patients with these conditions will be excluded from this study. Timely diagnosis and appropriate treatment may reduce the potential for complications of diverticular disease and thus, reduce the risk of GI perforations. Thus, patients will be made aware of the symptomatology potentially indicative of diverticular disease and instructed to alert the investigators as soon as possible if these symptoms arise. If patients develop GI perforations, TCZ will be discontinued permanently.

- **Demyelinating disorders.** Patients will be closely monitored for signs and symptoms potentially indicative of demyelinating disorders. Investigators will exercise caution when considering the use of TCZ in patients with preexisting or recent-onset demyelinating disorders. Treatment with TCZ will be interrupted during assessment of a potential demyelination event and be resumed only if the benefit/risk assessment of continuing study drug is favorable.

- **Hematologic abnormalities and bleeding events.** Patients with absolute neutrophil counts (ANC) less than 1,000 per mm^3 will not be eligible. Patients with platelets less than 100,000 per mm^3 will not be eligible. The risk mitigation strategies for neutropenia and thrombocytopenia are summarized in **Table 4** and **Table 5**, respectively.

- **Elevated liver enzymes.** TCZ will be discontinued if ALT or AST elevation > 5 x ULN, and ALT or AST elevation > 3 x ULN and at least one of the following: total bilirubin > 2 x ULN, international normalized ratio (INR) > 1.5, liver alkaline phosphatase > 2 x ULN or presence of worsening fatigue, nausea, vomiting, fever, rash, or eosinophilia. Patients active hepatic disease or hepatic impairment (including elevated transaminases ALT or AST >1.5x ULN) will not be enrolled in this trial. The risk mitigation strategies for patients with elevated hepatic enzymes are presented in **Table 6.**

- **Cardiovascular events and elevated lipids.** Patients with GCA are at increased risk for cardiovascular disorders; therefore, risk factors for cardiovascular disease (e.g., hypertension, hyperlipidemia) will be managed as part of their standard of care. For patients with LDL cholesterol levels ≥ 160 mg/dL, it is strongly recommended that investigators advise therapeutic lifestyle changes that may include initiation of lipid-lowering agents. Lipid-lowering agents should also be considered for patients with lower LDL cholesterol levels as part of their therapeutic lifestyle changes, depending on their overall risk as defined in NCEP ATP III (2002) or other national guidelines.

- **Malignancies.** The impact of treatment with TCZ on the development of malignancies is not known, but malignancies were observed in clinical studies with TCZ. TCZ is an immunosuppressant, and treatment with

immunosuppressants may result in an increased risk of malignancies. Patients with a history of malignancy (except for local basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix uteri that have been excised and cured) within 5 years of randomization will be excluded. TCZ administration will be discontinued for patients with malignancies.

- **Hypersensitivity and anaphylaxis after TCZ injection.** A systemic injection reaction is defined as an adverse event occurring during and within 24 hours after the SC injection of TCZ. This may include hypersensitivity reactions or anaphylactic reactions. The patients enrolled in this trial will be advised to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction. Signs of a possible hypersensitivity reaction include, but are not limited to the following: Fever, chills, pruritus, urticaria, angioedema, and skin rash. If anaphylaxis or other hypersensitivity reaction occurs, TCZ administration will be stopped immediately and discontinued permanently. TCZ will not be administered to patients with known hypersensitivity to TCZ. Subjects with a history of hypersensitivity reactions to monoclonal antibodies will be excluded from the trial.

- **Vaccinations.** The use of live vaccines will be prohibited during the study.

- **Risks in women of childbearing potential.** TCZ is not recommended during pregnancy or in women of childbearing potential not using effective contraception. Women of childbearing potential will be advised to avoid becoming pregnant while receiving treatment with TCZ and will be required by the protocol to use two effective forms of contraception.

- **GCA relapses.** Patients enrolled in this clinical trial will be followed closely and will have easy access to the investigators in case of disease relapse. In addition, patients will be instructed to start high doses of prednisone without delay and present emergently to the nearest hospital in case of worrisome visual symptoms including amaurosis, amaurosis fugax, episodic blurry vision or diplopia.

