UCLA (Primary Site)
University of Florida (Sub-site)

Study Title

Musculoskeletal Ultrasound in Predicting Early Dose Titration with Tocilizumab

Study Drug
Tocilizumab (ACTEMRA®)

Support Provided By
Genentech

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1. *Section 11.0 – Reporting of Adverse Events*

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1.0 INTRODUCTION

1.1 Disease Background

Despite significant advances, more sensitive RA outcome measures are needed to aid in therapeutic decision making. Sonography or ultrasound (US), a tool increasingly available in rheumatologist's offices, is a sensitive imaging modality which can detect synovial hypertrophy (SH) and power Doppler synovitis activity (PDUS). This study aims to determine if early sonographic measures (4 weeks) in RA patients started on 4mg/kg of tocilizumab (TCZ), can predict 12 week change in disease activity and the need for dose escalation. We hypothesize that US measures of SH and PDUS can be used to determine whether synovitis is being controlled as early as the 2nd infusion of TCZ resulting in the ability to predict which patients may need to titrate the TCZ dose from 4mg/kg to 8mg/kg (maximum dose 800mg), and that this action will result in better ability to tailor dosing to achieve the optimal treatment response.

1.2 Tocilizumab Background

1.2.1 Tocilizumab

Tocilizumab (TCZ), formerly known as myeloma receptor antibody (MRA) is a recombinant humanized antihuman monoclonal antibody of the immunoglobulin IgG1 subclass directed against the IL-6R and produced by recombinant DNA technology. Clinical efficacy and safety studies of TCZ have been conducted or are ongoing in various disease areas, including adult-onset RA, systemic-onset juvenile idiopathic arthritis and polyarticular juvenile idiopathic arthritis.

The half-life of TCZ is approximately 7 days. The TCZ exposures were stable over 2- years of treatment. The observed mean (± SD) Ctrough at 8 mg/kg IV was 15.9 ± 12.0 at week 24 and 19.9 ± 17.0 at week 104. The observed mean (± SD) Ctrough at 4 mg/kg was 1.02 ± 6.14 at week 24 and 1.09 ± 2.77 at week 104.

The Roche clinical development program in adult RA, comprised five pivotal Phase 3 trials and two open-label, long-term treatment extension studies.

Further information on TCZ can be found in the Investigator's Brochure (IB).

1.3 Other Study Drug(s) Background

N/A

1.4 Study Rationale

The US FDA labeling for Actemra indicates use in RA patients refractory to or not responding to at least 1 TNF inhibitor, and also recommends that the starting dose be 4mg/kg every 4wks. The results of the RADIATE trial provide evidence

that the 4 mg/kg dose is unlikely to result in low disease activity or remission in these patients. Therefore, maintaining patients on 4mgkg may delay timely clinical responses, important for improving in function [1]. In the TAMARA study, conducted in Germany, TNF-IR and DMARD-IR patients were treated within the same protocol. TNF-IR patients treated with 8 mg/kg according to EU label showed clinically meaningful improvement (as also seen in the US)[2], but less compared to DMARD-IR patients, further supporting the importance of the 8 mg/kg dose [3]. We propose to use musculoskeletal ultrasound to examine initial response to TCZ to determine whether the early effect on synovitis is predictive of the likelihood of achieving a response in patients receiving the 4 mg/kg dose, and whether this effect then correlates with timing and magnitude of response.

Musculoskeletal Ultrasound

Musculoskeletal ultrasound use by rheumatologists is rapidly growing in the USA [4]. Compared to other advanced imaging techniques, it is an inexpensive, non-irradiating technique. Sonography can be utilized at point of care and does not require use of contrast to detect vascularity. A recent ACR whitepaper outlined the current status of the use of sonography in American Rheumatology practice. This paper and others have summarized the validity of use of musculoskeletal ultrasound in RA clinical trials studying the response to therapeutic agents [5-7]. Whilst sonography is more sensitive than x-ray in detecting erosions, it has the added advantage at inferring inflammation in synovial tissues by detecting blood flow in tissues without the use of contrast agents.

Radiographic assessments of joint space narrowing and erosions of the hands/feet (measures of damage) are considered the gold standard imaging outcome measurement, largely because these measures are validated to measure change in randomized controlled trials (RCTs), with change shown to be associated with function and disability. However, the advent of biologic agents has revolutionized the treatment of RA to the point that, in order to show a difference between 2 biologic treatments arms with radiographs requires a large sample size, and importantly, lack of sensitivity doesn't allow use to facilitate treatment decisions. Additional consideration for treatment decisions is that clinical composite measures such as DAS28, CDAI, and RAPID3 may not adequately reflect the totality of intra-articular inflammation contributing to joint damage. The use of musculoskeletal US in detecting synovial vascularity and hypertrophy is rapidly becoming a valuable imaging modality to sensitively assess therapeutic response in RA [8, 9].

The persistence of power Doppler US signal (PDUS) for vascularity within the joint may predict progression of erosive change. In a small cohort of 7 RA patients treated with TCZ at 8mg/kg (maximum dose 800mg) for one year, Hama et al. suggests that PDUS signal change mirrored clinical improvement and radiographic progression of erosions was associated with presence of PDUS signal [10]. Similar findings have been reported by other investigators who

treated patients with active RA with not only TCZ, but also other biologic agents [11-13].

Sonography may also be useful in assessing response, where suppression of PDUS signal after administration of biologic agents suggests response to therapy [11, 14], and persistence of Doppler signal may predict the risk of progressive erosive disease. It is this feature that we hypothesize will be useful in determining which patients may not respond to 4mg/kg, thus requiring an escalation in therapy to achieve an acceptable clinical response. Kume et al demonstrated the rapid response to 8mg/kg (maximum dose 800mg) Tocilizumab in biological therapy naive RA patients who were non responsive to low dose prednisone and methotrexate. The investigators were able to predict DAS28 response at 24 weeks based on Doppler activity at two weeks. Non responders did not show any change in Doppler activity at two weeks [15].

Thus, there is significant potential for the use of a sensitive imaging measure to optimize TCZ dosing regimens. There have been no studies, which have evaluated the utility in ultrasound measurements to determine escalation of tocilizumab therapy from a dosing of 4mg/kg to 8mg/kg (maximum dose 800mg).

We propose an open-label clinical study to evaluate the potential usefulness of US as an early indicator in measuring response to escalation dosing of tocilizumab.

