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Title: “Effect of Subcutaneous ACTEMRA on Inflamed Atherosclerotic Plaques in Patients With Rheumatoid Arthritis”

Contains Detailed Study protocol (with embedded SA

Protocol Date: Jun 3, 2019

Massachusetts General Hospital
&
Brigham and Women's Hospital
Harvard Medical School

Study Title

A MULTICENTER, OPEN-LABEL, PROOF-OF-ACTIVITY STUDY OF THE EFFECT OF SUBCUTANEOUS ACTEMRA ON INFLAMED ATHEROSCLEROTIC PLAQUES IN PATIENTS WITH RHEUMATOID ARTHRITIS

Study Drug
Tocilizumab (ACTEMRA®)

Support Provided By
Genentech

Sponsor Investigator
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Study Number: ML29520

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TABLE OF CONTENTS

1.0 INTRODUCTION

1.1 Disease Background

Patients with rheumatoid arthritis (RA) suffer significantly increased cardiovascular (CV) morbidity and mortality when compared to the general population [1-3]. Women with RA have a 2-3 fold higher risk of myocardial infarction, even in the absence of traditional coronary risk factors [4-6]. Several studies suggest that systemic inflammation accelerates atherogenesis in RA, perhaps by accentuation of both established as well as novel risk factor pathways [6-8].

1.2 Tocilizumab Background

Refer to the Tocilizumab Investigator Brochure for descriptions of completed Phase I, II, and III trials.

1.1.2 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.

For the intravenous (IV) formulation, the half-life of TCZ is approximately 12.9 days. The TCZ exposures were stable over 2- years of treatment. The observed mean (± SD) C_{trough} 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) C_{trough} at 4 mg/kg was 1.02 ± 6.14 at week 24 and 1.09 ± 2.77 at week 104.

The pharmacokinetics of subcutaneous (SC) TCZ was characterized using a population pharmacokinetic analysis using a database composed of 1759 rheumatoid arthritis patients treated with 162 mg SC every week, 162 mg SC every other week, and 8 mg/kg every 4 weeks for 24 weeks.

The pharmacokinetic parameters of TCZ did not change with time. For the 162 mg every week dose, the estimated mean (±SD) steady-state AUC_{1week}, C_{min} and C_{max} of TCZ were 8200 ± 3600 mcg•h/mL, 44.6 ± 20.6 mcg/mL, and 50.9 ± 21.8 mcg/mL, respectively. The accumulation ratios for AUC, C_{min}, and C_{max} were 6.83, 6.37, and 5.47, respectively. Steady state was reached after 12 weeks for AUC, C_{min}, and C_{max}.

For the 162 mg every other week dose, the estimated mean (±SD) steady-state AUC_{2week}, C_{min}, and C_{max} of TCZ were 3200 ± 2700 mcg•h/mL, 5.6 ± 7.0 mcg/mL, and 12.3 ± 8.7 mcg/mL, respectively. The accumulation ratios for AUC, C_{min}, and C_{max} were 2.67, 5.6, and 2.12, respectively. Steady state was reached after 12 weeks for AUC and C_{min}, and after 10 weeks for C_{max}.

The Roche clinical development program in adult RA, comprised five pivotal Phase 3 trials and two open-label, long-term treatment extension studies for the IV formulation and two pivotal Phase 3 trials with open-label, long-term treatment extension arms for the SC formulation.

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

1.3 Other Study Drug(s) Background

No other study drugs.

1.4 Study Rationale

In human studies of rheumatoid arthritis, anti-IL-6 therapy with tocilizumab is associated with reduction in disease activity [9] and a substantial reduction in CRP, an important biomarker of inflammation and a risk factor for atherothrombotic events. However, use of tocilizumab is associated with an elevation in LDL[10] and total cholesterol of unclear clinical significance. We hypothesize that, despite these observed effects on lipids, the use of tocilizumab therapy in RA patients may be associated with a reduction in atherosclerotic plaque inflammation.

Positron Emission tomography with[18]fluorine-2-deoxy-D-glucose (FDG), has become the gold-standard tool for evaluation of cancer [11-13]. FDG uptake reflects the rate of tissue glycolysis, which is higher in areas containing metabolically active tumor cells and in inflamed tissues. A large body of basic cellular physiology data demonstrate that activated macrophages have an unusually high metabolic rate [14,15]especially after classical/innate activation[16] hence avidly accumulate FDG [17]. Moreover, our group showed in an animal model[18], and was first to demonstrate in humans[19], that FDG uptake (in atherosclerotic plaques) correlates with the density of macrophages (determined histologically), findings that have been confirmed by several other groups[20-24]. Taken together, these data provide a solid foundation for investigating the use of FDG PET imaging for evaluation of inflammation.

Here we propose an open-label multi-center study that employs PET imaging of the carotid and coronary arteries and aorta to assess the effect of anti-IL-6 therapy on plaque inflammation in patients with rheumatoid arthritis. Secondary, exploratory evaluation will also examine correlations between atherosclerotic plaque inflammation and the inflammatory activity of the rheumatoid joint measured by PET-MR imaging, as well as how the changes in inflammation as measured by PET-MR correlate with lipid and inflammatory biomarkers. Certain centers of the brain responsible for fear perception are hypothesized to be sensitive to IL-6. Accordingly, we plan to evaluate fear center activities in the brain before and after reaction to IL-6 antagonist tocilizumab.

The Specific Aim of this Project:

Test the hypothesis that anti-IL-6 therapy is effective for reducing plaque inflammation (measured as PET-determined plaque metabolism) in patients with rheumatoid arthritis who are synthetic dMARD and anti-TNF inadequate responders. A secondary aim is to

test the hypothesis that the reduction in arterial activity relates to reductions in synovial activity.

2.0 OBJECTIVES

Test the hypothesis that anti-IL-6 therapy is effective for reducing plaque inflammation (measured as PET-determined plaque metabolism) in patients with rheumatoid arthritis. Secondary aims will test the hypothesis that the reduction in arterial activity relates to reductions in synovial activity and that it is independent of changes in LDL.

2.1 Primary

The primary objective of this study is to test the hypothesis that tocilizumab reduces arterial inflammation in individuals with RA. The primary efficacy endpoint will be change from baseline in carotid FDG uptake at 12 weeks post initiation of therapy with tocilizumab.

2.2 Secondary

Several additional objectives will be pursued, with the goal of providing an understanding of how tocilizumab leads to reduced arterial inflammation.

1) We will test the hypothesis that changes in inflammation occur within atherosclerotic plaques per se. MRI imaging, as part of the PET-MR procedure, will be used to focus this analysis of treatment effect within arterial locations that have demonstrable plaque.

2) We will test the hypothesis that reductions in arterial inflammation correlate with reductions in rheumatoid joint inflammation.

3) We furthermore hypothesize that reductions in arterial FDG uptake will be unrelated to changes in LDL.

4) We will also test the hypothesis that fear center (amygdala, and anterior cingulate cortex) activities, which reflects stress levels, will be reduced after randomization.