- **Risk of loss of confidentiality**. Each subject will be assigned a unique study number that does not include identifiers. The study code will be kept under lock and key of the site Principal Investigator's office. Strict confidentiality will be maintained when reviewing subjects' medical records. In all cases, access to protected health information will be limited to the fewest number of research staff required to complete a given trial aim. The data for the study will be stored on an SQL server on a shared drive that is password- protected and accessible only to study collaborators. All collaborators are CITI-certified and HIPAA- compliant. All workstations at all three participating sites are password protected and have updated antivirus software. Data will be stored behind the Partners firewall on the Partners server, which will be backed up nightly by the Partners Information Systems department to guard against data loss or corruption

Appendix 1. Mandatory Genentech Safety Language

SAFETY LANGUAGE INCLUDED IN THIS DOCUMENT IS MANDATORY AND MUST BE INCLUDED IN PROTOCOL OR A SEPARATE SAFETY DATA EXCHANGE AGREEMENT (SDEA) SHOULD BE CREATED

SAFETY REPORTING OF ADVERSE EVENTS

ASSESSMENT OF SAFETY

Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) per protocol. This includes all events of death, and any study specific issue of concern.

Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with giant cell arteritis (GCA) that were not present prior to the AE reporting period.
- Complications that occur because of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Serious Adverse Events

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.

• It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

Adverse Event Reporting Period

The study period during which AEs and SAEs as described in section j where the patient has been exposed to Genentech product must be reported Reporting period begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment (Modify statement depending up on section g).

Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the tocilizumab (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of the tocilizumab, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the tocilizumab; and/or the AE abates or resolves upon discontinuation of the tocilizumab or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the AE has an etiology other than the tocilizumab (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to tocilizumab administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section I), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

c. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

d. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

e. Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5 .0 Update current versions) will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age appropriate instrumental activities of daily living a
3	Severe or medically significant, but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living b,c
4	Life-threatening consequences or urgent intervention indicated d
5	Death related to adverse event d

NCI CTCAE □ National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v{X}.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a) Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b) Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

c) If an event is assessed as a "significant medical event," it must be reported as a serious adverse event

d) Grade 4 and 5 events must be reported as serious adverse events

Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated d
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v {5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event
d. Grade 4 and 5 events must be reported as serious adverse events

f. Pregnancy

If a female subject becomes pregnant while receiving the study drug or within 90 days after the last dose of study drug, or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug or within 90 days after the last dose of study drug, a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.

g. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior tocilizumab exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject [add if applicable-including pregnancy occurring in the partner of a male study subject] who participated in the study, this should be reported as an SAE adequately to Genentech drug Safety during follow up period

h. Case Transmission Verification of Single Case Reports

The Sponsor agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via Dr Unizony's staff emailing Genentech a Quarterly line-listing documenting single case reports sent by Dr Unizony's staff to Genentech in the preceding time period. The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The Sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by PI's staff to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech

i. AEs of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
    - Treatment-emergent ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN
    - Treatment-emergent ALT or AST > 3 × ULN in combination with clinical jaundice

The Tocilizumab Events of Special Interest are:

Adverse events of special interest for this study include the following:

- Infection
- Drug-induced liver injury
- Neutropenia
- Thrombocytopenia
- Bowel perforation
- Suspected transmission of an infectious agent by the study drug, as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

j. Exchange OF SINGLE CASE REPORTS

The PI will track all protocol-defined AE and pregnancy reports originating from the Study for the Product

Investigators must report all Adverse Events/ Serious Adverse events (SAEs), AEs of Special Interest (AESIs) pregnancy reports and special situation reports and product complaint (if applicable) adequately to Genentech within the timelines described below. The completed MedWatch or CIOMS I form or Genentech approved reporting forms should be faxed immediately upon completion to Genentech Drug Safety at:

All protocol-defined AEs, SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints *with* an AE should be sent to:
Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

All Product Complaints *without* an AE should be sent to:

Email: kaiseraugst.global_impcomplaint_management@roche.com

Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request

Serious adverse events (SAEs), pregnancy reports (including pregnancy occurring in the partner of a male study subject) AEs of special interest (AESIs) and Special Situation Reports, where the patient has been exposed to the Genentech Product, will be sent on a MedWatch form or CIOMS I form or on Genentech approved reporting forms to Genentech Drug Safety. Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

- SADRs

Serious AE reports that are related to the Product shall be transmitted to Genentech within fifteen (15) calendar days of the awareness date.