2.0 OBJECTIVES

2.1 Primary Aim

To determine if ultrasound power Doppler synovitis scores at 4 weeks or at baseline can provide early evidence to predict changes in disease activity at 12 weeks follow up in RA patients treated with 4mg/kg of TCZ.

Primary Hypothesis: We hypothesize that the change in US power Doppler synovial scores (from baseline to 4 weeks) or baseline PDUS will correlate with change in DAS28 scores at wk12.

2.2 Exploratory Aims

3.0 STUDY DESIGN

3.1 Description of the Study

3.1.1 Study Schema

This is a 24-week, double blind open label clinical trial study to evaluate 57 active RA patients who have moderate to severe disease activity with total PDUS≥10 of 34 joints evaluated by US (at screening to enter into the study). All patients will begin treatment with tocilizumab at a dose of 4mg/kg. Two study sites will recruit patients (UCLA and UF) using the same protocol, after standardizing US acquisition methods, as well as scoring. US synovitis scores will be acquired at screening, baseline, and pre-infusion at 4, 12, 16, and 24 weeks, to be able to determine whether change in pre-infusion synovitis score at 4 weeks can be used to predict change in disease activity at 12 weeks. This will provide evidence to whether such reading is useful in predicting which patients may require escalation of dose from 4 to 8 mg/kg. At 12 weeks, patients not meeting low disease activity within the 4mg/kg (disease activity score DAS28/ESR-4item≤3.2) will increase the tocilizumab dose to 8mg/kg (maximum dose 800mg) in a blinded manner to enable evaluation of these US-focused objectives in the context of the current FDA-approved label. The ultrasound scorer will not know information about patient's disease activity (TJC, SJC, labs etc) or if there was dose escalation at 12 weeks. The clinical assessor of disease activity will be blinded to the ultrasound scores. Additionally, the patient will also be blinded to dose escalation. If patients in the 4mg/kg arm achieve DAS28≤3.2

at 12 weeks, patients will continue with their current dose for the duration of the study. Please see the below Table for details on the blinding plan.

Blinding Plan

	Clinical Assessor	Ultrasound Scorer	Patient	Coordinator	Pharmacy	Monitor
Blinded to Escalation	YES	YES	YES	NO	NO	NO
Blinded to Clinical Assessment	NO	YES	NO	NO	N/A	N/A
Blinded to US Assessment	YES	NO	NO	NO	N/A	N/A

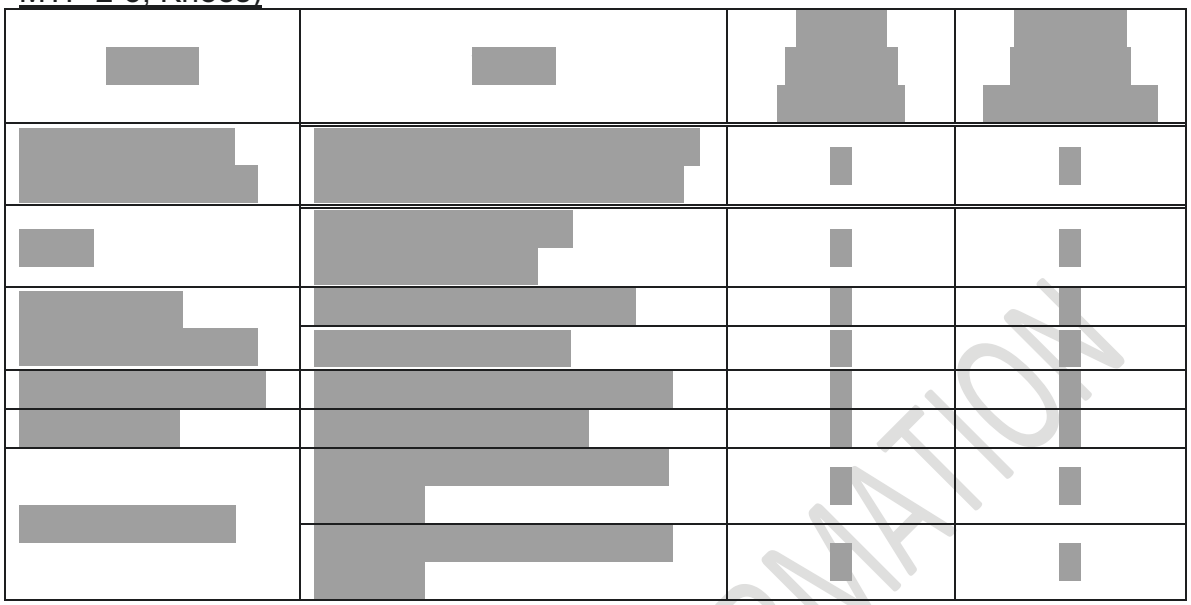
Thus, the overall goal is to evaluate the potential usefulness of US as an early indicator in measuring response to enable timely escalation of therapy with tocilizumab. Similarly, we will evaluate if US inflammatory scores at 16 weeks can provide information to predict response at 24 weeks.

At screening the following data will be recorded for each patient: age, sex, RA disease duration, rheumatoid factor status, anti-cyclic citrullinated antibody status, smoking status, alcohol consumption, comorbidities, current disease modifying anti-rheumatic drugs (DMARDs), and prior DMARDs/biologic agents.

In addition, US will be performed at screening. Patients with a PDUS score of less than 10 at screening will be excluded from the study. A detailed review of the inclusion and exclusion parameters will be performed prior to enrollment into the study. Patients will have US, DAS28/ESR-4 item, and HAQ assessments performed the same day. In addition, patients will have blood stored for biomarker assays at UCLA. US assessment (described below) will be performed at screening, baseline, 4, 12, 16, and 24 weeks, using standard methods for assessing synovitis and power Doppler. See below for a detailed account of the methodology for US scores. CDAI, DAS28/ESR-4 item, and ESR will be assessed at the following visits: screening, baseline, 4, 12, 16, and 24 weeks. The quality of life measure (HAQ-DI) will be assessed at the following visits: screening, baseline, 12, and 24 weeks. Adverse events and serious adverse events will also be recorded at each visit. hsCRP will be done at the following visits: screening, baseline, 12 weeks, and 24 weeks.