3.0 STUDY DESIGN

3.1 Description of the Study

Here we propose an open-label multi-center study that employs PET/MR imaging of the carotid and coronary arteries and aorta to assess the effect of anti-IL-6 therapy on arterial inflammation in patients with rheumatoid arthritis who are synthetic dMARD and anti-TNF inadequate responder. Secondary, exploratory evaluation will also examine correlations between atherosclerotic plaque inflammation and the inflammatory activity of the rheumatoid joint measured by PET-MR imaging, as well as how the changes in inflammation correlate with lipid and inflammatory biomarkers, and how stress levels are associated with inflammatory activity.

3.1.1 Study Schema

See Appendix A

3.2 Rationale for the Study Design and Dose

Despite the availability and broad use of several therapies for the modification of risk factors, cardiovascular disease remains the major cause of death worldwide. Additional modifiable mechanisms for the development of high-risk atheromatous plaques are needed. The role of inflammation has been highlighted in the pathogenesis of atherosclerosis in which immune mechanisms interact with metabolic risk factors to initiate, propagate, and activate plaque lesions in the vascular tree [36,37] . Inflammatory processes have thus become a target for the development of new therapies.

Patients with rheumatoid arthritis (RA) suffer significantly increased cardiovascular (CV) morbidity and mortality when compared to the general population [1-3]. Women with RA have a 2-3 fold higher risk of myocardial infarction, even in the absence of traditional coronary risk factors [4-6]. Several studies suggest that systemic inflammation accelerates atherogenesis in RA, perhaps by accentuation of both established as well as novel risk factor pathways [6-8].

Anti-inflammatory therapy in RA is associated with a reduction cardiovascular mortality. In patients with RA or psoriasis, methotrexate reduces CRP, IL-6, and TNF- , and at least 6 observational studies have shown that methotrexate is associated with reduced CVD risk and mortality in these populations[38-42]. Data from a large registry study suggests that anti-inflammatory therapies with TNF inhibitors may also be associated with significant reductions in fatal and nonfatal CVD outcomes [43].

In human studies of rheumatoid arthritis, anti-IL-6 therapy with tocilizumab is associated with reduction in disease activity [9] and a substantial reduction in CRP, an important biomarker of inflammation and a risk factor for atherothrombotic events. However, use of tocilizumab is associated with an elevation in LDL[10] and total cholesterol of unclear clinical significance. We hypothesize that, despite adverse effects on lipids, the use of tocilizumab therapy in RA patients may be associated with a reduction in atherosclerotic plaque inflammation.

Positron Emission tomography with[18]fluorine-2-deoxy-D-glucose (FDG), has become the gold-standard tool for evaluation of cancer [11-13]. FDG uptake reflects the rate of tissue glycolysis, which is higher in areas containing metabolically active tumor cells and in inflamed tissues. A large body of basic cellular physiology data demonstrate that activated macrophages have an unusually high metabolic rate [14,15]especially after classical/innate activation[16] hence avidly accumulate FDG [17]. Moreover, our group showed in an animal model[18], and was first to demonstrate in humans[19], that FDG uptake (in atherosclerotic plaques) correlates with the density of macrophages (determined histologically), findings that have been confirmed by several other groups[20-24]. Taken together, these data provide a solid foundation for investigating the use of FDG PET/CT imaging for evaluation of inflammation.

Imaging Atherosclerosis with FDG PET

Atherosclerosis disease activity can be defined as progression of atherosclerotic plaque and or development of atherothrombotic events. In a multi-center trial employing both PET/CT and MRI imaging, published in the *Lancet*, we previously demonstrated that changes in the PET/CT signal predict the rate of plaque expansion eighteen months later[27]. In a separate study in humans (N=144), we observed that the initial PET signal predicts the

subsequent rate of atherosclerotic plaque progression, based on CT imaging[44]. Several studies have shown an association between the FDG signal and clinical risk factors or risk scores[45-48] and soon after stroke [49]and MI[50]. Furthermore, higher arterial FDG uptake is predictive of an increased risk for *subsequent* stroke and MI[51,52]. Thus, there is substantial evidence to support the utility of FDG-PET/CT imaging to predict atherosclerotic disease progression and subsequent events.

The use of FDG-PET/CT imaging for evaluating changes in inflammation after interventions in human studies is well established. The PI's group has pioneered the use of PET/CT imaging for evaluating changes in atherosclerotic inflammation in response to treatment; the PI is/has been Study Chairman on over a half-dozen multi-center multi-modality imaging trials evaluating response to therapy. We, and others have shown that statin therapy (a well-described anti-inflammatory treatment in atherosclerosis) results in a significant reduction in arterial FDG uptake after 3 months [53-55]. **Moreover, we have shown that while statins provide a dose-dependent reduction in arterial inflammation (measured with PET), this change is independent of changes in LDL concentrations** [55]. Further, the PI has recently reported the results of multi-center PET/CT imaging trials that demonstrated anti-inflammatory efficacy of: p38 MAP kinase antagonism[56], high vs. low dose atorvastatin[30], and a novel innate-immune modulator lecinoxoid[57]. Others have observed modulation of the FDG-PET/CT signal after treatment with additional drug classes, including tumor necrosis factor antagonists and pioglitazone [60]. Additionally, PET/CT imaging has also been shown to predict *lack* of efficacy. We reported lack of efficacy of dalcetrapib, a CETP antagonist, on reducing atherosclerotic plaque inflammation[27]. The dalOUTCOMES Trial, of approximately 16,000 individuals, recently reported lack of efficacy of dalcetrapib on cardiovascular mortality[61], findings that were presaged by the FDG-PET/CT findings. Similarly, we reported lack of efficacy for GSK's LPPLA2 antagonist [62]. Subsequently, a trial of over 16000 subjects recently demonstrated lack of clinical efficacy of GSKs LPPLA2 antagonist in a similar population [63]. **Thus, for all four drug classes studied with FDG-PET for which CV outcomes trial data are also available[27,60,64,66], the directional changes on FDG PET imaging were consistent with the changes in clinical events noted in the CV endpoint trials[59,63,66,67].** ***Accordingly, available data suggest that FDG PET imaging of arterial inflammatory activity may provide clinically relevant insights.***

FDG PET Imaging in RA

Moreover, several groups have shown that arterial inflammation, measured using PET, is increased in RA[58,68], We recently observed in patients with RA that arterial inflammation correlates with joint activity by FDG-PET, (R=0.65, P=0.004)[68] . Others have shown that treatment of RA with anti-TNF therapy results in a reduction in arterial inflammation by PET [58].

Here we propose an open-label multi-center study that employs PET imaging of the carotid and coronary arteries and aorta to assess the effect of anti-IL-6 therapy on plaque inflammation in patients with rheumatoid arthritis. Secondary, exploratory evaluation will also examine correlations between atherosclerotic plaque inflammation and the inflammatory activity of the rheumatoid joint measured by PET-MR imaging, as well as

how the changes in inflammation as measured by PET-MR correlate with lipid and inflammatory biomarkers.

