INSTITUTION or COOPERATIVE GROUP NAME

University of Pittsburgh School of Medicine

Study Title
Tocilizumab in the Treatment of Refractory Polymyositis and Dermatomyositis

Study Drug
Tocilizumab (ACTEMRA®)

Support Provided By
Genentech

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1.0 INTRODUCTION

1.1 Disease Background

The idiopathic inflammatory myopathies (IIM) are rare diseases with an estimated incidence of 10 cases per million per year and are associated with substantial morbidity and mortality. The treatment of IIM is unsatisfactory, and no agents are currently FDA-approved for this indication. The rarity of IIM has led to a paucity of controlled prospective clinical trials. Other than the recently completed RIM (Rituximab in Myositis) Study [1], most reports involve single referral centers reporting retrospectively on small numbers of patients followed for relatively brief periods of time. To compound matters, our ability to accurately assess the effects of therapeutic interventions has been limited by unreliable and insensitive outcome measures as well as the dilemma of determining the relative contributions of potentially reversible disease activity versus irreversible damage to muscle in patients with myositis. However, through the efforts of the International Myositis Assessment and Clinical Studies (IMACS) Group, many of these deficiencies have been addressed with a revised definition of improvement agreed upon by an international panel of myositis experts at an International Consensus Conference held in Paris, France in June 2014 based on validated core set measures (CSM) that were utilized in the RIM Study [2]. The goal of this proposal is to perform a collaborative multi-center trial among adult rheumatologists and neurologists implementing published disease activity and damage measures in adult inflammatory myopathy to examine the efficacy of tocilizumab (anti-IL-6R) as a potentially important new therapeutic advance for these diseases. Through the study of a novel biologic agent we will seek to elucidate the determinants of disease response and non-response in adult polymyositis and dermatomyositis.

1.2 Tocilizumab Background and Rationale in IIM

Although there are several studies supporting the efficacy of tocilizumab in RA and systemic onset juvenile idiopathic arthritis, it's use in other autoimmune disorders has also been proposed [3, 4]. A consensus statement on blocking the effects of IL-6 in RA and other autoimmune conditions has been recently published [5]. IL-6 is involved in the growth and differentiation of many inflammatory cells. In addition to its initial role in triggering B-cell stimulating factor, it also induces T cell growth and differentiation and plays a critical role in both adaptive and innate immune responses. IL-6, produced by many cells including T cells, B cells, monocytes and endothelial cells, binds to its receptor (IL-6R) and subsequently triggers several intracellular pathways leading to the release of inflammatory mediators and stimulation of the immune system. Inhibition of IL-6 has been studied in phase II and III clinical trials of RA. It has led to a decrease in acute phase reactants and other indicators of chronic inflammation [5]. IL-6 is also a potential therapeutic target in systemic sclerosis [6], and since IL-6 induces differentiation of B cells into antibody forming cells and contributes to T cells transforming into effector cells, its use in SLE has also been suggested [7].

The use of TCZ in myositis proposed in this protocol is supported by the aforementioned rationale and its efficacy in other rheumatologic disorders. Patients with refractory polymyositis (PM) were treated with tocilizumab and responded favorably [8]. In

dermatomyositis, tissue inflammation implicates soluble cytokine networks contributing to disease pathogenesis. Work on a mouse model of myositis noted IL-6 as a mediator of muscle inflammation [9]. Other investigators studying peripheral blood samples and clinical data on both adult and juvenile dermatomyositis (DM) noted that serum levels of IL-6 were significantly correlated with disease activity [10]. In this same study, correlations between serum IL-6 levels and both the type I interferon gene and chemokine signatures were also identified in DM. These authors suggest that the coordinated dysregulation of IL-6 production and Type I interferon signaling implicates these pathways as contributing to disease pathogenesis in DM.

In a mouse model of PM, C protein-induced myositis (CIM), the pathology reportedly mimics that seen in human PM [11]. Mice were treated with anti-IL-6 receptor monoclonal antibodies or control antibodies and muscle tissue was histologically and immunohistochemically analyzed [12]. CIM was ameliorated in this mouse model implicating IL-6 in the development of myositis. These results not only identified this model as useful to understanding PM but they suggest that IL-6 blockade be considered as a new therapeutic approach in the treatment of myositis [12].

Thus, the collective findings described above provide evidence for the involvement of IL-6 in the pathogenesis of both adult PM and DM as well as supporting its role from animal models and human studies.

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

Not applicable

1.4 Study Rationale

As summarized in section 1.2, there is rationale for the use of TCZ in patients with autoimmune disorders and specifically myositis. Although, there has been a paucity of

myositis patients who have received TCZ, the immunologic profile of PM and DM and the therapeutic effects of IL-6 blockade in a mouse model of PM suggest IL-6 as a potential therapeutic target.

2.0 OBJECTIVES

2.1 Primary

We propose a multi-center, double-blind, randomized placebo-controlled proof of concept pilot study to evaluate the efficacy and tolerability of TCZ in patients with refractory adult PM and DM.

2.2 Secondary

The secondary objectives of this study will include assessing the rapidity of response to TCZ, the magnitude of the response to TCZ, the steroid-sparing effect of TCZ, the durability of response, the presence of adverse effects to TCZ and the determinants of treatment response and disease pathogenesis in patients receiving IL-6 blockade. To assess the predictors and determinants of response to TCZ, blood and tissue samples will be analyzed along with clinical and demographic data to be collected in order to study those clinical, pathologic and immunologic factors associated with a response or lack of response to IL-6 blockade (see Section 3.1.1, Future Tests)..

3.0 STUDY DESIGN

3.1 Description of the Study

We propose a multi-center, double-blind, randomized placebo-controlled proof of concept pilot study to evaluate the efficacy and tolerability of tocilizumab in patients with refractory adult PM and DM.