At entry into the study, all study subjects will receive 4mg/kg TCZ. After 12 weeks of treatment, patients will have assessment of disease activity by DAS28/ESR-4 item. If patients achieve DAS28$\leq$3.2 then the dosing of 4mg/kg will be continued. If the DAS28>3.2 then patients will be increased to 8mg/kg dosing (maximum dose 800mg). Study subjects and the ultrasonographer will be blinded to dose escalation assignment.

34-Joint US Scoring System (bilat wrists, bilat MCPs 2-5, bilat PIPs 2-5, bilateral MTP 2-5, Knees)



US assessments will be performed using the 34-joint US score. To date, no single US scoring system has been yet determined as the prevailing method. However, several US scoring systems have demonstrated that power Doppler synovitis and B-mode synovial hypertrophy scores are sensitive to change. For this proposal, selection of the specific 34 joints was based on maximizing precision, reliability, and feasibility for ultrasonography. Most US scoring systems weigh heavily on the hands and wrists. Some studies demonstrate the presence of normal amounts of fluid at the metarsophalangeal (MTP) joints and frequent presence of deformities such as hammer toes. Thus, these joints were excluded [16, 17]. Grey-scale synovial hypertrophy and power Doppler will be assessed for bilateral wrists (dorsal), MCPs 2-5 (dorsal and volar), and PIPs 2-5 (volar). All the above areas will be examined with B-Mode and power Doppler mode sonography (Table above). Standard OMERACT definitions will be used for effusion and synovial hypertrophy.

Our **primary endpoint** is the change in power Doppler US synovitis/PDUS score at 4 weeks. Each image will be scored 0-3 as described below for a maximum score of 96. We will also obtain synovial hypertrophy B-mode scores with the same maximum score of 96, as our **secondary endpoint**. The intraarticular power Doppler signals will be graded on a scale from 0 to 3 as follows: Grade 0: absent, no synovial flow. Grade 1: mild, 3 isolated signals, Grade 2: moderate, greater than 3 isolated signals or confluent signal in less than half of the synovial area, Grade 3: marked signals in more than half of the synovial area. B-mode grey scale synovial hypertrophy will be graded semiquantitatively from 0 to 3 as follows: Grade 0: absent, Grade 1: mild, Grade 2: moderate, and Grade 3: severe. The total inflammatory US score will add the synovial hypertrophy B-mode scores and power Doppler scores in order to obtain a comprehensive assessment of the US inflammatory burden. Each ultrasonographer (UCLA and UF) will re-read the US images obtained for the 57 patients (4 visits [baseline, 4

weeks, 12 weeks, and 24 weeks]). Scoring of the images will be performed as per OMERACT guidelines. Intra- and inter- reader reliability scores will be determined at the end of the study. The same ultrasonographer should be obtaining the images and scoring images at each site. In case of an emergency where the designated ultrasonographer cannot perform the ultrasound, a back-up ultrasonographer will perform the required ultrasound. However, we anticipate that this will be an unlikely scenario.

The US will be performed by a rheumatologist with expertise in musculoskeletal ultrasound and images will be digitally saved. The ultrasound scorer will be blinded to the clinical assessments and visa versa.

Standardization of Acquisition and Inter-/Intra-Reader Reliability
Prior to embarking on the randomized clinical trial, it is necessary that the ultrasonographers at UCLA and at UF both reliably acquire and score the images in a similar manner. Good agreement on image acquisition and scoring will be required prior to the start of the study. To achieve this goal, a 2-day standardization of acquisition and scoring of the ultrasound images will be performed.

Before the face-to-face meeting, the ultrasonographers will acquire images as described in our standard operating procedure (SOP) for the quality and reliability of image acquisition. SOP describes standardization of specific variables including: room temperature, ultrasound factors (B-mode gain, power Doppler gain, frequency, etc), gel use, and others. The SOP will include a reference atlas representing scans from each joint area. Both sites will review the SOP and atlas. Then, the ultrasonographers will obtain images on 1-2 patients which will be scored by all sonographic investigators. During a teleconference, any general differences will be discussed and resolved.

In order to standardize the US scoring process, the ultrasonographers will meet at a mutually convenient location. The morning of the first day, ultrasonographers will obtain images and score per protocol on 2-4 RA patients in a round robin approach. This process will be repeated in the evening that same day. Intra- and inter- reader reliability will be calculated later that evening. In addition, the scoring of images with the highest discordance will be flagged for highest priority for discussion for the following day. The flagged images will be discussed till mutual agreement is achieved. By convention, an ICC of >0.6 is considered good reliability and >0.8 is excellent reliability. It is our goal to strive for excellent reliability. If there are areas of disagreement in scoring, consensus will be reached and repeat scoring will be performed until ICCs are good (>0.7) [18, 19].

Addition of potential biomarkers: [redacted]

[redacted]

3.2 Rationale for the Study Design and Dose

It is clear that more sensitive RA outcome measures are required to aid in therapeutic decision making. This study will determine if early ultrasound (US) power Doppler synovitis scores (4 weeks), a sensitive measure of disease activity, can predict response to therapy (12 weeks) in RA patients started on tocilizumab (TCZ) at 4mg/kg. This cohort of RA patients will be at risk of joint damage and required to have PDUS≥10 at screening to be included in the study. Thus implying that earlier titration of TCZ dose from 4mg/kg to 8mg/kg (maximum dose 800mg) will result in better treatment response.

3.3 Outcome Measures

3.3.1 Primary Outcome Measures

Total power Doppler synovitis score of 34 joints (range 0-96)

[redacted]

3.3.3 Safety Outcome Measures

Serious adverse events
Adverse events
Laboratory values

3.4 End of Study

After treatment with TCZ for 24 weeks and one safety follow-up evaluation to evaluate any AEs.

4.0 STUDY POPULATION

4.0.1 Overview

This is an open label TCZ study of a prospective cohort of 57 RA patients treated initially with 4mg/kg tocilizumab (TCZ) over 24 weeks. The overall goal is to determine whether change in PDUS can be used to provide early information on which patients may be clinical responders at later time points, and permit dose escalation pre-infusion 2. Eligible patients will be started on 4 mg/kg TCZ every 4 wks, and will undergo ultrasound exam of 34 joints at screen, baseline, and pre-infusion 2, 4, 5, and 7 cycles. Patients who do not achieve at least a DAS28≤3.2 demonstrating clinical improvement by 12 weeks, will be dose escalated to 8 mg/kg (maximum dose 800mg) in a blinded manner described above.

