MECHANISTIC STUDIES OF B- AND T-CELL FUNCTION IN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH TNF ANTAGONISTS, TOCILIZUMAB, OR ABATACEPT (MAZERATI)

PREFACE

An Agency for Healthcare Research and Quality executive summary indicated that better comparative effectiveness trial designs are needed to determine the relative merits of existing versus new and expensive biologic drug therapies for rheumatoid arthritis (RA). There are now 9 biologic therapies approved for treating RA. Four classes of biologics (TNF antagonists, B-cell inhibitors, T-cell co-stimulator blocker, and Interleukin-6 receptor blocker) are approved for use in RA patients with moderate or severe disease activity. Several critical questions have arisen, such as 1) what therapy should be prescribed after failure of methotrexate and/or other oral disease modifying antirheumatic drugs (DMARDs) to adequately control disease activity; 2) what is the level of efficacy of the various biologic therapies when compared in head-to-head trials; and 3) what are the mechanisms associated with failure of methotrexate and/or other oral DMARD therapy and responsiveness to biologic therapies. The MAZERATI study will provide the foundation for answering these questions and determining the mechanisms associated with these biologic therapies.

MECHANISTIC STUDIES OF B- AND T-CELL FUNCTION IN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH TNF ANTAGONISTS, TOCILIZUMAB, OR ABATACEPT (MAZERATI)

Sponsored by:
National Institutes of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) (Pending) and Genentech, Inc.

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Draft or Version Number: 3.0

Day Month Year
20 Apr 2015

NCT02353780

Confidentiality Statement

Statement of Compliance

This trial will be conducted in compliance with the protocol, current GCPs recommended by the International Conference on Harmonization (ICH) and the applicable regulatory requirements for University of Pittsburgh. These include the tenets of the Declaration of Helsinki and review and approval by the IRB.

Signature Page 1

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator: _____
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Signed: _____ Date: _____
Name/Title

Signature Page 2

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

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Name/Title

Additional Investigators: _____
Print/Type

Signed: _____ Date: _____
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Table of Contents

Table of Contents

Table of Contents

Table of Contents

List of Abbreviations

AE	Adverse Event/Adverse Experience
CCP	Cyclic Citrullinated Peptide
CFR	Code of Federal Regulations
CIB	Clinical Investigator's Brochure
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRO	Contract Research Organization
DCC	Data Coordinating Center
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
FDA	Food and Drug Administration
FWA	Federal-Wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MedDRA ©	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
N	Number (typically refers to participants)
NCI	National Cancer Institute, NIH
NDA	New Drug Application
NIAID	National Institute of Allergy and Infectious Diseases, NIH
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office for Human Subjects Research
PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetics
QA	Quality Assurance
QC	Quality Control
RF	Rheumatoid Factor
SAE	Serious Adverse Event/Serious Adverse Experience
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
WHO	World Health Organization

Protocol Summary

Full Title	MECHANISTIC STUDIES OF B- AND T-CELL FUNCTION IN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH TNF ANTAGONISTS, TOCILIZUMAB, OR ABATACEPT (MAZERATI)
Short Title	MAZERATI
Clinical Trial Phase	Phase 4, investigator initiated
IND Sponsor (if applicable)	Not applicable
Conducted By	Investigator initiated and conducted at the University of Pittsburgh Medical Center
Co-Principal Investigators	Larry W. Moreland, MD Mandy McGeachy, PhD
Sample Size	90 subjects (30 subjects per treatment arm)
Study Population	Rheumatoid arthritis patients with an inadequate response to methotrexate and/or other oral DMARDs. Patients who are naïve to biological therapies
Accrual Period	July 1, 2014 to July 1, 2017
Study Design	One center, randomized, assessor-blinded, observational longitudinal assessment. Subjects will be randomized to treatment with an anti-TNF therapy, tocilizumab or abatacept and evaluated at baseline, and after 1, 3 and 6 months of therapy. All biologics will be administered subcutaneously (SQ). A blinded assessor will perform clinical disease activity assessments and blood samples will be obtained for mechanistic studies. After randomization, patients must take at least one dose of the assigned medication and must maintain their baseline prednisone and oral DMARD medications until they have received their first dose of assigned medication to be considered per protocol participants. Adjustments of study medication or oral DMARDs will not be permitted during the first 3 months of the study except as outlined in the protocol. Adjustments or additions of analgesics will be permitted throughout the study period. Following randomization and treatment initiation, study participants will be seen in the clinic at 1 month (3-5 weeks), 3 months (10-14 weeks), and 6 months (22-30 weeks) after the initiation of therapy; at each time point, a blinded clinical disease activity assessment will occur and blood samples will be obtained for mechanistic studies.