3.1.1 Study Schema

We will enroll 40 adult patients with refractory PM (n= ~20) or DM (n= ~20) using a 1:1 randomization scheme for active drug:placebo, thus enrolling 20 subjects to receive active drug and 20 subjects to receive placebo. An effort will be made to equalize the number of enrolled PM and DM patients. The myositis subset, PM and DM, will be treated as a stratification variable and a "balanced coin" approach will be employed to control treatment assignment within enrollment sites. Refractory patients are defined as having failed (or considered intolerant to) an adequate course of glucocorticoids *or* having failed glucocorticoids and at least one other immunosuppressive (IS) or immunomodulatory agent (e.g. methotrexate, azathioprine, cyclosporine, tacrolimus, mycophenolate mofetil, cyclophosphamide, IVIg, anti-TNF agent, and rituximab). An adequate trial of glucocorticoids in adult IIM generally includes prednisone (or an equivalent glucocorticoid) at a dose of at least 60 mg/day for one month, while an adequate trial of an IS agent generally will be at least 3 months at a dose known to be effective for other rheumatologic conditions. In this trial, subjects enrolled who have only

been treated with glucocorticoids will have received an initial adequate trial of glucocorticoids and then failed to respond to this initial trial or flared with features of active myositis as the steroids are being tapered.

Enrolled subjects will have active disease as defined by the following clinical core set measures (CSM) and subjects must meet at least 3 of the following 6 criteria of disease activity to be enrolled:

- Muscle weakness as defined by an MMT-8 score that is no greater than 136/150 (see Appendix B)
- Patient global VAS with a minimum value of 2.0cm on a 10cm scale
- MD global VAS with a minimum value of 2.0cm on a 10cm scale
- HAQ disability index with a minimum value of 0.25
- Elevation of at least one of the muscle enzymes (CK, AST, ALT, aldolase, LDH) at a minimum level of 1.3x the ULN
- Global extramuscular disease activity (a composite of constitutional, cutaneous, skeletal, gastrointestinal, pulmonary and cardiac activity) score with a minimum value of 1.0cm on a 10cm VAS scale on the Myositis Disease Activity Assessment Tool (MDAAT)

All 6 CSM will be assessed at the screening visit and every 4 weeks thereafter prior to administration of TCZ which will be given at a dose of 8mg/kg (maximum dose 800mg) for 6 additional visits followed by a final closing visit (at which time study drug will not be administered). Thus, there will be a screening visit (no drug) followed by visits at weeks 0,4,8,12,16, and 20 with a week 24 closing visit. The newly determined ***definition of improvement*** (DOI) for this trial is a composite established by international consensus among various adult and pediatric myositis experts. The DOI necessitates achieving ≥ 20 points based on the model noted in Table 1.

Table 1.

1000Minds Model (absolute % change)	
Core Set Measure	**Improvement score for each level of CSM**
MD Global Absolute % Change	
Up to <=5%	0
>5% up to <=15%	7.5
>15% up to <=25%	15
>25% up to <=40%	17.5
>40%	20
Patient Global/Parent Global Absolute % Change	
Up to <=5%	0
>5% up to <=15%	2.5
>15% up to <=25%	5
>25% up to <=40%	7.5
>40%	10
MMT/CMAS Absolute % Change	
Up to <=2%	0
>2% up to <=10%	10

>10% up to <=20%	20
>20% up to <=30%	27.5
>30%	32.5
HAQ/CHAQ Absolute % Change	
Up to <=5%	0
>5% up to <=15%	5
>15% up to <=25%	7.5
>25% up to <=40%	7.5
>40%	10
Muscle Enzyme/CHQ-PF50 Absolute % Change	
Up to <=5%	0
>5% up to <=15%	2.5
>15% up to <=25%	5
>25% up to <=40%	7.5
>40%	7.5
Extra Muscular VAS/DAS Absolute % Change	
Up to <=5%	0
>5% up to <=15%	7.5
>15% up to <=25%	12.5
>25% up to <=40%	15
>40%	20
Total Improvement Score is sum of score achieved in each CSM	

Total improvement score ≥ cut points determines Minimal, Moderate and Major Improvement

Profile	**Improvement Category**	**Cut point on total improvement score**
Adult	Minimal Moderate Major	≥20 ≥40 ≥60

The primary endpoint will be the average of the Total Improvement Scores at each of the six follow-up points. Repeated measures analysis will be used to compare the two treatment groups and adjustments will be made for the baseline CSM values. The total improvement score will be calculated by adding the improvement scores of all six core set measures based on the new consensus driven improvement criteria in myositis (as shown in table 1).

Additional secondary endpoints include: (1) comparison of the time to first DOI between the 2 arms, (2) comparison of the individual CSM in subjects over time between the 2 arms (repeated measures analysis), (3) comparison of the steroid-sparing effect (calculated using prednisone dose equivalents) between the treatment and placebo arms, (4) assessment of the magnitude of the effect size between both treatment arms by comparing the proportion of subjects having Total Improvement Scores ≥ 20 (minimal), 40 (moderate) and 60 (major), (5) the difference in adverse events between the control and treatment arms. The durability of the treatment response will be assessed by (6)

comparing the proportion of subjects meeting DOI in the treatment and placebo arms ***on 2 consecutive visits***, (7) determination of the time to flare [meeting the definition of worsening (DOW)] in those who earlier met the DOI.(8) comparing the proportion of subjects meeting the DOI in the treatment and placebo arms using the previously published definition of improvement by IMACS for adult myositis [2] utilizing the six CSM: 3 of 6 CSM improved by ≥ 20%, with no more than 2 CSM worsening by ≥ 25% (a worsening measure cannot be the MMT).

There are preliminary criteria suggested for myositis disease worsening [13] which include: (1) physician global worsening of ≥ 2 cm on the 10 cm VAS and/or worsening of the manual muscle testing by ≥ 20%, or (2) global extra muscular organ disease activity worsening by ≥ 2 cm on a 10 cm VAS, or (3) any 3 of 6 CSM worse by ≥ 30%. Subjects meeting these criteria will be considered treatment failures if they did not first meet criteria for DOI. Treatment failures will also be defined as those subjects not achieving the DOI during the 24-week treatment period.

Strategies for (1) allowing "escape" therapies and (2) insuring that the original randomization treatment scheme is not revealed are discussed in Section 4.4.

A biospecimen repository will be developed with specimens (serum, cells etc.) collected at each study visit for future studies. Baseline muscle biopsies and a repeat muscle biopsy at or after the time that a subject meets DOI will be encouraged. The collected samples and muscle biopsies will be stored for future experimental studies. No specific studies or analysis of the muscle biopsies are included in this proposal. We will consider submission of ancillary proposals to conduct experiments designed to further elucidate biomarkers and basic physiologic and cellular mechanisms of disease resulting from tocilizumab therapy.

Future Tests:
The Specimen Repository samples will be used for two types of research:
1) immunologic and 2) genetic.