Approximately two thirds of the patients will be recruited from UCLA 200 Medical Plaza [over 17 rheumatologists], at the Santa Monica UCLA-based adult rheumatology practice with three full time and one part time rheumatologists who see patients 5 days a week and 3 part-time rheumatologists. There will be a second site at the University of Florida, where the remaining one third of patients will be recruited.

4.1 Inclusion Criteria

Patients must have rheumatoid arthritis. Patients will be included in the trial based on the following criteria:

1) Patient must meet 1987 ACR criteria,
2) Age ≥ 18 years of age,
3) Baseline DAS28/ESR>4.4,
4) Stable concomitant DMARDs for more than 1 month (methotrexate, leflunomide, plaquinel, sulfasalazine, or no DMARDs). However, if the patient is not on DMARD, history of DMARD use required.
a. If not on DMARD (and the patient satisfies the above statement), the patient can opt for monotherapy with tocilizumab or combination therapy OR
b. If on biologic monotherapy, can opt for monotherapy with tocilizumab or DMARD combination therapy (ie. patients cannot be on biologic with TCZ)
6) Power Doppler score of ≥10 at screening.

General Medical Concerns:

- Normal organ function, except if abnormal due to the disease under investigation
- Men and women of reproductive potential must agree to use an acceptable method of birth control during treatment and for six months after completion of treatment.
- Subject has provided written informed consent.

4.2 Exclusion Criteria

A patient will be excluded if the answer to any of the following statements is "yes".

General:

1. Major surgery (including joint surgery) within 8 weeks prior to baseline or planned major surgery within 6 months after baseline.

Excluded Previous or Concomitant Therapy:

2. Treatment with any investigational agent within 4 weeks (or 5 half-lives of the investigational drug, whichever is longer) of baseline.
3. Previous treatment with any cell-depleting therapies, including

investigational agents or approved therapies, some examples are CAMPATH, anti-CD4, anti-CD5, anti-CD3.
4. Previous treatment with anti-CD19 and anti-CD20 within 6 months of start of the study.
5. Treatment with intravenous gamma globulin, plasmapheresis or Prosorba column within 6 months of baseline.
6. Immunization with a live/attenuated vaccine within 4 weeks prior to baseline.
7. Previous treatment with TCZ.
8. Any previous treatment with alkylating agents such as chlorambucil, or with total lymphoid irradiation.
9. Use of prednisone > 10mg at baseline.

Exclusions for General Safety:

10. History of severe allergic or anaphylactic reactions to human, humanized or murine monoclonal antibodies.
11. Evidence of serious uncontrolled concomitant cardiovascular, nervous system, pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine (include uncontrolled diabetes mellitus) or gastrointestinal disease (including complicated diverticulitis, ulcerative colitis, or Crohn's disease.)
12. Current liver disease as determined by principal investigator unless related to primary disease under investigation
13. Known active current or history of recurrent bacterial, viral, fungal, mycobacterial or other infections (including but not limited to tuberculosis and atypical mycobacterial disease, Hepatitis B and C, and herpes zoster, but excluding fungal infections of nail beds).
14. Any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks of baseline or oral antibiotics within 2 weeks prior to baseline.
15. Active TB requiring treatment within the previous 3 years. Patients should be screened for latent TB and, if positive, treated following local practice guidelines prior to initiating TCZ. Patients treated for tuberculosis with no recurrence in 3 years are permitted.
16. Primary or secondary immunodeficiency (history of or currently active) unless related to primary disease under investigation.
17. Evidence of active malignant disease, malignancies diagnosed within the previous 5 years (including hematological malignancies and solid tumors, except basal and squamous cell carcinoma of the skin or carcinoma in situ of the cervix uteri that has been excised and cured), or breast cancer diagnosed within the previous 5 years.
18. Pregnant women or nursing (breast feeding) mothers.
19. Patients with reproductive potential not willing to use an effective method of contraception.
20. History of alcohol, drug or chemical abuse within 1 year prior to screening.
21. Neuropathies or other conditions that might interfere with pain

evaluation unless related to primary disease under investigation.
22. Patients with lack of peripheral venous access.
23. Body weight of > 150 kg.

Laboratory Exclusion criteria (at screening):
24. Serum creatinine > 1.6 mg/dL (141 µmol/L) in female patients and > 1.9 mg/dL (168 µmol/L) in male patients. Patients with serum creatinine values exceeding limits may be eligible for the study if their estimated glomerular filtration rates (GFR) are >30.
25. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1.5 times upper limit of normal (ULN)
26. Total Bilirubin > ULN
27. Platelet count < 100 x 10^9/L (100,000/mm3)
28. Hemoglobin < 85 g/L (8.5 g/dL; 5.3 mmol/L)
29. White Blood Cells < 3.0 x 10^9/L (3000/mm3)
30. Absolute Neutrophil Count < 2.0 x 10^9/L (2000/mm3)
31. Absolute Lymphocyte Count < 0.5 x 10^9/L (500/mm3)
32. Positive Hepatitis BsAg, or Hepatitis C antibody
33. HIV positive

4.3 Immunization during TCZ therapy

Live vaccines cannot be given concurrently with Tocilizumab as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving Tocilizumab. Because IL-6 inhibition may interfere with the normal immune response to new antigens, patients should be brought up to date on all recommended vaccinations, except for live vaccines, prior to initiation of therapy with Tocilizumab.

4.4 Criteria for Premature Withdrawal

Patients have the right to withdraw from the study at any time for any reason. There should be an attempt to have all patients complete the withdrawal visits or safety follow-ups as detailed in the Schedule of Assessments.

If the patient decides to prematurely discontinue study treatment (“refuses treatment”), he/she should be asked if he/she can still be contacted for further information. The outcome of that discussion should be documented in both the medical records and in the CRF. A complete final evaluation at the time of the patient’s withdrawal should be made with an explanation of why the patient is withdrawing from the study. Before categorizing a patient as lost to follow-up, the investigator must attempt to contact the patient or a responsible relative by telephone followed by registered mail to determine if any new AEs occurred, follow-up of any ongoing AE and to establish as completely as possible the reason for the withdrawal.

When applicable, patients should be informed of circumstances under which their participation may be terminated by the investigator without the patient’s consent. The

investigator may withdraw patients from the study in the event of intercurrent illness, adverse events, treatment failure, lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits), or any reason where it is felt by the investigator that it is in the best interest of the patient to be terminated from the study. The reason(s) for withdrawal must be documented and explained to the patient.