Fear center activation & Inflammation

We propose to have an optional fMRI imaging session, as part of the PET-MR session to measure activation of the brain's fear centers before and after looking at a series of faces (called the overt faces test). It is well-established by epidemiological studies that stress begets atherosclerosis. More recently, elegant animal studies show that emotional stress causes monocyte release from the bone marrow, and that IL6 intensifies the perception of stress[59]. One such study (attached) shows that IL6 antagonism reduces stress behavior. This is in line with several studies showing that inflammation intensifies stress behavior. By using techniques that effectively induces fear during PET-MR imaging (overt face test), we seek to measure BOLD signal changes in the fear center as a physiological measurement of psychological stress, and we seek to test the hypothesis that tocilizumab reduces the mental stress response (a reduction in the fMRI signal in fear centers of the brain).

Fig 1 Arterial FDG uptake in an individual with RA

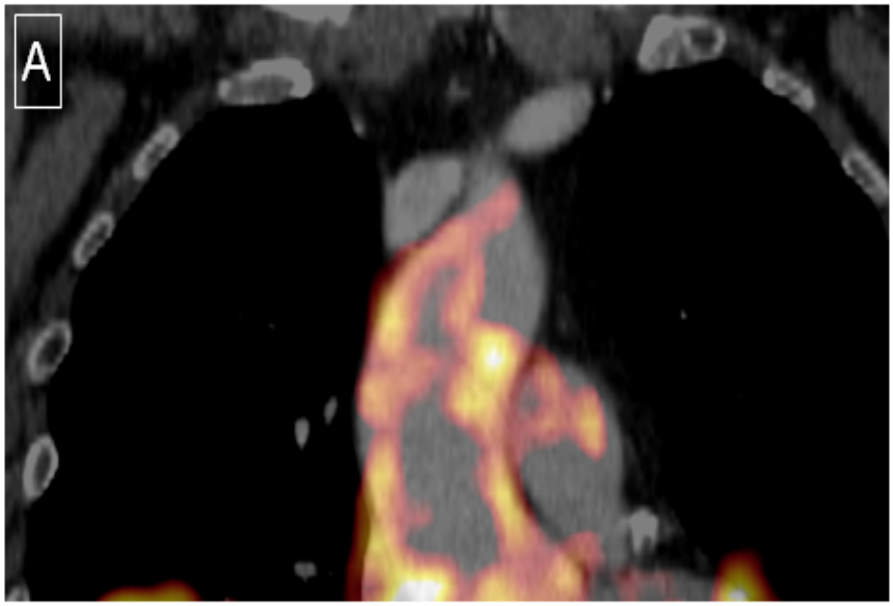


Fig 2 Synovial FDG uptake in an individual with RA

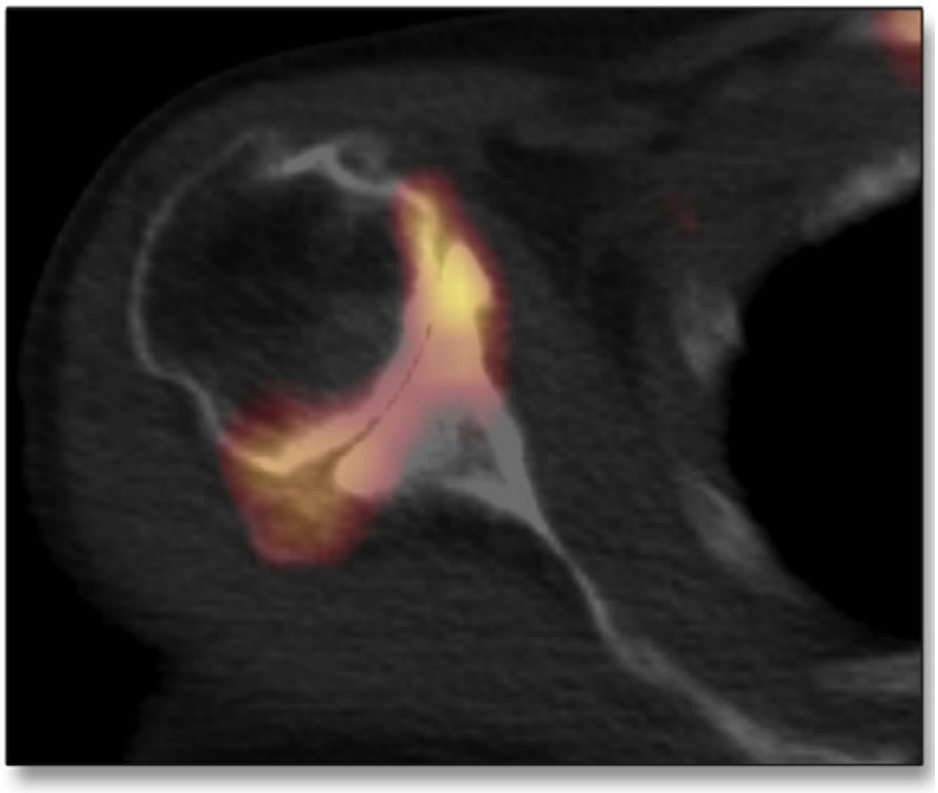


Fig 3 Arterial Inflammation (FDG uptake) in RA vs. Matched Controls

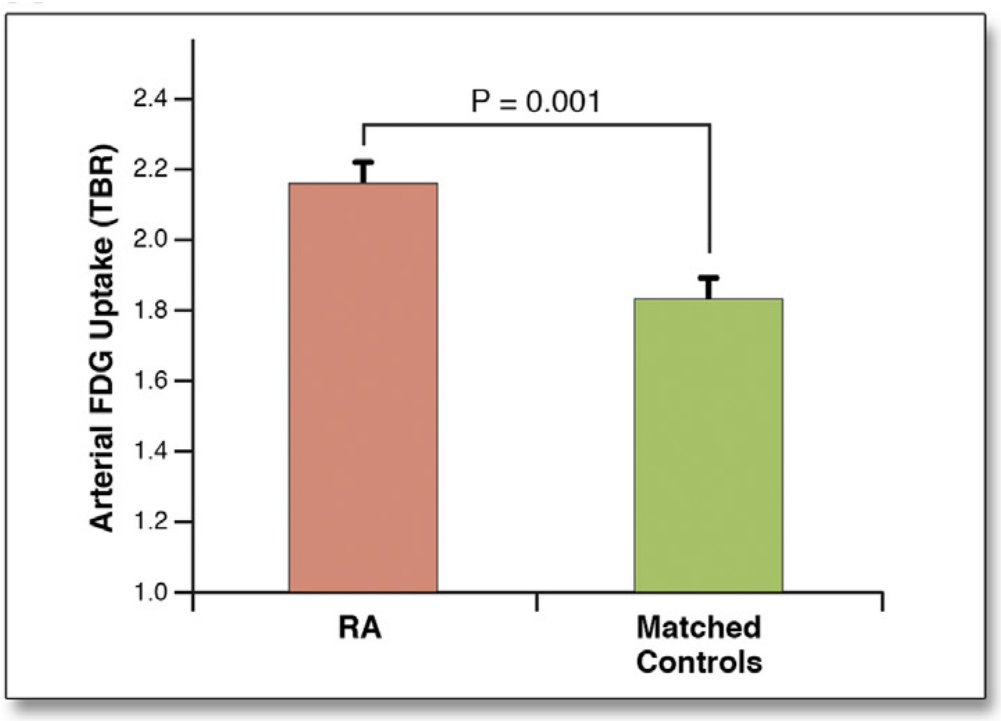
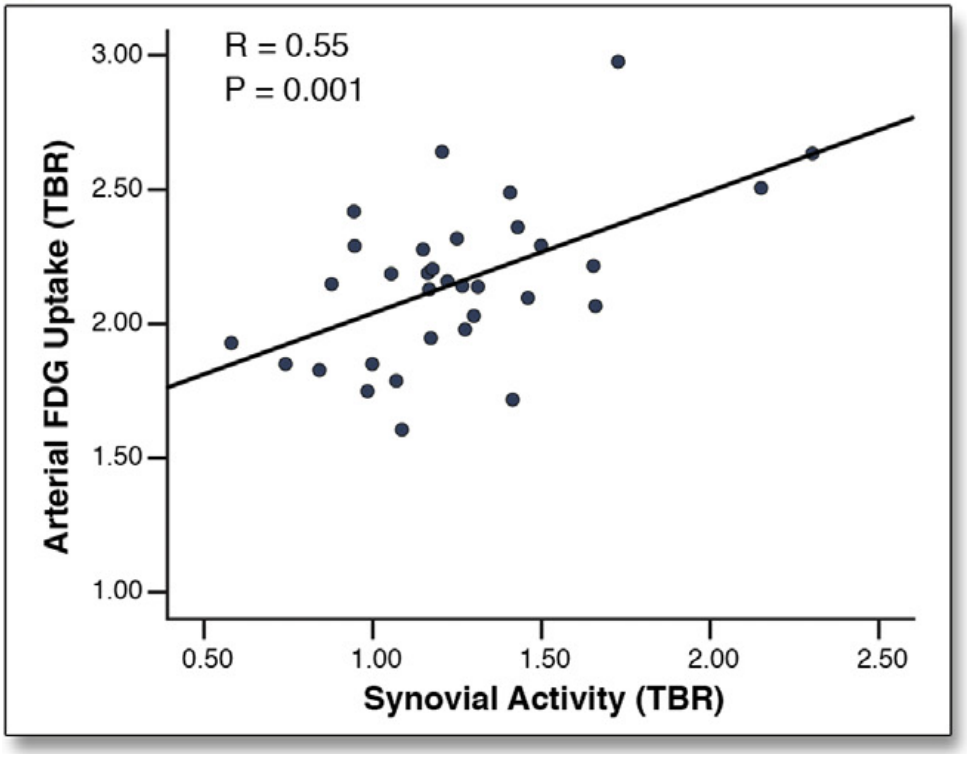


Fig 4 Close Relationship between Arterial vs. Synovial FDG uptake


R = 0.55
P = 0.001
3.00
2.50
2.00
1.50
1.00
Arterial FDG Uptake (TBR)
0.50
1.00
1.50
2.00
2.50
Synovial Activity (TBR)

The Specific Aim of this Project:
Test the hypothesis that anti-IL-6 therapy is effective for reducing plaque inflammation (measured as PET-determined plaque metabolism) in patients with rheumatoid arthritis who are synthetic dMARD and anti-TNF inadequate responders. A secondary aim is to test the hypothesis that the reduction in arterial activity relates to reductions in synovial activity

Protocol Overview:

- 21 subjects with rheumatoid arthritis who are synthetic dMARD inadequate and anti-TNF responders who desire initiation of therapy with tocilizumab (weekly SC administration) will be recruited.
- Subjects will undergo preliminary clinical screening involving medical and medication history interview, physical examinations, vital sign and symptoms measurements, TB test, IMT test, and blood draws.
- Subjects will undergo a secondary screening, using PET-MR imaging to identify the presence of atherosclerotic plaque inflammation, defined as a TBR $\geq$ 1.7 (target-to-background ratio of the SUV).