1. Immunology Research

   Tests to be performed on the stored blood and/or muscle biopsy samples include the following: T and B cell flow cytometry, RNA-Seq analysis, autoantibody testing for the presence of myositis associated autoantibodies, serum interferon (IFN)-inducible chemokines, Th1, Th2, Th17, innate, and regulatory cytokines at baseline and later time points in this clinical trial to identify a biomarker signature predicting responsiveness to IL-6 blockade. These immunology tests will be conducted in a research laboratory, not a public certified laboratory. Therefore, subjects will not be informed of these results.

2. Genetic Research

   Tests may include:
   a) Immunogenetic testing. This includes testing for components of the immune system that are inherited.

b) Genetic analysis. While the exact nature of the genetic research studies is not fully known, they may involve identifying genes that can: 1) increase the risk of developing autoimmune illnesses such as myositis, 2) modify the severity of autoimmune disease, or 3) control components of the immune system (immunogenetic studies).
c) The development of cell lines. Techniques have been developed which allow evaluation of genes and DNA. DNA might be examined directly. Some of the blood cells might be made into a "cell line" that can be grown indefinitely in the laboratory. A cell line gives researchers an unlimited supply of DNA that can be used for future research studies without having to draw additional blood in the future.

3.2 Rationale for the Study Design and Dose

It is difficult to estimate the timing of response to anti-IL-6 therapy but given the general timing of response to biologic therapy in rheumatic disease patients we anticipate that a 24-week trial is adequate in a pilot study of myositis. In addition, we will employ the dose of TCZ that has been used in most of the RA trials to date. For a pilot, proof of concept study we will not employ a dose escalation design.

3.3 Outcome Measures

The outcome measures used in this trial are those agreed upon by IMACS and have been employed in the RIM Study and include the following clinical core set measures (CSM):

- The MMT-8 **(Appendix B)**
- Patient global VAS recorded on a 10cm scale
- MD global VAS recorded on a 10cm scale
- HAQ disability index
- At least one of the muscle enzymes (CK, AST, ALT, aldolase, LDH)
- Global extramuscular disease activity (a composite of constitutional, cutaneous, skeletal, gastrointestinal, pulmonary and cardiac activity) score recorded on a 10cm VAS scale on the Myositis Disease Activity Assessment Tool (MDAAT)

3.3.1 Primary Outcome Measures

The primary outcome will be to compare the average Total Improvement Scores at visits 2 through 7 during the 6-month treatment period between the treatment and placebo arms. Repeated measures analysis will be used to compare the two treatment groups and adjustments will be made for the baseline CSM values. The total improvement score will be calculated by adding the improvement scores of all six core set measures based on the new consensus driven improvement criteria in myositis (as shown in table 1).

3.3.2 Secondary Outcome Measures

Additional secondary endpoints include: (1) comparison of the time to first DOI between the 2 arms, (2) comparison of the individual CSM in subjects over time between the 2

arms (repeated measures analysis), (3) comparison of the steroid-sparing effect (calculated using prednisone dose equivalents) between the treatment and placebo arms, (4) assessment of the magnitude of the effect size between both treatment arms by comparing the proportion of subjects having Total Improvement Scores ≥ 20 (minimal), 40 (moderate) and 60 (major), (5) the difference in adverse events between the control and treatment arms. The durability of the treatment response will be assessed by (6) comparing the proportion of subjects meeting DOI in the treatment and placebo arms ***on 2 consecutive visits***, (7) determination of the time to flare [meeting the definition of worsening (DOW)] in those who earlier met the DOI.(8) comparing the proportion of subjects meeting the DOI in the treatment and placebo arms using the previously published definition of improvement by IMACS for adult myositis [2] utilizing the six CSM: 3 of 6 CSM improved by ≥ 20%, with no more than 2 CSM worsening by ≥ 25% (a worsening measure cannot be the MMT).

3.3.3 Safety Outcome Measures

Safety is being assessed in one of the secondary endpoints listed above in Section 3.3.2. We will statistically compare the frequency of the following adverse events between the treatment and placebo arms:

- Infections including all opportunistic infections and non-serious infections as defined by those treated with IV anti-infectives
- Myocardial infarction/acute coronary syndrome
- GI perforation and related events
- Malignancies
- Hypersensitivity reactions and anaphylaxis
- Demyelinating disorders
- Stroke
- Bleeding events
- Hepatic events

Similarly, we will analyze the proportion of serious adverse events between the treatment and placebo arms. In addition, the number and percent of patients with AEs during the treatment period will be summarized.

3.4 End of Study

As described above, the end of the study (closing visit) is week 24 but 2 additional visits 3 months and 6 months after the closing visit at week 24 have been added to assess durability of TCZ response and safety. These 2 additional study points are not only critical to the study from the standpoint of assessing safety and the durability of treatment response, but also provide an opportunity to collect valuable subject specimens for assessing biomarkers and indicators of disease response and relapse.

4.0 STUDY POPULATION

4.0.1 Overview: Target Population

This trial will generally target a refractory population of adult PM and DM patients. Most enrolled patients will have failed a trial of glucocorticoids and at least one immunosuppressive or immunomodulatory agent (similar entry criteria as the RIM Study). However, we will also enroll patients who have failed an adequate trial of glucocorticoids or who are flaring with active disease as steroids are being tapered. Nevertheless, subjects only failing glucocorticoids will likely be a minority of the patients who are enrolled in the trial.

In addition to active myositis demonstrated by objective muscle weakness (low MMT-8 score), we will also enroll DM patients with less severe muscle weakness but a significant skin rash and/or other extramuscular features that qualify them for enrollment (see Section 3.1 above and Inclusion Criteria below). Thus, this trial allows us to study an additional subset of patients not enrolled in the RIM Study [1] who have demonstrable myositis and/or extramuscular disease activity but who fail to meet the single MMT-8 criterion [i.e. an MMT-8 score that is ≥ 136/150 (see Appendix B)]. However, a secondary endpoint of this trial allows us to analyze the individual CSM over time in subjects receiving drug and placebo so they can still be compared throughout the trial (i.e. using repeated measures analysis).

4.1 Inclusion Criteria

Patients will be included in the trial based on the following criteria:

1. Definite or probable PM or DM by the criteria of Bohan and Peter (as modified by IMACS) in adults over the age of 18. We will also allow enrollment of JDM patients (considered to have DM) over the age of 18 who otherwise meet the inclusion criteria stipulated below.