- Other SAEs

Serious AE reports that are unrelated to the Product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

- AESIs

AESIs shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

- Pregnancy reports

While such reports are not serious AEs or Adverse drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy (including pregnancy occurring in the partner of a male study subject), where the fetus may have been exposed to the Product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 30 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to Genentech within thirty (30) calendar days of the awareness date.

Special situation reports

In addition to all SAEs, pregnancy reports and AESIs, the following Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech within thirty (30) calendar days:

- Data related to the Product usage during pregnancy or breastfeeding
- Data related to overdose, abuse, off-label use, misuse, inadvertent/erroneous administration, medication error (including potentially exposed in case of medication errors or intercepted medication errors) or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol
- Lack of therapeutic efficacy
- Drug interaction
- Use of a Medicinal Product in a Pediatric and Elderly population (in addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population)

Occasionally Genentech may contact the reporter for additional information, clarification, or status of the patient for whom an adverse event was reported

Product Complaint Guidelines

WHAT IS A PRODUCT COMPLAINT?

A product complaint is any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness or performance of a product after it has been released and distributed to the commercial market or clinical trial.

HOW DO I FILE A COMPLAINT?

For all Investigator Initiated Studies (interventional and non-interventional): Product Complaints with an AE (adverse event) should be reported via email/fax to: usds_aereporting-d@gene.com OR 650-238-6067

Product Complaints without an AE (adverse event) should be reported via email to:
- For Interventional Investigator Initiated Studies: kaiseraugst.global_impcomplaint_management@roche.com
- For Non-Interventional Investigator Initiated Studies: us-acmo-d@gene.com

All complaints must be filed within 1 business day for pre-approved products and 15 calendar days for approved products. Complaints can be reported using a Medwatch, CIOMS or any Genentech-approved reporting form (same as SAEs, AESI etc.).

REPORTING REQUIREMENTS FOR ADVERSE EVENTS ORIGINATING FROM PATIENT REPORTED OUTCOMES

Although sites are not expected to review the PRO data, if physician/study personnel become aware of a potential adverse event during site review of the PRO questionnaire data, he/she will determine whether the criteria for an adverse event have been met and, if so, these must be reported using the Adverse Event and Special Situation Reporting Form or MedWatch form.

MEDWATCH 3500A REPORTING GUIDELINES

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

<u>Follow-Up Information</u>

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

- MedWatch 3500A (Mandatory Reporting) form is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

Reporting to Regulatory Authorities, Ethics Committees and Investigators

Genentech as the Marketing Authorization Holder will be responsible for the reporting of individual case safety reports from the study to the regulatory authority in compliance with applicable regulations

Genentech will be responsible for the expedited reporting of safety reports originating from the Study to the EMA through Eudravigilance Clinical Trial Module (EVCTM).

Dr Unizony will be responsible for the distribution of safety information to its own investigators, where relevant. Dr Unizony will be responsible for the distribution of safety information to Site IRB:

Partners Human Research Committee

399 Revolution Drive

Suite # 710

Somerville MA, 02145

857-282-1900

For questions related to safety reporting, please contact Genentech/Roche Drug Safety:

Tel: (888) 835-2555

Fax: (650) 225-4682 or (650) 225-4630

AGGREGATE REPORTS

IND ANNUAL REPORT

All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech

Copies of such reports should be emailed to Genentech at: Genentech Drug Safety CTV mail box: ctvist_drugsafety@gene.com

Other Reports

Dr Unizony will forward a copy of the Final Study Report to Genentech/Roche upon completion of the Study.

STUDY CLOSE-OUT

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech/Roche. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech/Roche. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

actemra-gsur@gene.com

And to Genentech Drug Safety CTV oversight mail box at: ctvist_drugsafety@gene.com

QUERIES

Queries related to the Study will be answered by Dr Unizony However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech/Roche shall have the final say and control over safety queries relating to the Product. Dr Unizony agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech/Roche.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

SAFETY CRISIS MANAGEMENT

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Product is used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.