- Approximately 18-20 patients who pass a primary clinical screening will be treated in an open-label manner with tocilizumab. This will be done either in addition to MTX or as monotherapy.
- Plaque inflammation will be assessed using PET plaque imaging of the carotids and thoracic aorta at week 12.
- Baseline and 12 week PET-MR imaging of the patient's dominant hand/wrist will also be completed in order to evaluate the response to treatment in the diseased joints as well as correlations between changes in joint and plaque inflammation as assessed by FDG PET.
- Baseline MRI imaging of the arterial wall, as part of the PET-MR procedure, will be performed in order to identify structurally evident atherosclerotic plaques. The localization of atherosclerotic plaques allows for a plaque-specific analysis of treatment effect.
- Patients will have the option to participate in fMRI imaging during the PET MR imaging session to assess the blood oxygenated level dependent signal changes of psychological stress induced by overt faces test.

In summary:
Arterial PET imaging has been studied extensively in trials by the cardiology community, and is now being used in several studies by the rheumatology community. It is accepted that the arterial signal:1) reflects atherosclerotic inflammation, 2) predicts CV disease risk, and 3) changes in response to treatment predict therapeutic efficacy on the target. We hypothesize that Actemra will greatly reduce arterial inflammation in plaques, and will do so in proportion to the reduction in synovial activity (and in a manner that is unrelated to changes in LDL).

Implications to the medical community:

- That Actemra may be effective at reducing atherosclerotic pathology
- This may translate in a reduction in CV risk

- Beneficial changes in the joints may be mirrored by beneficial changes in the arterial milieu.
- That as patients experience a reduction in joint symptoms, they may also experience concordant improvements in atherosclerotic disease.
- These beneficial changes may be seen despite the small changes in LDL (since the atherosclerotic disease in RA is driven by systemic inflammation…not the LDL)

Possible next steps in this line of research:

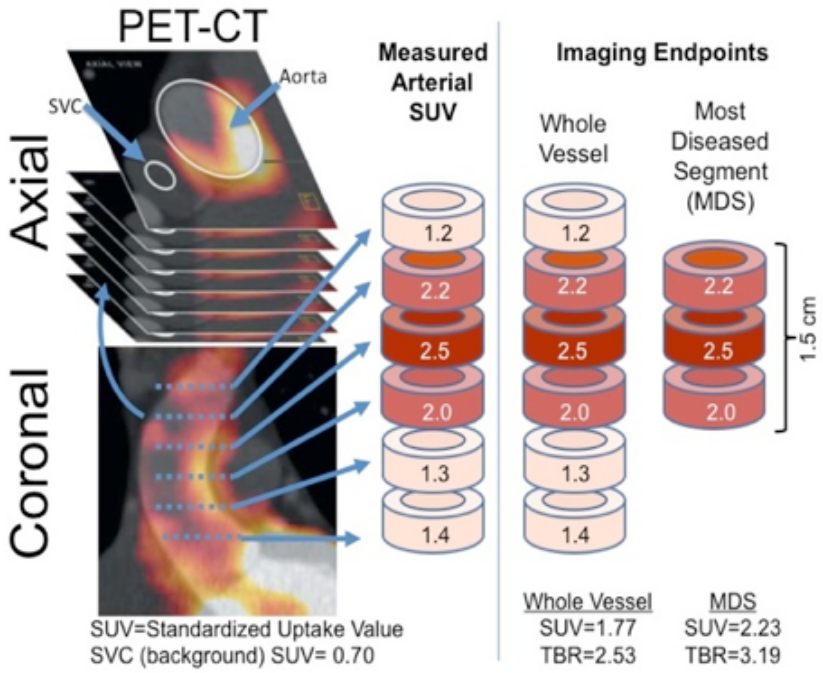
Develop a "Treat to New Targets" imaging study in RA to test the hypothesis that more aggressive treatment of RA (beyond current approaches) provides a greater benefit in terms of improvements in atherosclerotic plaque inflammation.