2. Subjects must either have the classic rash(es) of DM (heliotrope, Gottron sign or Gottron papules), possess one of the myositis-associated autoantibodies (anti-synthetase, anti-SRP, anti-Mi-2, anti-PM-Scl, anti TIF1-γ and anti-MDA5), or have the diagnosis of PM agreed upon by a 3-member Adjudication Committee consisting of a rheumatologist, neurologist and neuromuscular pathologist.

3. Refractory myositis patients are defined (see Section 3.1.1) as having failed (or considered intolerant to) an adequate course of glucocorticoids or having failed glucocorticoids and at least one other immunosuppressive (IS) or immunomodulatory agent (e.g. methotrexate, azathioprine, cyclosporine, tacrolimus, mycophenolate mofetil, cyclophosphamide, IVIg, anti-TNF agents, and rituximab).

4. Subjects must have at least 3/6 of the following abnormal CSM (see below) including an MMT ≤ 136/150 *or* subjects with an MMT > 136/150 must have 3 of the following abnormal CSM *plus* a cutaneous VAS on the MDAAT of ≥ 3 cm on a 10 cm scale. Criteria for core set measures for study entry:
    a. Patient global VAS with a minimum value of 2.0cm on a 10cm scale.
    b. MD global VAS with a minimum value of 2.0cm on a 10cm scale.
    c. HAQ disability index with a minimum value of 0.25

d. Elevation of at least one of the muscle enzymes (CK, AST, ALT, aldolase, LDH) at a minimum level of 1.3x the ULN.
e. Global extramuscular disease activity score with a minimum value of 1.0cm on a 10cm VAS scale on the Myositis Disease Activity Assessment Tool (MDAAT).

5. If on prednisone, the dose must be stable for 4 weeks prior to the screening visit. Tapering of the prednisone dose will only be allowed after the subject meets the DOI or if safety/toxicity issues supervene.
    a. Prednisone Tapering: Prednisone should be held constant without tapering or escalation (unless there is a serious adverse event or disease flare) until the subject has achieved the DOI. Then, tapering of prednisone may commence using a schedule approximating a 20-25% taper of the existing dose every 4 weeks based on the clinical judgment of the clinical site investigator. Prednisone tapering using the aforementioned guidelines can be commenced at any time if: (a) the patient achieves the DOI or (b) there are complications or circumstances that, in the clinical site investigator's opinion, necessitate the tapering of corticosteroids.

    b. Prednisone at Entry: It is also recommended that patients be on less than 1mg/kg/day of prednisone at study entry.

    c. Prednisone Dosing During Flare: If in the clinical site investigator's opinion there are complications or worsening of disease that necessitate an increase in the prednisone dose then the smallest reasonable increase should be considered.

6. If an IS agent was discontinued prior to the screening visit there may be a washout as stipulated below or individualized according to the patients treating physician:
    a. 4 week washout for methotrexate and tofacitinib
    b. 8 week washout for any other IS agent (e.g. azathioprine, cyclosporine, tacrolimus, mycophenolate mofetil)
    c. 3 month washout for leflunomide, IVIg or cyclophosphamide
    d. 6 month washout for rituximab
    e. 8 week washout for infliximab,adalimumab, golimumab, certolizumab
    f. 2 week washout for etanercept
    g. 1 week washout for anakinra

7. If an IS agent is continued, the dose must remain stable for 4 weeks prior to the screening visit and at least until the DOI is met or if safety/toxicity issues supervene. Concomitant IS medications permitted include methotrexate, azathioprine, cyclosporine, mycophenolate mofetil, and tacrolimus. IVIg will also be allowed as an immunomodulatory agent. Careful patient safety monitoring along with ACR guidelines for monitoring these medications will be employed if those toxicity monitoring laboratory studies are not already being assessed as part of this trial. No concomitant biologic agents are allowed (rituximab, anti-TNFs, abatacept) as well as cyclophosphamide or tofacitinib as concomitant immunosuppressive agents. Investigators will be certain to assess and classify adverse events as being secondary

to either study drug as well as any concomitant immunosuppressive agent(s). That is, there should be attribution of the AE to the appropriate agent.

8. Normal organ function, except if abnormal due to the disease under investigation

9. Men and women of reproductive potential must agree to use an acceptable method of birth control during treatment and for three months after completion of treatment.

10. Subject has provided written informed consent.

4.2 Exclusion Criteria

A patient will be excluded if any of the following criteria are met:

1. Subjects under the age of 18.

2. Severe muscle damage defined as a global muscle damage score >5 on a 10cm VAS scale on the Muscle Damage Index (MDI).

3. Cancer-associated myositis, defined as the diagnosis of myositis within 2 years of the diagnosis of cancer except basal or squamous cell skin cancer or carcinoma in situ of the cervix that has been excised and cured and at least 5 years since excision. Also, evidence of active malignant disease, malignancies diagnosed within the previous 5 years (including hematological malignancies and solid tumors) or breast cancer diagnosed within the previous 10 years.

4. 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).

5. Any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks of screening or oral antibiotics within 2 weeks prior to screening.

6. 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.
    a. Quantiferon Gold (QG) is required for patients positive PPD results, who have previously received bacilli Calmette Guerin vaccination, OR for patients, who in the investigator's opinion, may be anergic.

For all other patients the following procedures for screening will be followed:

    b. If the patient has had a negative PPD or QG test result within the past year, **and** has not traveled to endemic areas **and** has not been exposed to a known case within the previous 12 months, then no further

screening will be required.

c. If the patient has not been screened for TB within the previous 12 months, then the local site will order the appropriate test (PPD or QG acceptable), according to their clinical standard of care.

d. **If QG is used and the results are indeterminate**, the patient will be rescreened using PPD.

7. Primary or secondary immunodeficiency (history of or currently active) unless related to primary disease under investigation.

8. Pregnant women or nursing (breast feeding) mothers.

9. Patients with reproductive potential not willing to use an effective method of contraception.

10. History of alcohol, drug or chemical abuse within 1 year prior to screening or any medical condition or physical or psychological state that the PI feels would not allow the subject to safely complete the study.

11. Initiation of an exercise program for muscle strengthening within 4 weeks of the screening visit or initiation of a muscle strengthening exercise program during the study.

12. Major surgery (including joint surgery) within 8 weeks prior to screening or planned major surgery within 6 months following randomization.

13. Treatment with any investigational agent within 4 weeks (or 5 half-lives of the investigational drug, whichever is longer) of screening.