If the reason for removal of a patient from the study is an adverse event, the specific event will be recorded on the CRF. There should be an attempt to follow the patient until the event has resolved or stabilized.

An excessive rate of withdrawals can render the study non-interpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw, all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible.

5.0 TREATMENT PLAN

This is a Phase IV double blind randomized clinical trial with TCZ dosed 4mg/kg every 4 weeks infusions for 24 weeks. Patients will step up to 8mg/kg (maximum dose 800mg) of TCZ if they do not achieve a goal of DAS28$\leq$3.2. This research study protocol allows the subject to receive up to 7 infusions of Tocilizumab. We estimate enrolling 3 patients per month at UCLA and 2 patients per month at the University of Florida, thus ending enrollment in approximately 6-9 months. It was critical that we added the second site in order to decrease the time of patient enrollment, which would have been >12months with one site. We anticipate that the last visit of the last patient will be at 18 months.

Even if the treatment is shown to be of benefit, additional infusions of Tocilizumab beyond that allowed in the protocol cannot be given to the subject while she/he is participating in this study.

6.0 STUDY MEDICATION

6.1 Tocilizumab

Tocilizumab (ACTEMRA®) is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin IgG1κ (gamma 1, kappa) subclass with a typical H_2L_2 polypeptide structure. Each light chain and heavy chain consists of 214 and 448 amino acids, respectively. The four polypeptide chains are linked intra- and inter-molecularly by disulfide bonds. Tocilizumab has a molecular weight of approximately 148 kDa.
Tocilizumab is supplied as a sterile, preservative-free solution for intravenous (IV) infusion at a concentration of 20 mg/mL. Tocilizumab is a colorless to pale yellow liquid, with a pH of about 6.5. Single-use vials are available containing 80 mg/4 mL, 200 mg/10 mL, or 400 mg/20 mL of Tocilizumab. Injectable solutions of Tocilizumab are formulated in an aqueous solution containing disodium phosphate dodecahydrate and sodium dihydrogen phosphate dehydrate (as a 15

mmol/L phosphate buffer), polysorbate 80 (0.5 mg/mL), and sucrose (50 mg/mL).

Tocilizumab will be provided free of charge by Genentech. The Sponsor/Investigator of the study will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all study drug in accordance with 21 Code of Federal Regulations (C.F.R.), Part 312.57 and 312.62 and Genentech requirements.

6.1.1 Tocilizumab Dosage and Administration

The recommended dose of tocilizumab for adult patients is 4mg/kg and titration up to 8 mg/kg (maximum dose 800mg) given once every four weeks as an IV infusion. Tocilizumab can be used alone or in combination with MTX and/or other DMARDs.

Tocilizumab should be diluted to 100 mL by a healthcare professional with sterile 0.9%w/v sodium chloride solution using aseptic technique Tocilizumab is recommended for IV infusion over 1 hour.

For individuals whose body weight is more than 100 kg, doses exceeding 800 mg per infusion are not recommended.

One vial containing 400 mg TCZ or two vials containing 200 mg TCZ will be required for each 50 kg body weight to achieve an 8 mg/kg (maximum dose 800mg) dose. The number of vials to be used depends on the patient's body weight as follows:

1. One 400-mg vial (or two 200-mg vials) is used for patients with a body weight ≤50 kg.

2. Two 400-mg vials (or four 200-mg vials) are used for patients with a body weight >50 kg combination of the 400-mg and 200-mg vials may be used but the total dose should not exceed 800 mg

6.1.2 Tocilizumab Storage

Tocilizumab should not be used after the expiry date (EXP) shown on the pack.

For vials: Store between 2ºC – 8ºC, do not freeze. Keep the container in the outer carton in order to protect from light.

For prepared infusion solution: The prepared infusion solution of tocilizumab is physically and chemically stable in 0.9% w/v sodium chloride solution at 30ºC for 24 hours.

From a microbiological point of view, the prepared infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to

use are the responsibility of the user and would not be longer than 24 hours at 2ºC – 8ºC, unless dilution has taken place in controlled and validated aseptic conditions.

6.1.3 Tocilizumab Overdosage

There are limited data available on overdoses with Tocilizumab. One case of accidental overdose was reported in which a patient with multiple myeloma received a dose of 40 mg/kg. No adverse drug reactions were observed. No serious adverse drug reactions were observed in healthy volunteers who received single doses of up to 28 mg/kg, although all 5 patients at the highest dose of 28 mg/kg developed dose-limiting neutropenia.

In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate symptomatic treatment.

7.0 DOSE MODIFICATION/TOXICITY MANAGEMENT

A number of measures will be taken to ensure the safety of patients participating in this study. These measures will be addressed through exclusion criteria (see Section 4.2) and routine monitoring as follows.

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, blood pressure, and laboratory measurements. Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study.

7.1 Tocilizumab

Opportunistic Infections and Serious Infections

Physicians should exercise caution when considering the use of TCZ in patients with a history of recurring infection or with underlying conditions (e.g. diabetes) which may predispose patients to infections. Tocilizumab should not be administered in patients with active infection. The effects of TCZ on CRP, neutrophils, and the signs and symptoms of infection should be considered when evaluating a patient for a potential infection.

Vigilance for timely detection of serious infection is recommended for patients receiving biologic agents for treatment of moderate to severe RA as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reaction. Patients must be instructed to contact their physician immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment.

If a patient develops a serious infection, administration of TCZ is to be interrupted until the infection is controlled. The clinician should consider the benefit-risk before resuming treatment with tocilizumab.

Gastrointestinal Perforations

Timely diagnosis and appropriate treatment may reduce the potential for complications of diverticulitis and thus reduce the risk of GI perforations. Therefore, patients should be made aware of the symptomatology potentially indicative of diverticular disease, and they should be instructed to alert their healthcare provider as soon as possible if these symptoms arise. In patients with a history of symptomatic diverticulosis, diverticulitis or chronic ulcerative lower GI disease such as Crohn's disease, ulcerative colitis or other chronic lower GI conditions that might predispose to perforations, the clinician should consider the benefit-risk before using TCZ. Discontinuation of TCZ is recommended for patients who develop GI perforations.