The Parties agree that Genentech/Roche shall have the final say and control over safety crisis management issues relating to the Product. Dr Unizony agrees that it shall not answer such queries from media and other sources relating to the Product but shall redirect such queries to Genentech/Roche.

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET Genentech Supported Research

AE / SAE FAX No: (650) 238-6067

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	**[DD] / [MON] / [YY]**
Follow-up Report Date	**[DD] / [MON] / [YY]**

Subject Initials Enter a dash if patient has no middle name)	_____

SAE or Safety Reporting questions, contact Genentech Drug Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

10. REFERENCES

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2. Salvarani C, Cantini F, Hunder GG: **Polymyalgia rheumatica and giant-cell arteritis**. *Lancet* 2008, **372**(9634):234-245.
3. Stone JH, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, Brouwer E, Cid MC, Dasgupta B, Rech J *et al*: **Trial of Tocilizumab in Giant-Cell Arteritis**. *N Engl J Med* 2017, **377**(4):317-328.
4. Strand V, Dimonaco S, Tuckwell K, Klearman M, Collinson N, Stone J: **Health-Related Quality of Life in Patients with Giant Cell Arteritis Treated with Tocilizumab in a Randomized Controlled Phase 3 Trial [Abstract]**. *Arthritis Rheumatol* 2017, **69 (suppl 10)**.
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Table 1. Schedule of events

EVALUATION	STUDY VISIT (week +/- 7 days)																	
	SC	**BL**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56/ EW[8, 9]**	**flare**
Informed Consent (remote)	X																	
I/E Criteria (remote)	X																	
Demographics and medical history (remote)	X																	
GCA history evaluation[1]	X																	
AE Assessment (remote)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Con. Meds (remote)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
***Evaluation for LTBI[3] (remote)**	X																	
TCZ Administration		X	X															
Signs/symptoms of GCA activity[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
***ESR (onsite)**	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
***CRP (onsite)**	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
***Blood Chemistry[5] (onsite)**	X		X	X	X		X		X		X		X		X	X	X	X
***CBC (onsite)**	X		X	X	X		X		X		X		X		X	X	X	X

Fasting lipid profile[6] (onsite)		X					X		X		X					X		
EVALUATION	**STUDY VISIT (week +/- 7 days)**																	
	SC	**BL**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56/EW[8, 9]**	**flare**
*HBsAg, anti-HBc Ab and anti-HCV Ab (onsite)	**X**																	
UA (onsite)	**X**																	
*CXR (onsite)	**X**																	
HbA1c (onsite)		**X**							**X**							**X**		
Pregnancy test7 (onsite)	**X**																	
DNA10	**X**																	
Serum/plasma10	**X**		**X**		**X**				**X**							**X**		**X**
*EKG (onsite)	**X**																	
PROs11 (remote)		**X**							**X**							**X**		**X**
GTI12		**X**							**X**							**X**		
Imaging13																**X**		

STAT quantitative serum hCG pregnancy		**x**														**x**		

1. Including date of diagnosis, date of temporal artery biopsy, date of prednisone initiation, and initial prednisone dose.
2. Complete examination including assessments of the skin, head, eyes, throat, neck, lungs, heart, abdomen, lymph nodes, and musculoskeletal (MSK) system.
3. Interferon gamma releasing assay (IGRA) such as quantiferon gold or T spot test. Alternatively, a PPD test can be performed.
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, triglycerides.
7. If last menstrual period within 12 months of screening visit.
8. Week 56 visit will be a safety follow up visit. 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 4 weeks after the visit preceding the withdrawal.

10. Plasma for mass spectrometry will be collected at screening and week 52 or during disease flare. DNA and serum will be obtained at several timepoints for mechanistic studies TBD.

11. PROs including patient VAS, EQ-5D-5L, SF-36 and FACIT-fatigue score.

12. Glucocorticoid toxicity index (GTI).

13. Skull base to mid-thigh positron emission tomography/magnetic resonance (PET/MR) (±4-week time window is allowed at baseline visit and week 52). Bone density assessment by DXA (dual-energy x-ray absorptiometry) (±2-week time window is allowed at baseline visit and week 52).