14. Previous treatment with the following cell-depleting therapies, including investigational agents or approved therapies: CAMPATH, anti-CD4, anti-CD5, and anti¬CD3.

15. Immunization with a live/attenuated vaccine within 4 weeks prior to baseline.

16. Previous treatment with TCZ.

17. History of severe allergic or anaphylactic reactions to human, humanized or murine monoclonal antibodies.

18. 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.)

19. Patients with lack of peripheral venous access.

20. Body weight of > 150 kg.

21. Abnormal laboratory values noted below:
    a. Serum creatinine > 1.6 mg/dL in female patients and > 1.9 mg/dL 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.
    b. Platelet count < (100,000/mm^3); hemoglobin < 8.5 g/dl and WBC count < 3000/mm^3; Absolute Neutrophil Count < 2.0 x 10^9/L (2000/mm3); Absolute Lymphocyte Count < 0.5 x 10^9/L (500/mm3)

22. Positive hepatitis BsAg or hepatitis C antibody

4.3 Immunization during TCZ therapy

Live/attenuated vaccines should not be given within 4 weeks prior to baseline and during the study 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. No data are available on the effectiveness of vaccination in 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. Every attempt will be made to have all patients complete the remaining study visits 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.

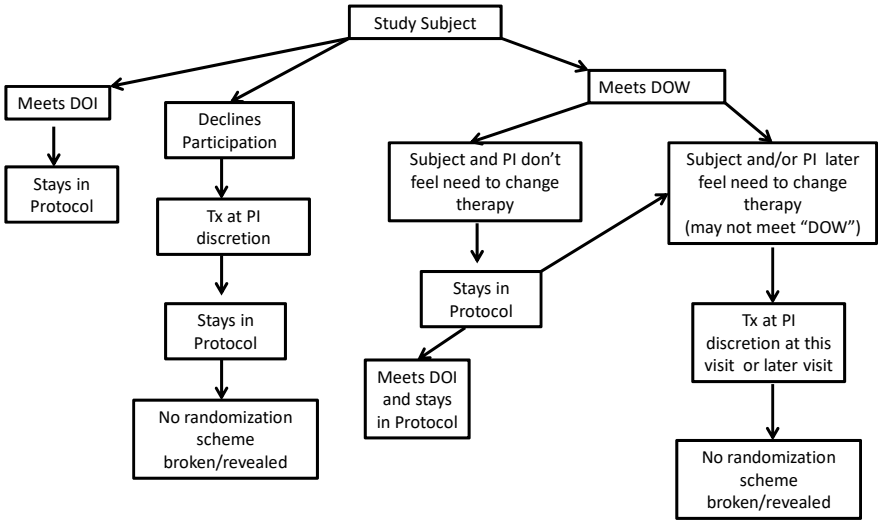
An excessive rate of withdrawals can render the study non-interpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw, all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible.

Specifically related to this trial, there are several scenarios for subjects as they are followed through the 24 week trial:

1. Subjects improve and will be followed for the duration of the trial.
2. Subjects can withdraw from the study at any time. They are then treated at the discretion of the PI but should continue to be followed at the regular study time points for the duration of the trial. No randomization scheme will be broken/revealed.
3. If the criteria for the DOW are formally met but the subject and PI do not feel it is necessary to change therapies, then the subject will remain on protocol.
4. If criteria for the DOW is formally met and the subject and/or the PI feel that other "escape" therapy is necessary *or* if the subject and PI feel that worsening has occurred such that other escape therapy is necessary without formally meeting DOW criteria, then the subject will be treated at the discretion of the PI and no randomization scheme will be broken/revealed. Subjects will continue to be followed at the regular study time points for the duration of the trial.

   ***Note: Investigators will be encouraged to wait until at least Week 8 before designating subjects as treatment failures eligible to receive "escape" therapies.*

   The following is a summary of what is described above:



Scheme for Subject Retention in Trial

5.0 TREATMENT PLAN

This is a Phase II, double-blind, randomized, placebo-controlled proof of concept trial of refractory adult PM and DM. TCZ will be given at a dose of 8mg/kg by IV infusion every 4 weeks at 6 time points (0,4,8,12,16,20).

We will enroll 40 adult patients with refractory PM (n= ~20) or DM (n= ~20) using a 1:1 randomization scheme for active drug:placebo, thus enrolling 20 subjects to receive active drug and 20 subjects to receive placebo. We hope to enroll 40 subjects at an enrollment rate of ~2 subjects/month such that recruitment will encompass a period of 20 months. This research study protocol allows the subject to receive up to "6" infusions of tocilizumab. 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 H2L2 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 or designee 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 8 mg/kg 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.

When the Investigational Drug Service (IDS) at the University of Pittsburgh is involved with the study protocol and prepares an IV drug that is to be blinded the following steps are taken:

1. The pharmacist will be the only unblinded study personnel and they will follow whatever the study protocol dictates. They can create and maintain the randomization list for the study based off of the randomization schema outlined in the protocol.
2. The label will read **"Drug Name and Strength" or PLACEBO.** This is placed on every label regardless if is drug or placebo.
3. If the drug preparation is slightly colored or cloudy, they will wrap the IV bag in an amber bag so as to not allow the blinded personnel to decipher the color of the solution.
4. The placebo formulation will be the same total volume as the study medication preparation and will be normal saline (unless otherwise specified).

For individuals whose body weight is more than 100 kg, doses exceeding 800 mg per will not be given.

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 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.

6.2 Other Study Drug(s)

Placebo will be prepared as described above in Section 6.1.1.

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 (Note: The following are considered adverse events of special interest and they should be reported in an expedited fashion should they occur while using 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., diverticulitis, 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 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. TCZ should not be given in the setting of active infection.

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. 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 will be excluded. 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 Tables 1 and 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 as clinically appropriate
< 500	Discontinue tocilizumab.

ANC = absolute neutrophil count

Patients withdrawn from tocilizumab treatment due to a reduced neutrophil count should be monitored for signs of infection, with treatment as deemed appropriate by the sponsor or designee, and should have a repeat white blood cell count with differential performed weekly until the ANC is above 1000 cells/mm^3 (1.0 x 10^9/L). If the ANC does not return to above 1000 cells/mm^3 (1.0 x 10^9/L) within 2 months (or sooner if deemed necessary by the sponsor or designee), a hematology referral is recommended.

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 as clinically appropriate
< 50,000	Discontinue tocilizumab.