Demyelinating Disorders

The impact of treatment with TCZ on demyelinating disorders is not known; events were rarely reported. Patients should be closely monitored for signs and symptoms potentially indicative of central demyelinating disorders. Physicians should exercise caution in considering the use of TCZ in patients with pre-existing or recent onset demyelinating disorders. Treatment with tocilizumab should be interrupted during assessment of a potential demyelination event and only resumed if the benefit of continuing study drug is favorable.

Hematologic Abnormalities and Bleeding Events

Decreases in neutrophil and platelet counts have been observed following treatment with TCZ in combination with MTX. In addition, there may be an increased risk of neutropenia in patients who have previously been treated with a TNF antagonist.

The risk mitigation strategies for neutropenia and thrombocytopenia are summarized in Table 1 and Table 2, respectively. For patients with concomitant medications associated with hematologic toxicity, the reduction or interruption of the suspected medication is recommended prior to modifying TCZ.

Table 1: Neutropenia Risk Mitigation

ANC (cells/mm^3)	Action
> 1000	Maintain dose.
500 – 1000	Interrupt tocilizumab dosing. When ANC increases to > 1000, resume tocilizumab at 4 mg/kg and increase to 8 mg/kg (maximum dose

	800mg)as clinically appropriate
< 500	Discontinue tocilizumab.
ANC = absolute neutrophil count	

Table 2: Thrombocytopenia Risk Mitigation

Platelet count (cells/mm^3)	Action
> 100,000	Maintain dose.
50,000 – 100,000	Interrupt tocilizumab dosing. When platelet count increases to > 100,000, resume tocilizumab at 4 mg/kg and increase to 8 mg/kg(maximum dose 800mg) as clinically appropriate
< 50,000	Discontinue tocilizumab.

Elevated Liver Enzymes and Hepatic Events

Elevations in ALT and AST have been observed during treatment with the study medications.

Table 3:

Lab Value	Action
> 1 to 3x ULN	Dose modify concomitant DMARDs if appropriate For persistent increases in this range, reduce tocilizumab dose to 4 mg/kg or interrupt tocilizumab until ALT/AST have normalized Restart with 4 mg/kg or 8 mg/kg(maximum dose 800mg), as clinically appropriate
> 3 to 5x ULN (confirmed by repeat testing)	Interrupt tocilizumab dosing until < 3x ULN and follow recommendations above for >1 to 3x ULN For persistent increases > 3x ULN, discontinue tocilizumab
> 5x ULN	Discontinue tocilizumab

Cardiovascular Events and Elevated Lipids

Patients with RA have an increased risk for cardiovascular disorders, therefore, risk factors for cardiovascular disease (eg, hypertension, hyperlipidemia) should be managed as part of their standard of care. See section on Drug Interactions. For patients with LDL cholesterol ≥160 mg/dL, it is strongly recommended that investigators advise therapeutic lifestyle changes that may include initiation 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 or other national guidelines.

Malignancies

The impact of immunosuppression on the development of malignancies is not known, however an increased rate of some malignancies, notably lymphoma, has been observed in RA patients. Although no imbalance of malignancies was observed in controlled clinical trials of TCZ, malignancies have been identified as a concern for other biologics. It is recognized that identification of such events in TCZ-treated patients may require a longer period of surveillance. TCZ should be discontinued in patients with malignancies (with the exception of local basal or squamous cell carcinoma of the skin that is completely excised with free margins).

Hypersensitivity or Anaphylaxis:

An infusion/dose reaction is defined as an adverse event occurring during and within 24 hours after the infusion or subcutaneous injection of tocilizumab. This may include hypersensitivity reactions or anaphylactic reactions.

Signs of a possible hypersensitivity reaction include but are not limited to:

- fever, chills, pruritus, urticaria, angioedema, and skin rash.
- cardiopulmonary reactions, including chest pain, dyspnea, hypotension or hypertension.

Healthcare professionals administering TCZ infusions should be trained in the appropriate administrative procedures, be able to recognize the symptoms associated with potential anaphylactic or hypersensitivity reactions, and have the appropriate medication available for immediate use in case of anaphylaxis or hypersensitivity reaction during or after administration of TCZ. Healthcare professionals should also instruct patients to seek medical attention if they experience symptoms of a hypersensitivity reaction outside of the clinic.

If a patient has symptoms of anaphylaxis or serious hypersensitivity, or requires an interruption of the study drug because of symptoms of anaphylaxis or hypersensitivity, administration of TCZ must be discontinued permanently and the patient should be withdrawn from the study. The patient should be treated according to the standard of care for management of the hypersensitivity reaction. A blood sample for the presence of anti-tocilizumab antibodies should be obtained at time of event and at least 6 weeks after the last dose.

*6 weeks for the RA indication. For other indications consultation with the clinical pharmacology group will be required to assess how many weeks after the last dose testing should be conducted.

Viral Reactivation
Though rarely reported within the TCZ program due to exclusion criteria at study entry, reactivation of viral and other serious infections (e.g. EBV or TB) has been observed with biologic therapies for RA, including TCZ.

Drug Interaction

- The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (eg, IL-6) during chronic inflammation. Therefore, it is expected that for molecules that antagonize cytokine activity, such as TCZ, the formation of CYP450 enzymes could be normalized. When starting or stopping therapy with TCZ, patients taking medications which are individually dose-adjusted and metabolized via CYP450, 3A4, 1A2, or 2C9 (e.g. atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, ciclosporin, or benzodiazepines) should be monitored as doses may need to be adjusted to maintain their therapeutic effect. Given its long elimination half-life (t1/2), the effect of tocilizumab on CYP450 enzyme activity may persist for reaction
- ALT or AST value > 5X ULN or persistent elevation > 3X ULN
- Platelet count (cells/mm^3) < 50,000
- ANC (cells/mm^3) < 500

8. CRITERIA FOR SUBJECT DISCONTINUATION

Subjects who meet the following criteria should be discontinued from the study:

8.1 Tocilizumab-Specific Criteria

- Severe or life-threatening anaphylaxis or hypersensitivity

Subjects who are carriers of hepatitis B at the time of discontinuation from study treatment will continue to be followed for clinical and laboratory signs of active HBV infection and for signs of hepatitis.

8.2 General Criteria

- Inability of subject to comply with study requirements

Determination by the investigator that it is no longer safe for the subject to continue therapy several weeks after stopping
therapy.