3.3 Outcome Measures

PET/MR Imaging will be performed at entry (prior to randomization) and again at week 12 (while still on study drug) using methods that have been previously reported by our group[21,25-28], and following detailed image acquisition guidelines. In brief, FDG is administered intravenously (10mCi) after an over-night fast. Imaging is performed 2 hours later using a PET-MR scanner with the patient in the supine position. Imaging is performed across approximately 4-8 bed positions, covering the neck, chest, and upper abdomen and selected joints. MR attenuation correction is performed. Each of the 2 imaging visits will be associated with 7mSv, with 14 mSv in total of radiation exposure, which is substantially less than the 50mSv annual limit accepted by IRBs. Women of childbearing potential will undergo a serum pregnancy test on day of imaging prior to image acquisition.

Arterial PET Image Analysis: will be performed by an experienced observer, as previously reported**.** A dedicated multi-modality workstation is used for analysis by an experienced observer. Image analysis is performed after careful assessment of image quality. Using the attenuation MR image that was generated during PET-MR imaging, we will identify the vessels of interest (right and left carotid arteries as well as the ascending aorta). Thereafter, regions of interest (ROIs) are drawn around the vessel (in axial orientation) to provide a maximum standardized uptake values (SUV) for each region of interest. The SUV is the decay-corrected tissue concentration of FDG (in kBq/ml) divided by the injected dose per body weight (kBq/g).This is repeated along the length of the vessel (every ~3.5 mm along the long axis of the vessel) to provide a stack of ROIs that compose the whole vessel (**Fig**). Then, the **background corrected maximum SUVs are averaged to provide a whole vessel target-to-background ratio (TBR).**

Arterial PET Endpoints: The primary PET/MR parameter used to evaluate vascular inflammation is the arterial TBR. **Plaque-Based Analysis:** MRI Imaging of the artery wall will be performed, and will allow the identification of atherosclerotic plaques within the wall of the aorta and carotid arteries. This method has been used previously by our group in the context of multi-center trials[31].



Synovial PET/MR Imaging: will be performed as previously reported by our group[32], and as adopted from prior studies [33-35]. We will measure FDG uptake in the wrists in all subjects and will additionally measure activity in the glenohumeral, acromioclavicular, and acetabulofemoral joints. Prior studies have suggested that the FDG-PET signal derived from the shoulder joints of RA patients provides a sensitive tool to assess synovial inflammation.(31) After manual co-registration using anatomical landmarks (from the MR datasets), target joints will be identified and a ROI will be placed in axial section. Care will be taken to avoid spill-over activity from surrounding tissues. The maximum SUV for each joint will be recorded and the average of all SUVs was calculated as a measure of synovial activity in each individual. Synovial TBR will be calculated in a similar fashion to arterial TBR (as ratio to mean venous blood SUV).

Psychological Stress Assessment: The Perceived Stress Scale survey, a 10-question survey will be administered during the imaging visits to measure overall perceived Psychological Stress level. During the PET-MR imaging session, subjects will have the option to perform the tasks as previously reported from prior studies using overt faces, which will induce elevated stress levels. A series of overt fearful faces will be shown to the subject. The BOLD signal changes in the brain tissues during these tasks in the MR scan will be calculated as a measure of stress activity.

3.3.1 Primary Outcome Measures

The primary outcome measures will be the change in arterial inflammation based on FDG PET - from initial imaging (just before Actemra Rx) to repeat imaging (at week 12).

3.3.2 Secondary Outcome Measures

Several secondary outcome measures will be assessed.

1) To test the hypothesis that changes in inflammation occur within atherosclerotic plaques per se, we will perform a secondary analysis limited to arterial locations that manifest arterial wall thickening on MRI (a plaque-based analysis). In this analysis, we will measure the change in carotid or aortic *plaque* FDG uptake at 12 weeks post randomization. MRI imaging will be used to focus this analysis of treatment effect within arterial locations that have demonstrable plaque.
2) To test the hypothesis that reductions in arterial inflammation correlate with reductions in rheumatoid joint inflammation, we will additionally measure rheumatoid joint FDG uptake during the imaging visits.
3) We furthermore hypothesize that reductions in arterial FDG uptake will be unrelated to changes in LDL. Accordingly, changes in LDL will be compared to changes in arterial inflammation over time.
4) We hypothesize that BOLD signals at fear centers of the brain including the amygdala and the rostral anterior cingulate cortex (ACC) will be reduced after RA subjects are treated with ACTEMRA.

3.3.3 Safety Outcome Measures
Standard safety laboratory and clinical assessments will be performed

3.4 End of Study
Approx.13 weeks after initiation of Actemra in the last patient enrolled.

4.0 STUDY POPULATION

4.0.1 Overview
Subjects with rheumatoid arthritis who are inadequate responder to anti-TNF and dMARDS that are not currently on statins and who desire initiation of therapy with subcutaneous Actemra will be recruited from two major medical centers (Massachusetts General Hospital and Brigham and Women's Hospital). Subjects recruited from Brigham and Women's Hospital will complete imaging procedures at Massachusetts General Hospital, Charlestown Navy Yard.

4.1 Inclusion Criteria
Patients must have Rheumatoid Arthritis. Patients will be included in the trial based on the following criteria:

- Adults aged 40-75
- Diagnosis of RA according to the revised 1987 American College of Rheumatology (ACR; formerly American Rheumatism Association), criteria.
- Patients who have had an inadequate response to non-biologic disease-modifying anti-rheumatic drug (DMARD) and/or anti-TNF.
- Presence of plaque inflammation, identified during secondary screening, defined as a target to baseline (TBR ratio) ≥ 1.7 in the carotid artery or ascending aorta.

- Not wheelchair or bedbound.

- At screening, active RA, defined as ≥4 swollen joints (28 joint count) and ≥ 4 tender joints (28 joint count) and CDAI score ≥ 10.

- If using other non-biologic DMARDS, (ex: methotrexate, sulfasalazine, hydroxychloroquine, azathioprine, cyclosporine, leflunomide), patient must demonstrate inadequate response, be on stable dose(s) for at least 4 weeks prior to baseline visit. For methotrexate: patients must be on stable does for at least 2 weeks.