Patients withdrawn from tocilizumab treatment due to a reduced platelet count should have a repeat platelet count performed weekly until the count is above 100,000 cells/mm^3 (100 x 10^9/L). If the platelets do not return to above 100,000 cells/mm^3 (100 x 10^9/L) within 2 months (or sooner if deemed necessary by the sponsor or designee), a hematology referral is recommended.

Elevated Liver Enzymes and Hepatic Events

Elevations in ALT and AST have been observed during treatment with TCZ, but patients with myositis may have elevated levels of transaminases due to active myositis. Thus, these levels will be closely followed and compared to the elevation of other muscle enzymes in order to monitor hepatic toxicity and make appropriate adjustments in either concomitant therapy or TCZ.

Patients withdrawn from tocilizumab treatment due to elevated liver function tests should have repeat tests performed, as clinically appropriate, until levels return to baseline. If the patient's liver function tests have not returned to baseline within 6 months (or sooner, if deemed necessary by the sponsor or designee), an ultrasound and/or liver biopsy should be considered.

Cardiovascular Events and Elevated Lipids

Patients with some connective tissue diseases 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 some patients with autoimmune disorders. 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, pruritis, 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.

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 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, cyclosporine, 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 several weeks after stopping therapy.

8.0 CRITERIA FOR SUBJECT DISCONTINUATION

8.1 Tocilizumab-Specific Criteria

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

- anaphylaxis or hypersensitivity reaction or requires an interruption of the study drug because of symptoms of anaphylaxis or hypersensitivity (TCZ should be permanently discontinued from these patients)
- ALT or AST value > 5X ULN or persistent elevation > 3X ULN
- Platelet count (cells/mm^3) < 50,000
- ANC (cells/mm^3) < 500

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

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.

9.0 CRITERIA FOR STUDY DISCONTINUATION

See Section 4.4.

10.0 CLINICAL AND LABORATORY EVALUATIONS

Week	0-14 days before	0	4	8	12	16	20	24	3 mo Follow Up	6 mo Follow Up
Visit	**Screen**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Study Drug Administration		x	x	x	x	x	x			
Safety Laboratory Testing										
Urine Pregnancy (if applicable)	x		x	x	x	x	x	x	x	x
WBC	x		x	x	x	x	x	x	x	x
Platelets	x		x	x	x	x	x	x	x	x
Neutrophils/Monocytes/Eosinophils Basophils	x		x	x	x	x	x	x	x	x
Hemoglobin	x		x	x	x	x	x	x	x	x
Hematocrit	x		x	x	x	x	x	x	x	x
ALT	x		x	x	x	x	x	x	x	x
AST	x		x	x	x	x	x	x	x	x
Aldolase	x		x	x	x	x	x	x	x	x
LDH	x		x	x	x	x	x	x	x	x
CK, total	x		x	x	x	x	x	x	x	x
BUN	x		x	x	x	x	x	x	x	x
Creatinine	x		x	x	x	x	x	x	x	x
Electrolytes	x		x	x	x	x	x	x	x	x
IgG quantitative	x		x		x		x			
IgM quantitative	x		x		x		x			
Serologies (varicella, HCV, HBV)	x									
Lipid Panel	x			x					x	
Anti-TCZ autoantibodies & PK/PD*		x								
Data Collection										
Screening Demographics	x									
Screening Evaluation	x									
Screening Criteria	x									
Randomization Form		x								
Patient Global Assessment	x		x	x	x	x	x	x	x	x
Health Assessment Questionnaire	x		x	x	x	x	x	x	x	x
MMT-8	x		x	x	x	x	x	x	x	x
MDAAT	x		x	x	x	x	x	x	x	x
MDI	x						x			x
Physician Global Assessment	x		x	x	x	x	x	x	x	x
Physician Assessment of Change			x	x	x	x	x	x	x	x
SF 36 QoL Questionnaire		X	x	x	x	x	x	x	x	x
Brief Evaluation		x	x	x	x	x	x	x	x	x
Muscle Biopsy		x					x			
Adverse Event Monitoring		x	x	x	x	x	x	x	x	x
Biospecimen Repository Collection		x	x	x	x	x	x	x	x	x

* If a hypersensitivity event occurs, these tests will be done at the time of the event and 6 weeks later

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

See Section 10.0

- Neutrophils should be monitored every 4 to 8 weeks following initiation of therapy, then at approximately 3 month intervals
- Platelets should be monitored ever 4 to 8 weeks following initiation of therapy, then at approximately 3 month intervals
- ALT and AST levels should be monitored every 4 to 8 weeks following initiation of therapy, then at approximately 3 month intervals
- Assessment of lipid parameters should be performed approximately 4 to 8 weeks following initiation of TCZ therapy, then at approximately 6 month intervals

Anti-TCZ antibodies, TCZ levels and sIL6-R are to be collected at baseline, at the time of any event of hypersensitivity or anaphylaxis that is potentially related to TCZ and 6 weeks subsequent to the event.

Baseline samples for immunogenicity testing will be drawn and stored for all patients but analyzed only for those patients meeting the criteria below.

Post-baseline, for patients who meet any of below criteria, immunogenicity samples will be additionally collected at the time of the event, and then again at least 6 weeks post-hypersensitivity for IV and 8 weeks post-hypersensitivity for SC.

Event:
anaphylaxis

serious hypersensitivity
study treatment (Actemra) discontinuation due to hypersensitivity (serious or non-serious)

Immunogenicity assays: screening, confirmation and IgE

PK-PD samples should be collected at the same time points as immunogenicity samples

All patients experiencing events related to serious hypersensitivity or anaphylactic reactions that cause the patient to be withdrawn from TCZ treatment dose for anti-TCZ and PK/PD testing.

Reports of the results of these analyses will be provided to the investigator for patients testing positive for anti-TCZ antibodies. Sample logistics and handling will be managed by Covance Laboratories.**10.3 Post-Treatment Evaluations**

See Section 10.0

11.0 REPORTING OF ADVERSE EVENTS

11.1 Adverse Event and Reporting Definitions

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 temporally associated with or occurring during the use of an investigational product whether or not considered related to the investigational product.

Additionally, an AE can be any of the following:

- *Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)*
- *Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.*
- *Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram, x-ray) that is associated with symptoms or leads to a change in tocilizumab or concomitant treatment or discontinuation from tocilizumab.*

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**, and non-serious adverse events of special interest, whether **expected** or **unexpected**, and whether or not considered related to the tocilizumab.