9.0 CRITERIA FOR STUDY DISCONTINUATION

As stated above.

10.0 CLINICAL AND LABORATORY EVALUATIONS

Procedure	Pre-Treatment Screening Visit 1	During Treatment Visit 2 Baseline Visit	During Treatment Visit 3 4-week Visit	During Treatment Visit 4 8-week Visit	During Treatment Visit 5 12-week Visit	During Treatment Visit 6 16-week Visit	During Treatment Visit 7 20-week Visit	During Treatment Visit 8 24-week Visit	Safety Follow-up
Visit Time Window			+/- 1 weeks	+/- 1 weeks	+/- 1 weeks	+/- 1 weeks	+/- 1 weeks	+/- 1 weeks	
Eligibility Assessments									
Informed Consent	X								
Inclusion/Exclusion Criteria	X	X							
Medical History	X								
Safety Assessments									
Chest X-ray (PA lateral)	X[1]								
PPD skin testing	X[2]								
Quantiferon (if +PPD or patient from endemic area)	X[2]								
Physical Examination	X								
Targeted Physical Examination		X	X		X	X		X	
Vital Signs	X	X	X	X	X	X	X	X	
Assessment of Signs and Symptoms		X	X		X			X	
Adverse Events Assessment		X	X	X	X	X	X	X	X
CBC and Chem Panel Tests[3]	X[3]	X[3]		X	(X)	X	(X)	X	
Lipid Panel		X		X				X	
HIV, Hepatitis B and C Serologies	X[4]								
Rheumatoid Factor and CCP	X[5]								
hsCRP	X	X			X			X	
ESR	X	X	X		X	X		X	
Urine Pregnancy Test	X	X	X	X	X	X	X	X	
Efficacy Assessments									

Procedure	Pre-Treatment Screening Visit 1	During Treatment Visit 2 Baseline Visit	During Treatment Visit 3 4-week Visit	During Treatment Visit 4 8-week Visit	During Treatment Visit 5 12-week Visit	During Treatment Visit 6 16-week Visit	During Treatment Visit 7 20-week Visit	During Treatment Visit 8 24-week Visit	Safety Follow-up
Joint Assessment	X	X	X		X	X		X	
MD Global	X	X	X		X	X		X	
Patient Global	X	X	X		X	X		X	
CDAI	X	X	X		X	X		X	
DAS28/ESR	X	X	X		X	X		X	
HAQ-DI and other questionnaires	X	X			X			X	
Infusion of TCZ		X	X	X	X	X	X	X	
Serum/blood for biomarker testing[6]	X	X			X			X	
Ultrasound 34 joint Scoring	X	X	X		X	X		X	
Ultrasound 34 joint Re-read		X	X		X	X		X	

1. If a chest X-ray or CT scan of chest was done within the past 3 months, there is no need to repeat.

2. PPD skin testing or Quantiferon does not have to be done if either procedure was done within the past 3 months.

3. CBC and Chem panel laboratory tests do not have to be done if they were done within the past 4 weeks. Additional testing may be conducted for safety reasons.

4. Hepatitis B and C Serologies do not have to be done if they were done within the past 3 months.

5. Rheumatoid Factor and CCP tests do not have to be done at screening if they were done previously.

6. Biomarker testing may be performed at either screening and/or baseline. Patients have the right to refuse biomarker testing.

** Study procedures may be repeated per PI discretion (Items #1 to #5 above, ie. For sero-negative RA patients, PI may repeat RF and CCP to ensure they did not sero-convert. Chest x-ray may be repeated if an abnormality requires further assessment.)

10.1 Pre-Treatment Evaluations

Unless otherwise specified, the following evaluations must be performed within four weeks prior to the date of each patient's initial treatment with Tocilizumab:

- Pregnancy test (serum or urine) for women of childbearing potential.
- Medical history and documentation of the rationale for treatment of the patient's disease with Tocilizumab.
- Physical examination, including vital signs, blood pressure, performance status and tumor assessment.
- Hematology: complete blood count (CBC) with differential and platelet count.
- Serum Chemistries: Total bilirubin, SGOT(AST), and SGPT (ALT),
- Lipid Panel

10.2 Evaluations During Treatment

10.2.1 Laboratory evaluations for safety

- Neutrophils should be monitored every 4 to 8 weeks
- Platelets should be monitored ever 4 to 8 weeks
- ALT and AST levels should be monitored every 4 to 8 weeks
- Assessment of lipid parameters should be performed approximately 4 to 8 weeks following initiation of TCZ therapy, then at approximately 6 month intervals

10.3 Post-Treatment Evaluations

Each patient will receive a telephone call or we will extract information from primary rheumatologist's visit approximately 1 to 2 months after the study to evaluate for any adverse events or serious adverse events.

11.0 REPORTING OF ADVERSE EVENTS

11.1 Adverse Event and Reporting Definitions

In the event of an adverse event, the first concern will be for the safety of the subject. Investigators are required to report to Genentech Drug Safety any **serious adverse event**, whether **expected** or **unexpected**, for which there is a reasonable possibility the experience may have been caused by Tocilizumab.

The Sponsor-Investigator further agrees to forward reports to Genentech of serious adverse events regardless of relationship with the use of the Investigational medicinal product.

All events meeting these criteria will be reported for the time period beginning with any amount of exposure to Tocilizumab through the protocol-defined follow-up period. Serious criteria, definitions, and guidance for reporting follow.

An **adverse event (AE)** is any untoward medical occurrence in a subject participating in an investigational trial or protocol regardless of causality assessment. An adverse event can be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, syndrome or disease associated with or occurring during the use of an investigational product whether or not considered related to the investigational product.

Serious adverse events (SAE) are adverse events occurring at any dose which meet one or more of the following **serious criteria**:

- Results in **death** (i.e. the AE caused or lead to death)
- Is **life-threatening** (i.e. the AE placed the subject at immediate risk of death; it does not apply to an AE which hypothetically might have caused the death if it were more severe)
- Requires or prolongs inpatient **hospitalization** (i.e. the AE inpatient hospitalization or prolonged a hospitalization beyond the expected length of stay; hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not SAEs by this criterion)
- Is **disabling** (i.e. the AE resulted in a substantial disruption of the subject's ability to carry out normal life functions)
- Is a **congenital anomaly/birth defect** (i.e., an adverse outcome in a child or fetus of a subject exposed to the trial drug prior to conception or during pregnancy)
- It does not meet any of the above serious criteria but **may jeopardize the subject** and **may require medical or surgical intervention** to prevent one of the outcomes listed above

SAEs include any sign, symptom or medical condition that meets any of the above criteria and emerges during Tocilizumab treatment or during a post-treatment follow-up period that (1) was not present at the start of treatment and is not a chronic condition that is part of the patient's medical history, OR (2) was present at the start of treatment or as part of the patient's medical history but worsened in severity and/or frequency during therapy.