*Note: The following will not be required/collected at screening unless abnormal:

- Clinical labs (if collected 10 days prior to screening: CBC, creatinine, BUN, AST, ALT, total bilirubin, alkaline phosphatase, ESR, CRP, urinalysis
- Serology profile (30 days prior to screening): TB and hepatitis panel
- CXR imaging: Not required if collected within 30 days prior to screening visit
- EKG: Not required if collected within 30 days prior to screening visit unless cardiovascular risk is indicated.

*Note: Phone call Assessments: If for unforeseen circumstances a subject cannot come to one or two non-consecutive study visit (excluding baseline, week 1 and week 52), the study investigator will contact the subject, to see if you are taking the study drug correctly and to collect information about his orher health and well-being.
SC = screening; 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 surface 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; phys. = physician

Table 2. Prednisone Taper Regimens

Week	Initial prednisone dose (mg)*				
1	60	50	40	30	20
2	50	40	30	20	20
3	40	30	20	15	15
4	30	20	15	15	15
5	20	15	15	10	10
6	15	10	10	10	10
7	10	5	5	5	5
8	5	2.5	2.5	2.5	2.5
cumulative dose (mg)	1610	1207.5	962.5	752.5	682.5

(*) 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.

Table 3. Prednisone Escape Therapy

Week	Initial prednisone dose (mg)*				
1	60	50	40	30	20
2	50	40	30	20	20
3	40	30	20	15	15
4	30	20	15	15	15
5	20	15	15	10	10
6	15	10	10	10	10
7	10	5	5	5	5
8	5	2.5	2.5	2.5	2.5
cumulative dose (mg)	1610	1207.5	962.5	752.5	682.5

Table 4. Risk mitigation for neutropenia

ANC (cells/mm^3)	Action
> 1000	Maintain dose
500 – 1000	If neutropenia persists, interrupt SC dosing (for patients on OL TCZ reduce dose from SC qw to SC q2w) When ANC increases to > 1000 cells/mm^3, resume SC dosing or increase TCZ dosing to SC qw, as clinically appropriate
< 500	Discontinue SC injection/TCZ permanently after repeat confirmation

ANC= absolute neutrophil count; qw = every week; q2w = every 2 weeks; SC = subcutaneous; TCZ= tocilizumab; OL = open label

Note: Patients withdrawn from the study because of a reduced ANC must be followed closely for signs of infection, with treatment as deemed appropriate by the investigator, and must have a repeat white blood cell count with differential count performed weekly until the ANC is > 1000 cells/mm³ (1.0×10^9/L). If the ANC does not return to > 1000 cells/mm³ within 2 months (or sooner if deemed necessary by the investigator), a hematology referral is recommended.

Table 5. Risk Mitigation for Thrombocytopenia

Platelet count (cells/mm^3)	Action
> 100,000	Maintain dose
50,000 – 100,000	If thrombocytopenia persists, interrupt SC dosing (for patients on OL TCZ reduce dosing from SC qw to SC q2w) When platelet count increases to > 100,000 cells/mm^3, resume SC dosing or increase to TCZ SC qw dosing, as clinically appropriate
< 50,000	Discontinue SC injection/TCZ permanently after repeat confirmation

qw= every week; q2w= every 2 weeks; SC = subcutaneous; TCZ = tocilizumab; OL = open label

Note: Patients withdrawn from the study because of a reduced platelet count must repeat platelet tests weekly until the count is above 100,000 /mm³ (100×10^9/L). If the platelets do not return to > 100,000 cells/mm³ (100×10^9/L) within 2 months (or sooner if deemed necessary by the investigator), a hematology referral is recommended.