The sponsor or designee further agrees to forward reports to Genentech of serious adverse events and non-serious adverse events of special interest, regardless of attribution to 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.

Serious adverse events (SAE) (Immediately Reportable to the Sponsor) 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** (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.

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. Investigators will be certain to assess and classify adverse events as being secondary to either study drug as well as any concomitant immunosuppressive agent(s). That is, there should be attribution of the AE to the appropriate agent.
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 (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 TCZ, 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 TCZ; and/or the AE abates or resolves upon discontinuation of TCZ or dose reduction and, if applicable, reappears upon re-challenge.

No

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

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.

The terms "severe" and "serious" are <u>not</u> synonymous. Severity refers to the intensity of an AE (rated as mild, moderate, or severe; see section on "Assessment of Severity of Adverse Events"); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the CRF.

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 5.1.2), 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". This includes death attributed to progression of underlying disease.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event CRF. Generally, only one such event should be reported. The term "sudden death" should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event CRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. If the death is attributed to progression of underlying disease, progression should be captured on the Adverse Event CRF.

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. Pregnancy

If a female subject becomes pregnant while receiving investigational therapy or within 90 days after the last dose of study drug, a report should be completed and expeditiously submitted to the 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 TCZ should be reported as an SAE. A Clinical Trial Pregnancy Reporting Form should be completed by the sponsor within 24 hours after learning of the pregnancy should not be recorded on the Adverse Event CRF. The sponsor should counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

Abortions
Any spontaneous abortion should be classified as an SAE (as the sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event CRF, and reported to the sponsor within 1 working day after learning of the event (see section on "Reporting Requirements for Pregnancies").

Congenital Anomalies/Birth Defects
Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be classified as an SAE, recorded on the Adverse Event CRF, and reported to the sponsor within 1 working day after learning of the event (see section on "Reporting Requirements for Pregnancies").

f. Post-Study Adverse Events

The investigator should expeditiously report any SAE or non serious AESI occurring after a subject has completed or discontinued study participation if attributed to prior TCZ exposure regardless of how much time has elapsed since study participation. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE. All unrelated SAEs must be reported during the study and up to 3 months after the last dose of study drug, even if the study has been closed.

g. Reconciliation

The sponsor agrees to conduct reconciliation for the product. Genentech and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange monthly line listings of cases received by the other party. 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.

11.2 Reporting of Serious Adverse Events Associated with Tocilizumab

Immediate Reporting Requirements

The Investigator must report the following events to Genentech Drug Safety within 24 hours after learning of the event, regardless of relationship to study drug:

- *SAEs.*

- *Non-serious and serious AEs of special interest.*
- *Pregnancies.*

The Investigator must report new significant follow-up information for these events to Genentech Drug Safety within 1 working day after becoming aware of the information. New significant information includes the following:

- *New signs or symptoms or a change in the diagnosis.*
- *Significant new diagnostic test results.*
- *Change in causality based on new information.*
- *Change in the event's outcome, including recovery.*
- *Additional narrative information on the clinical course of the event.*

Investigators must also comply with local requirements for reporting SAEs to the local health authority and IRB/EC.

All serious adverse events (SAEs) for which there is a reasonable possibility the experience may have been caused by Tocilizumab (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.)

AND:

Chester V. Oddis, M.D.
University of Pittsburgh School of Medicine
Division of Rheumatology and Clinical Immunology
South 705, Biomedical Science Tower
3500 Terrace Street
Pittsburgh, PA 15261
Phone: 412-383-8861
Fax: 412-383-8864
email: cvo5@pitt.edu

AND:

University of Pittsburgh
Institutional Review Board
3500 Fifth Avenue
Hieber Building, Suite 106
Pittsburgh, PA 15213
Main Phone: (412) 383-1480
Main Fax: (412) 383-1508

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.

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 24 hours 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 all opportunistic infections and non-serious infections as defined by those treated with IV anti-infectives
- Myocardial infarction/acute coronary syndrome
- GI perforation and related events
- Malignancies
- Hypersensitivity reactions
- Demyelinating disorders
- Stroke
- Bleeding events
- Hepatic events

Guided questionnaires have been prepared for the 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 one working day). 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).

Study Close-Out
Any study report submitted to the FDA by the Sponsor or designee should be copied to Genentech. 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. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

[Clinical Operations Contact Information Here]

12.0 EVALUATION OF RESPONSE

The outcome measures used in this trial are those agreed upon by IMACS and include the following clinical core set measures (CSM):

- The MMT-8 **(Appendix B)**
- Patient global VAS recorded on a 10cm scale
- MD global VAS recorded on a 10cm scale
- HAQ disability index

- At least one of the muscle enzymes (CK, AST, ALT, aldolase, LDH)
- Global extramuscular disease activity (a composite of constitutional, cutaneous, skeletal, gastrointestinal, pulmonary and cardiac activity) score recorded on a 10cm VAS scale on the Myositis Disease Activity Assessment Tool (MDAAT)

All 6 CSM will be assessed at the screening visit and every 4 weeks thereafter prior to administration of TCZ for 6 additional visits followed by a final closing visit. The newly determined primary outcome for this trial is a composite established by international consensus among various adult and pediatric myositis experts. Patients who achieve a score ≥20 points based on the model in Table 1 are considered to have minimal improvement. The proportion of patients having a score ≥20 at each of the time points in the two treatment groups will provide an indication of the clinical relevance of the effect of treatment.

13.0 STATISTICAL CONSIDERATIONS

13.1 Determination of Sample Size

The sample size is justified based on this trial being a *proof of concept* pilot study. We have proposed a study population of 40 subjects being recruited among sites that were active enrollers in the RIM Study. This will allow us to determine an estimate of the effect size of the study drug and placebo and to assess feasibility and safety in a pilot trial. If the estimate of time to improvement is consistent with a benefit of TCZ compared to placebo as measured by the primary endpoint and secondary endpoints 1, 2 and 4, then a larger study including both adult and juvenile myositis will be proposed with the potential incorporation of sites outside of the United States.

13.2 Planned Efficacy Evaluations

13.2.1 Primary Efficacy Variables

The primary endpoint will be to compare the average Total Improvement Scores at visits 2 through 7 during the 6-month treatment period between the treatment and placebo arms. Repeated measures analysis will be used to compare the two treatment groups and adjustments will be made for the baseline CSM values. The total improvement score will be calculated by adding the improvement scores of all six core set measures based on the new consensus driven improvement criteria in myositis (as shown in table 1).