- If taking corticosteroids (prednisone or equivalent), the following guidelines must be followed in order to be enrolled and remain on trial:
  - Dose must be relatively stable for at least 3 weeks before imaging . Relatively stable allows for adjustments of the dose of up to 2.5 mg, as long as the dose is not further adjusted during the last 1 week prior to imaging).
  -Dose should not exceed 10 mg daily of prednisone (or equivalent) the 3 weeks prior to imaging.
  -During the first 3 weeks **after** baseline imaging: The steroid dose may be transiently increased (up to 20mg daily) as needed to control symptoms. However, the steroid dose must be tapered back to the pre-scan dose level (+/- 2.5mg) by 3 weeks after initial imaging.
  -Beyond the first 3 weeks after baseline imaging: Additional changes (increases or decreases of +/- 2.5mg) are allowed (to achieve comfort)

- Any investigational treatment not mentioned elsewhere must be discontinued for 4 weeks or 5 half lives, whichever is longer, prior to the baseline visit. Exposure to any investigational biologics should be discussed with the Sponsor.

- Signed informed consent (and informed assent of minor, if applicable).

- *Note: a positive arterial PET scan is still required, thus the subjects will all still need to have confirmation of arterial inflammation before they are treated with study drug

General Medical Concerns:

- Men and women of reproductive potential must agree to use an acceptable method of birth control during treatment and for twelve 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 screening or planned major surgery within 6 months following randomization.

Excluded Previous or Concomitant Therapy:

1. Treatment with any investigational agent within 4 weeks (or 5 half-lives of the investigational drug, whichever is longer) of screening.
2. Previous treatment with any cell-depleting therapies, including investigational agents or approved therapies, some examples include: CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19 and anti-CD20.
3. Treatment with intravenous gamma globulin, plasmapheresis or Prosorba column within 6 months of baseline.
4. Immunization with a live/attenuated vaccine within 4 weeks prior to baseline.
5. Previous treatment with TCZ, Rituximab (within 1 year of Visit 1), Abatacept (within 3 months of Visit 1)
6. Any previous treatment with alkylating agents such as chlorambucil, or with total lymphoid irradiation.

Exclusions for General Safety:

7. History of severe allergic or anaphylactic reactions to human, humanized or murine monoclonal antibodies.
8. 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, Crohn's disease, or other symptomatic lower GI conditions that might predispose to perforations.)
9. Diagnosis of liver disease or elevated hepatic enzymes, as defined by ALT, AST, or both > 1.5 x the upper limit of age-determined normal (ULN) or total bilirubin > ULN.
10. 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
11. Any history of recent serious bacterial, viral, fungal, mycobacterial or other opportunistic infections.
12. Have serologic evidence of current or past HIV, Hepatitis B, or Hepatitis C.
13. Positive QuantiFERON TB, T-spot TB test, or PPD skin test, history of tuberculosis, or active TB infection without at least 4 weeks of adequate therapy for TB.

14. Active infection with EBV as defined by EBV viral load ≥ 10,000 copies per mL of whole blood.
15. Active infection with CMV as defined by CMV viral load ≥ 10,000 copies per mL of whole blood.
16. Any of the following hematologic abnormalities, confirmed by repeat tests:
    a. White blood count <3,000/μL or >14,000/μL;
    b. Lymphocyte count <500/μL;
    c. Platelet count <100,000 /μL;
    d. Hemoglobin <8.0 g/dL; or
    e. Neutrophil count <2,000 cells/μL.

17. 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.
18. Primary or secondary immunodeficiency (history of or currently active) unless related to primary disease under investigation.
19. Any medical or psychological condition that in the opinion of the principal investigator would interfere with safe completion of the trial.
20. History of other malignancy within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer.
21. Pregnant women or nursing (breast feeding) mothers.
22. Patients with reproductive potential not willing to use an effective method of contraception.
23. History of alcohol, drug or chemical abuse within 1 year prior to screening.
24. Neuropathies or other conditions that might interfere with pain evaluation unless related to primary disease under investigation.
25. Rheumatic autoimmune disease other than RA, including SLE, MCTD, scleroderma, polymyositis, or significant systemic involvement secondary to RA (e.g., vasculitis, pulmonary fibrosis or Felty's Syndrome). Secondary Sjogrens syndrome with RA is allowable.
26. Prior history of, or current inflammatory joint disease other than RA (e.g., gout, Lyme disease, seronegative spondyloarthropathy including reactive arthritis, psoriatic arthritis, arthropathy of inflammatory bowel disease).
27. Relatively significant radiation exposure over the course of the year prior to randomization. Significant exposure is defined as:
    i) More than 2 PCI within 12 months of randomization
    ii) More than 2 myocardial perfusion studies within the past 12 months
    iii) More than 2 CT angiograms within the past 12 months
    iv) Any subjects with history of radiation therapy.

30. Prior history of diverticulitis

31. Contra-indications to PET-MR Imaging:

30a) Cardiac pacemaker that is not PET-MR compatible

30b) Surgical aneurysm clips

30c) Neurostimulator

30d) Implanted pumps

30e) Metal fragments in body / eyes

30f) Nitroglycerin patch that cannot be removed

30g) Colored contact lenses should not be worn in scanner

30h) Certain cochlear implants

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 TCZ. Results from the VISARA vaccination study suggest TCZ- and MTX-treated RA pts have comparable recall response to TTV, but response to 23VPPV is slightly reduced with TCZ. If possible, pneumococcal polysaccharide vaccination should be given before initiating TCZ to maximize response. These data are for two TCZ infusions and may only reflect initial effects of TCZ on the humoral immune response. The effects of long-term dosing are not addressed. Because IL-6 inhibition may interfere with the normal immune response to new antigen, patients should be brought up to date on all recommended vaccinations, except for live vaccines, prior to initiation of therapy with TCZ. The impact of SC dosing of TCZ on vaccination responses has not been evaluated.

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 follow-up phone calls 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

Open-label, pilot study
Actemra will be given to approx. 20 subjects at a dose of 162 mg subcutaneously q week.
Estimated rate of accrual rate: 3 individuals per month recruited from 2 large RA centers: Massachusetts General Hospital and Brigham and Women's Hospital in Boston.
Estimated date of study completion, including time of follow-up: Mar. 2015

This research study protocol allows the subject to receive weekly SC administrations of Actemra for up to 12 weeks. Even if the treatment is shown to be of benefit, additional SC administrations of Actemra beyond that allowed in the protocol cannot be given to the subject while she/he is participating in this study. Continued treatment decisions and safety follow up beyond Week 13 will be at the discretion of the patient's treating rheumatologist.

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 for SC injection at a concentration of 162 mg (0.9 ml) in a pre-filled syringe. Tocilizumab is a colorless to pale yellow liquid, with a pH of about 6.5.

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

Actemra will be self-administered by subjects after instruction by the nurse or physician: 162 mg will be administered subcutaneously every week X12 weeks.

Administration Guidelines for Adult Patient Population

- Subjects will be instructed to inject the full amount in the syringe (0.9 mL), which provides 162 mg of ACTEMRA, according to the directions provided in the Instructions For Use (IFU).
- Injection sites will be rotated with each injection.
- Subjects will be instructed not to inject the ACTEMRA into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact.

6.1.2 Tocilizumab Storage

Do not use beyond expiration date on the container, package or prefilled syringe. ACTEMRA must be refrigerated at 2oC to 8oC (36°F to 46°F). Do not freeze. Protect the vials and syringes from light by storage in the original package until time of use, and keep syringes dry. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If visibly opaque particles, discoloration or other foreign particles are observed, the solution should not be used.