Table 6. Hepatic Enzyme Elevation Risk Mitigation

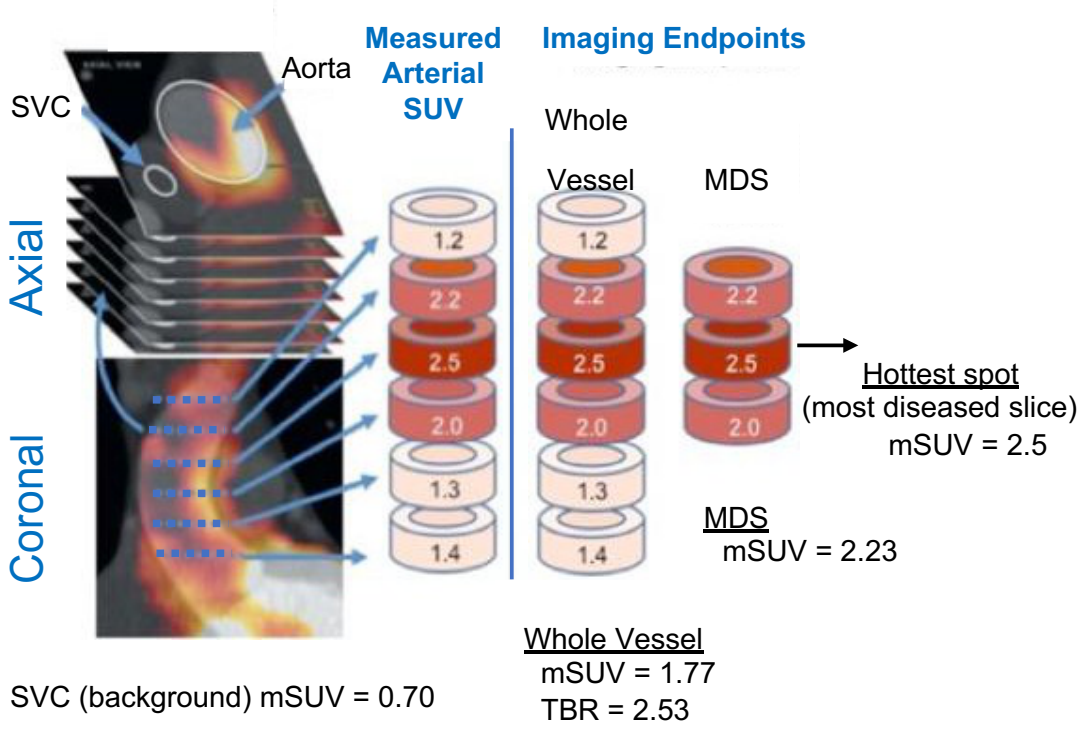
ALT or AST Values	Action
>1 [a] to 3×ULN	Reduce and if necessary, interrupt concomitant hepatotoxic drugs. If ALT/AST levels return to baseline, concomitant hepatotoxic drug may be resumed. For persistent increases in this range, interrupt SC/TCZ dosing (for patients on OL TCZ reduce dosing from SC qw to SC q2w). When ALT/AST levels return to baseline, [a] resume SC dosing or increase to TCZ qw, as clinically appropriate.
>3 to 5×ULN	Interrupt SC injection/TCZ until <3×the ULN (confirmed by repeat testing) and then follow the instructions above. For persistent increases in this range, SC injection/TCZ should be discontinued.
>5×ULN	Laboratory tests should be repeated to confirm value. If confirmed, SC injection/TCZ should be discontinued.

qw = every week; q2w= every 2 weeks; SC = subcutaneous; TCZ = tocilizumab; ULN = upper limit of normal, OL = open label.

a The ULN or the patient's baseline value, whichever is higher.

Patients withdrawn from the study because of elevated liver function test results must have repeat tests performed as clinically indicated until levels return to baseline values. If the patient's liver function test results have not returned to normal or to the patient's baseline level within 6 months (or sooner if deemed necessary by the investigator), a specialist referral is recommended and an ultrasound and liver biopsy should be considered.

Figure 1. Positron emission tomography/magnetic resonance (PET/MR) 18-FDG uptake determinations



mSUV = maximum standardized uptake value, MDS = most diseased segment, TBR = target to background ratio, SVC = superior vena cava

SIGNATURE OF INVESTIGATOR

I agree to conduct the study outlined above in accordance with the terms and conditions of the protocol, ICH guidelines on GCP and with applicable regulatory requirements. All information pertaining to the study shall be treated in a confidential manner.

Dr. Sebastian Unizony, M.D Principal Investigator	Date (day/month/year)

Study title

TOCILIZUMAB PLUS A SHORT PREDNISONE TAPER FOR GIANT CELL ARTERITIS

Study Drug

Tocilizumab (Roche / Genentech)

Study Drug and Financial Support Provided By

Roche / Genentech

Version Date: January 21, 2020