13.2.2 Secondary Efficacy Variables

Additional secondary endpoints include: (1) comparison of the time to first DOI between the 2 arms, (2) comparison of the individual CSM in subjects over time between the 2 arms (repeated measures analysis), (3) comparison of the steroid-sparing effect (calculated using prednisone dose equivalents) between the treatment and placebo arms, (4) assessment of the magnitude of the effect size between both treatment arms by comparing the proportion of subjects having Total Improvement Scores ≥ 20 (minimal), 40 (moderate) and 60 (major), (5) the difference in adverse events between the control

and treatment arms. The durability of the treatment response will be assessed by (6) comparing the proportion of subjects meeting DOI in the treatment and placebo arms ***on 2 consecutive visits***, (7) determination of the time to flare [meeting the definition of worsening (DOW)] in those who earlier met the DOI.(8) comparing the proportion of subjects meeting the DOI in the treatment and placebo arms using the previously published definition of improvement by IMACS for adult myositis [2] utilizing the six CSM: 3 of 6 CSM improved by ≥ 20%, with no more than 2 CSM worsening by ≥ 25% (a worsening measure cannot be the MMT).

13.3 Methods of Analysis

The primary analysis will compare the average Total Improvement Score in the two treatment groups at visits 2 through 7 during the 6 month treatment period. We will use repeated measures analysis and adjust for baseline CSM values. Such an analysis uses all of the information provided by the Total Improvement Score but does not incorporate information on whether there has been a clinically meaningful difference. Therefore, we have included as a secondary endpoint (secondary endpoint 4), a comparison of the proportion of patients in the two groups that have minimal, moderate or major improvement.

For analysis of the 8 **secondary endpoints** noted in Section 13.2.2, we will use the following methods:
(1) Kaplan-Meier plots will summarize the time to improvement in the two arms and to compare the time to improvement between the 2 groups the log rank test will be used.
(2) The average monthly values of the individual CSM between the 2 treatment arms will be analyzed using a repeated measures analysis adjusted for baseline values.
(3) The two sample t-test (or when appropriate the Mann-Whitney statistic) will be used to analyze and compare the average steroid-sparing effect between the treatment and placebo arms.
(4) The effect size between treatment arms will be assessed by comparing at each time point the proportion of patients having minimal, moderate and major improvement. Binary repeated measures will be used to test equality of proportions between the two groups.
(5) The chi-square statistic will summarize the difference in proportion of adverse events between the placebo and study drug arms.
(6) Kaplan-Meier plots will summarize the time to improvement (on 2 consecutive visits) in the two arms and to compare this time to improvement between the 2 groups the log rank test will be used.
(7) Kaplan-Meier plots will similarly summarize the time to disease flare (DOW) in the two arms and to compare the time to flare/worsening between the 2 groups the log rank test will be used.
(8) Kaplan-Meier plots and the logrank test will be used to compare the two treatment groups using the previously published definition of improvement proposed by IMACS.

14.0 RETENTION OF RECORDS

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 will be retained.

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APPENDIX A: STUDY FLOW CHART/SCHEMA

Week	0-14 days before	0	4	8	12	16	20	24	3 mo Follow Up	6 mo Follow Up
Visit	**Screen**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Study Drug Administration		x	x	x	x	x	x			
Safety Laboratory Testing										
Urine Pregnancy (if applicable)	x		x	x	x	x	x	x	x	x
WBC	x		x	x	x	x	x	x	x	x
Platelets	x		x	x	x	x	x	x	x	x
Neutrophils/Monocytes/Eosinophils Basophils	x		x	x	x	x	x	x	x	x
Hemoglobin	x		x	x	x	x	x	x	x	x
Hematocrit	x		x	x	x	x	x	x	x	x
ALT	x		x	x	x	x	x	x	x	x
AST	x		x	x	x	x	x	x	x	x
Aldolase	x		x	x	x	x	x	x	x	x
LDH	x		x	x	x	x	x	x	x	x
CK, total	x		x	x	x	x	x	x	x	x
BUN	x		x	x	x	x	x	x	x	x
Creatinine	x		x	x	x	x	x	x	x	x
Electrolytes	x		x	x	x	x	x	x	x	x
IgG quantitative	x		x		x		x			
IgM quantitative	x		x		x		x			
Serologies (varicella, HCV, HBV)	x									
Lipid Panel	x			x					x	
Anti-TCZ autoantibodies & PK/PD*		x								
Data Collection										
Screening Demographics	x									
Screening Evaluation	x									
Screening Criteria	x									
Randomization Form		x								
Patient Global Assessment	x		x	x	x	x	x	x	x	x
Health Assessment Questionnaire	x		x	x	x	x	x	x	x	x
MMT-8	x		x	x	x	x	x	x	x	x
MDAAT	x		x	x	x	x	x	x	x	x
MDI	x						x			x

Physician Global Assessment	x		x	x	x	x	x	x	x	x
Physician Assessment of Change			x	x	x	x	x	x	x	x
SF 36 QoL Questionnaire			x	x	x	x	x	x	x	x
Brief Evaluation		x	x	x	x	x	x	x	x	x
Muscle Biopsy		x					x			
Adverse Event Monitoring		x	x	x	x	x	x	x	x	x
Biospecimen Repository Collection		x	x	x	x	x	x	x	x	x

***** If a hypersensitivity event occurs, these tests will be done at the time of the event and 6 weeks later

APPENDIX B: MMT-8

MMT- 8 is a set of 8 designated muscles tested unilaterally (potential score 0-70 and usually tested on the right side unless contraindicated) or bilaterally (potential score 0-140) and if axial (neck flexor) testing is included, potential score = 150. The scale of 150 is proposed for this trial.

Muscle Groups	Right (0 – 10)	Left (0 – 10)
Axial Muscles (0 – 10)		
Neck Flexors	**0-10**	
Proximal Muscles (0 – 50)		
Deltoid	**0-10**	**0-10**
Biceps brachii	**0-10**	**0-10**
Gluteus maximus	**0-10**	**0-10**
Gluteus medius	**0-10**	**0-10**
Quadriceps	**0-10**	**0-10**
Distal Muscles (0 – 20)		
Wrist extensors	**0-10**	**0-10**
Ankle dorsiflexors	**0-10**	**0-10**
MMT- 8 score (0 – 150)	**0-70**	**0-80**

APPENDIX C: FDA MEDWATCH 3500A FORM

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

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