6.1.3 Tocilizumab Overdosage

There are limited data available on overdoses with TCZ. 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 Drugs

N/A

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., 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 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 TCZ.

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 TCZ 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

[Modify as appropriate for values related to specific indication]

ANC (cells/mm^3)	Action
> 1000	Maintain dose.
500 – 1000	Interrupt tocilizumab dosing. When ANC increases to > 1000, resume tocilizumab as clinically appropriate and as described below: For patients receiving subcutaneous ACTEMRA, resume ACTEMRA at every other week and increase frequency to every week 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 as clinically appropriate For patients receiving subcutaneous ACTEMRA, resume ACTEMRA at every other week and increase frequency to every week 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 the study medications.

Table 3:

Lab Value	Action
> 1 to 3x ULN	Dose modify concomitant hepatotoxic medications For patients receiving subcutaneous ACTEMRA, reduce injection frequency to every other week or hold dosing until ALT or AST have normalized. Resume ACTEMRA at every other week and increase frequency to every week 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

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 RA have an increased risk for cardiovascular disorders, therefore, risk factors for cardiovascular disease (e.g., 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/injection reaction is defined as an adverse event occurring during and within 24 hours after the infusion or subcutaneous injection of TCZ. 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 subcutaneous injections 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 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-TCZ antibodies should be obtained at time of event and at least 6 weeks or 8 weeks after the last SC dose, respectively.

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 (e.g., 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, cyclosporin, 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 TCZ on CYP450 enzyme activity may persist for several weeks after stopping therapy.

7.2 Other Study Drug(s)

None given

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

For a given subject, criteria for study discontinuation:

A) Any significant adverse events or loss of consent.

B) Lab values that will trigger discontinuation are shown in Section 7.1

10.0 CLINICAL AND LABORATORY EVALUATIONS

10.1 Pre-Treatment Evaluations

The following evaluations must be performed within four weeks prior to the date of each patient's initial treatment with TCZ:

- Pregnancy test (serum) for women of childbearing potential on the day of imaging.
- Medical history and documentation of the rationale for treatment of the patient's disease with TCZ.
- Physical examination, including vital signs, blood pressure, performance status and tumor assessment.
- Hematology (within 2 weeks of treatment): complete blood count (CBC) with differential and platelet count.
- Serum Chemistries: glucose, BUN, creatinine, uric acid, total bilirubin, alkaline phosphatase, LDH, total protein, albumin, SGOT(AST), SGPT (ALT), and calcium.

10.2 Evaluations During Treatment

- Neutrophils will be monitored at baseline, week 4 following initiation of therapy, then at the post study visit.
- Platelets will be monitored at baseline, week 4 following initiation of therapy, then at the post study visit.
- ALT and AST levels will be monitored at baseline, week 4 following initiation of therapy, then at the post study visit.
- Assessment of lipid parameters will be assessed at the post study visit.

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

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 testing.

Reports of the results of these analyses will be provided to the investigator for patients testing positive for anti-TCZ antibodies.

10.3 Post-Treatment Evaluations

Subjects will return at week 10-12 for post-treatment evaluation. Evaluation will included physical exam and history as well as laboratory assessments as shown in the schedule of events.

Subjects of both sexes must practice adequate birth control for a minimum of twelve months post-treatment.

11.0 REPORTING OF ADVERSE EVENTS

11.1 Safety Reporting of Adverse Events

Assessment of Safety

Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to {study drug}, all events of death, and any study specific issue of concern.

Adverse Events

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

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with tocilizumab that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).

If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.

Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

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

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

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

Adverse Event Reporting Period
The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

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

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

Yes
There is a plausible temporal relationship between the onset of the AE and administration of the tocilizumab and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of

response to the tocilizumab; and/or the AE abates or resolves upon discontinuation of the tocilizumab or dose reduction and, if applicable, reappears upon re-challenge.

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

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

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

Procedures for Eliciting, Recording, and Reporting Adverse Events

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

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

Specific Instructions for Recording Adverse Events
Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms
If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is ok 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 11.2), 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".

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 the {study drug} should be reported as an SAE.

f. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior tocilizumab exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

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.

h. AEs of Special Interest (AESIs)

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the Product (see listing in section 11.3 below).

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 24 hours 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.

SAE Reporting
Investigators must report all SAEs to Genentech within the timelines described above. The completed MedWatch/case report should be faxed immediately upon completion to Genentech Drug Safety using the SAE fax cover sheet (Appendix C) at:

(650) 225-4682
OR
(650) 225-5288

- Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.
- Serious AE reports that are related to the tocilizumab and AEs of Special Interest (regardless of causality) will be transmitted to Genentech within 24 hours of the Awareness Date.
- Serious AE reports that are unrelated to the tocilizumab will be transmitted to Genentech within 24 hours of the Awareness Date.
- Additional Reporting Requirements to Genentech include the following:
- Any reports of pregnancy following the start of administration with the tocilizumab will be transmitted to Genentech 24 hours of the Awareness Date.

- All Non-serious Adverse Events originating from the Study will be forwarded in quarterly reports to Genentech.

Note: Investigators should also report events to their IRB as required.

MedWatch 3500A Reporting Guidelines
In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

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 patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom and adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at
http://www.fda.gov/medwatch/getforms.html

Additional Reporting Requirements for IND Holders
For Investigator-Sponsored IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report:
The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of tocilizumab. An unexpected adverse event is one that is not already described in the

tocilizumab Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

15 Calendar Day Written Report
The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of tocilizumab. An unexpected adverse event is one that is not already described in the tocilizumab investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).
Randomization Codes for blinded clinical trials

FDA fax number for IND Safety Reports:
Fax: 1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech Drug Safety:
Fax: (650) 225-4682 or (650) 225-5288

And to the Site IRB:
Partners Human Research Committee
Tel: 617-424-4100, Fax: 617-424-4199

For questions related to safety reporting, please contact Genentech Drug Safety:
Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-5288

IND Annual Reports
Copies to Genentech:
All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. Copies of such reports should be faxed to Genentech Drug Safety:

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Study Close-Out
Any study report submitted to the FDA by the Sponsor-Investigator 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:

E-mail:ACTEMRA IST Central Mailbox: actemra-gsur@gene.com

11.3 AEs of Special Interest (AESIs)

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.

12.0 EVALUATION OF RESPONSE

Arterial inflammation will be assessed at imaging visits

13.0 STATISTICAL CONSIDERATIONS

13.1 Determination of Sample Size

Sample size calculation for primary endpoint:

Assuming total of 21 enter and 18 patients complete study, the probability is 98 percent that the study will detect a treatment difference at a two-sided 0.05 significance level. This is based on the assumption that the within-patient standard deviation of the response variable is 0.244 and the minimal meaningful detectable difference is 0.25 (10%). To achieve a cohort of 18 completers, 21 individuals will need to be enrolled for imaging screening.

Derivation of assumptions:

1) A **minimum meaningful expected change in TBR** on therapy of **10%** is based on the observation that high dose statins are associated with 18% reduction in TBR, (53,54), and anti-TNF therapy in RA is associated with a 17% reduction in arterial TBR, see Maki-Petaja et al, Circulation 2012) (49). The anticipated average baseline value of 2.5 is

based on the average of GLACIER (2.55) as well as Maki-Petaja et al (2.5). Hence a 10% reduction would be 0.25.