Expected adverse events are those adverse events that are **listed** or characterized in the current Investigator Brochure.

Unexpected adverse events are those **not listed** in the current Investigator Brochure or not identified. This includes adverse events for which the specificity

or severity is not consistent with the description in the Investigator Brochure For example, under this definition, hepatic necrosis would be unexpected if the Investigator Brochure only referred to elevated hepatic enzymes or hepatitis.

11.2 Reporting of Serious Adverse Events Associated with Tocilizumab

All serious adverse events (SAEs) (this applies to both expected and unexpected events) should be recorded on a MedWatch 3500A Form and faxed to:

Genentech Drug Safety
Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4683

This must be reported to Genentech within 24 hours.

(Please use the safety reporting fax cover sheet attached to this document for your fax transmission.)

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:

- Treatment regimen (dosing frequency, combination therapy)
- 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

Follow-up information:

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 subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, suspect drug, 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)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the subject for whom and adverse event was

reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above.

Study Drug Relationship:

The investigator will determine which events are associated with the use of the study drugs. For reporting purposes, an AE should be regarded as possibly related to the use of the investigational product if the investigator believes:

- There is a clinically plausible time sequence between onset of the AE and Tocilizumab administration; and/or
- There is a biologically plausible mechanism for Tocilizumab causing or contributing to the AE; and
  - The AE cannot be attributed solely to concurrent/underlying illness, other drugs, or procedures.

11.3 Pregnancy

Female patients should use a reliable means of contraception during the study and for a minimum of 6 months after the last dose of study medication. A female patient must be instructed to stop taking the study medication and immediately inform the investigator if she becomes pregnant during the study. The investigator should report all pregnancies within 24 hours to the Genentech Drug Safety, using the *Clinical Trial Pregnancy Reporting Form*\provided by Genentech Drug Safety. The investigator should counsel the patient, discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until the conclusion of the pregnancy. Pregnancies occurring up to 3 months after the completion of the study medication must also be reported to the investigator. Abortion, whether therapeutic or spontaneous, should always be classified as serious (as Genentech considers these medically significant), recorded on the appropriate eCRF and expeditiously reported to the Sponsor or its designee.

11.4 Actemra Events of Special Interest

Adverse events of special interest (non-serious and serious) are required to be reported by the Investigator to Genentech Drug Safety within 1 working day after learning of the event (see Section 11.2 for reporting instructions**). Non-serious and serious AEs** of special interest for this study include the following:

- Infections (including opportunistic infections and non serious infections as defined by those treated with IC anti-infectives).
- Myocardial infarction/acute coronary syndrome.
- GI perforation and related events.
- Malignancies.
- Anaphylaxis/Hypersensitivity reactions.
- Demyelinating disorders.

- Stroke.
- Bleeding events.
- Hepatic events.

Guided questionnaires have been prepared for the AEs of special interest. The same guided questionnaires are utilized for Serious Infections and opportunistic infections, therefore there are 9 guided questionnaires and 10 categories of AEs of special interest.

The notification of AEs of special interest (including non-serious events of special interest) will follow the established procedures for AEs and SAEs in the study (i.e., documented and reported to Genentech Drug Safety or its designee within 24 hours). Guided questionnaires have been prepared for the AEs of special interest and will be sent to the investigator(s) to obtain more detailed information, as necessary. The documentation and reporting requirements for those AEs of special interest will be further described in a separate document (Actemra Events of Special Interest Guidance Document).

12.0 EVALUATION OF RESPONSE

Primary Outcome Measure: change in PDUS
Secondary Outcome Measure: change in B-Mode grey scale synovial hypertrophy

13.0 STATISTICAL CONSIDERATIONS

13.1 Determination of Sample Size

13.1.1 Primary Aim

We plan to enroll 57 subjects. We will not include patients into the analyses who had different ultrasonographers at baseline and 1 month visits (4 patients potentially excluded with change in ultrasonographer from Ben-Artzi to Ranganath at UCLA site). We assume a 5% missed visit/dropout rate at 3 months and a 10% dropout rate at 24 weeks resulting in an expected 48 evaluable subjects at for the 12 week analyses and 45 for the 24 week analyses. For the primary aim, we will have 80% power to detect correlation between PDUS at 1 month and change in DAS28/ESR at 3 months of at least 0.382 assuming a test for the correlation coefficient with a two sided 0.05 significance level. Kume et al observed a correlation between 2-week PDUS and 24 week change in DAS28 in RA patients treated with 8 mg of Tocilizumab of 0.62.

For the exploratory aim [redacted]

13.2 Planned Efficacy Evaluations

13.2.1 Primary Efficacy Variables

The primary analysis will be a single predictor linear regression model with change in DAS28 from baseline to 12 weeks as the outcome and change in PDUS scores from baseline to 4 weeks as the predictor. Additional analyses will add covariates to the linear regression model such as demographic measures (age, sex)

13.2.2 Exploratory Analyses

Exploratory Analyses:

Exp Aim 1:

Exp Aim 2:

Exp Aim 3:

[redacted]

14.0 RETENTION OF RECORDS

We will retain all documentation of adverse events, records of trial drug receipt and dispensation, and all IRB correspondence for at least 2 years after the investigation is completed.

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APPENDIX A: Safety Reporting Fax Cover Sheet

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET
Investigator Sponsored Trials

SAE FAX No: (650) 225-4682
Alternate Fax No: (650) 225-4683

Study Number (Genentech study number)	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date (DD/MON/YYYY)	_____ / _____ /_____
Follow-up Report Date (DD/MON/YYYY)	_____ / _____ /_____

Subject Initials (Please enter a dash if the patient has no middle name)	_____ - _____ -_____

PLEASE PLACE MEDWATCH REPORT or IND SAFETY REPORT BEHIND THIS COVER SHEET

Please contact Genentech Safety for any questions regarding SAE or IND Safety reporting at (888) 835-2555