3) The **standard deviation of the difference between the two values for the same patient of 0.24** is based on two recently completed studies, on single center experience (Elkhawad et al, SD for change 0.188 in the placebo group) [66], and one multi-center trial (GLACIER Trial, SD for change in the placebo group 0.30). We have employed an average SD based on these two studies,. However, we believe that this is a conservative estimate of the SD for change since we think the SD for this study will closer to that observed in Elkhawad et al (a single-imaging center trial) than in GLACIER (a multi-imaging center trial).

4) A **combined drop-out rate of 12% is anticipated**. This drop-out rate is based on an anticipated 6% imaging screen failures plus 6% drop-out after randomization. The imaging screen failure rate is chosen conservatively, based on similar trials. Note, in this population with active joint disease, we anticipate a screen failure rate of less than 5%. The 6% drop-out rate after randomization is based on similar multi-center trial experiences such as GLACIER (5.4%.drop-out there)

Sample size calculation for secondary endpoint analysis (correlation between changes in artery wall and changes in synovial activity). The probability is 80 percent that the study will detect a relationship between the independent and the dependent variables at a two-sided 0.05 significance level, if the true change in the dependent variables is 0.704 units per unit change in the independent variable. This is based on the assumption that the standard deviation of the two PET variables are similar (0.24).

13.2 Planned Efficacy Evaluations

13.2.1 Primary Efficacy Variables

Change in arterial inflammation in the carotids, measured as a target to background ration (TBR) of the standardized uptake values (SUVs) in the artery divided by the SUV in the blood (blood background)

13.2.2 Secondary Efficacy Variables

1) Change in carotid *plaque* FDG uptake (TBR) at 12 weeks post randomization. MRI imaging will be used to focus this analysis of treatment effect within arterial locations that have demonstrable plaque.

2) Change in rheumatoid joint (dominant wrist first, mean shoulders, second) FDG uptake (TBR) 0-12 weeks post randomization.

4) Correlations between change in atherosclerotic plaque FDG uptake (TBR) and change in rheumatoid joint FDG uptake 0-12 weeks post randomization.

5) Correlations between change in atherosclerotic plaque FDG uptake (TBR) and change in LDL 0-12 weeks post randomization.

5) Correlation between change in atherosclerotic plaque FDG uptake (TBR) and CRP 0-12 weeks post randomization.

6) Correlation between change in BOLD signals in the amygdala and anterior cingulate cortex with atherosclerotic plaque FDG uptake

13.3 Methods of Analysis

A paired T-test will be used to compare baseline and post-treatment measures of arterial inflammation. Similar approach will be used to assess change in mean joint inflammation. Correlation coefficients and scatter plots will be used to assess the magnitude of the association between arterial inflammation (TBR) and joint inflammation. These results will be supported by adjusted linear regression analyses. A similar analysis strategy will be applied to assess the correlations of the changes in TBR and the changes in joint inflammation from baseline to week 12. The linear regression analyses will also adjust for baseline values

14.0 RETENTION OF RECORDS

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

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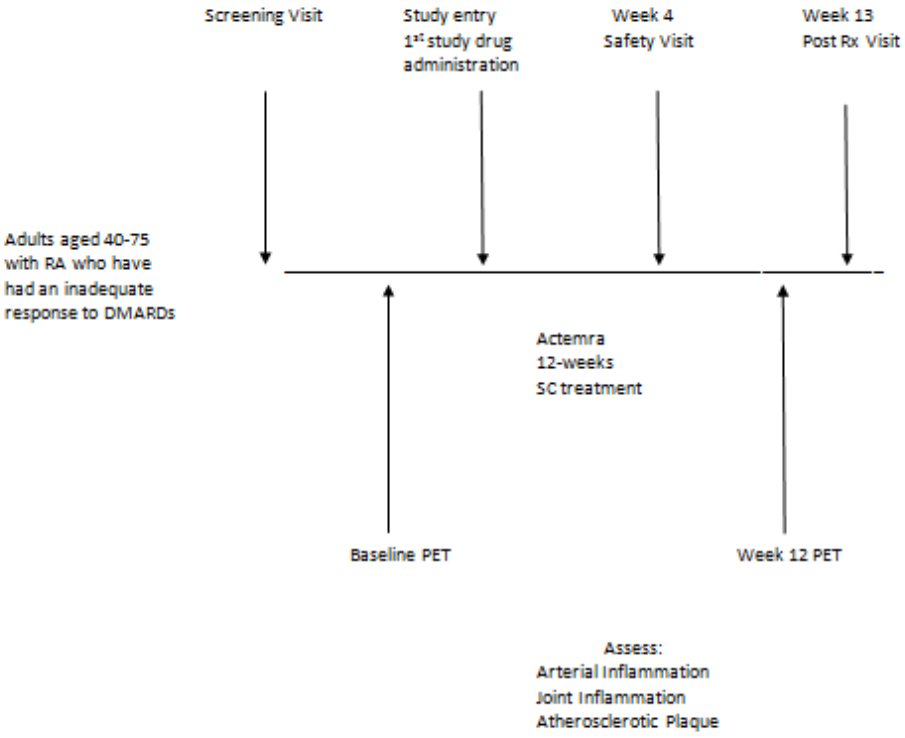
APPENDIX A: STUDY FLOW CHART/SCHEMA



APPENDIX B: SCHEDULE of EVENTS

	EVENT	-2 to -28 days	-1 to -14 days	0	4 weeks	12 ± 1 week	within 10 days of imaging
		Screening	Baseline Imaging	Rx Initiation	Clinical Follow-Up	Final Imaging	Post Study F/U Visit
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
EXAMINATIONS	Inclusion/Exclusion Criteria	x					
	Informed Consent	x					
	Medical and Surgical History	x		x	x		x
	Weight, BMI, Blood Pressure	x		x	x		x
	Concomitant Medications	x		x	x		x
	Adverse Event			x	x		x
	DAS-28	x					x
	CDAI	x		x	x		
	Subject VAS	x		x	x		x
	Physician Global	x		x	x		x
	Swollen & Tender Joint Count	x		x	x		x
Blood Tests							
	Creatinine	x			x		
	BUN	x			x		
	CBC (diff)	x			x		x
	Glucose	x					
	Fasting Lipid Profile	x					x
	LFT	x			x		x
	HIV	x					
	HEP B	x					
	HEP C	x					
	Uric Acid	x					
	Calcium	x					
	CRP	x					x
	ESR	x					x
	Inflammatory Biomarkers	x					x
	Pregnancy Test		x		x	x	
Imaging							
	Arterial FDG PET		x			x	
	Arterial MRI		x			x	
	Synovial FDG PET		x			x	
	Carotid IMT		x			x	
Other Tests	TB Test (PPD, T-spot, or QuantiFERON)	x					
	Stress Scale		x			x	

APPENDIX C: GENENTECH SAFETY REPORTING FAX COVER SHEET

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SAFETY REPORTING FAX COVER SHEET
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Study Number (Genentech study number)	
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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

Page 1 of ___