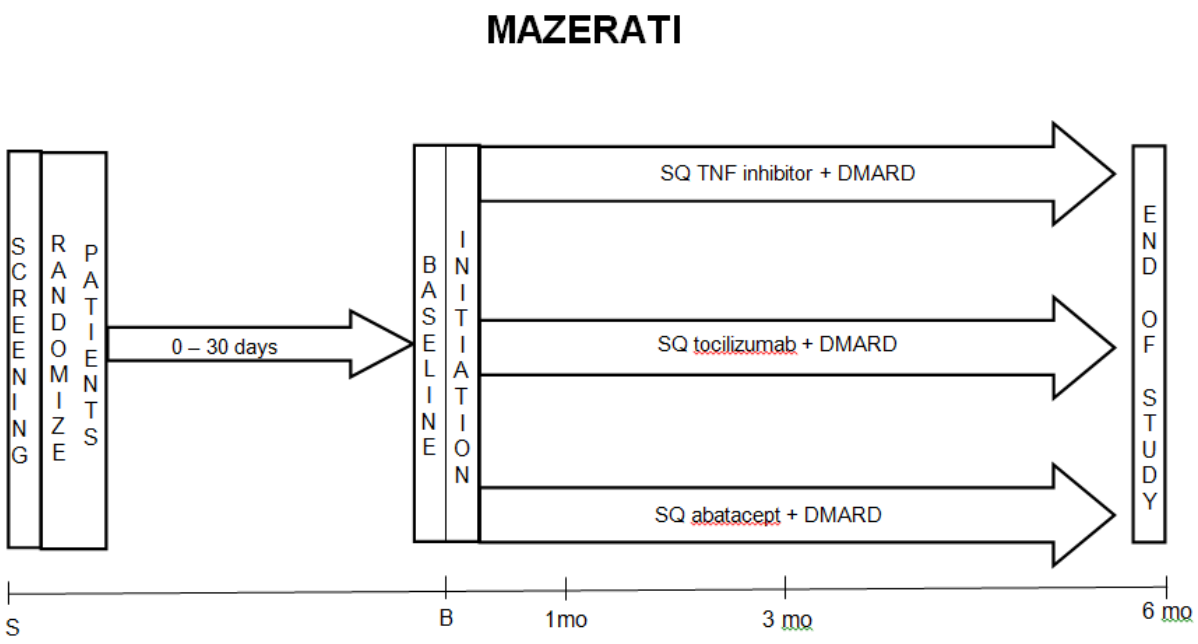
	The occurrence and severity of unanticipated problems and events will be recorded continuously throughout the study. **Inclusion Criteria:** • Must provide (sign) written informed consent to participate • Diagnosis of RA by a physician as defined by the 1987 and/or 2010 ACR criteria. • 18 years of age or older at the time of diagnosis of RA. • Patient age is greater than or equal to 18 yrs and less than or equal to 64 yrs. • RA Disease Activity CDAI > 10 • If using oral corticosteroids, must have been on stable dose (≤ 10 mg/day) for at least 2 weeks prior to study drug initiation. • PPD and/or Quantiferon TB-Gold negative or if PPD and/or Quantiferon TB-Gold positive documentation of therapy with INH for at least 1 month prior to study initiation and negative chest x-ray. • Must have been treated within the past year with methotrexate (MTX), leflunomide (LEF), hydroxychloroquine (HCQ) and/or sulfasalazine (SSZ) for ≥ 3 months. • Prior or concurrent use of other oral DMARD therapy, including LEF, SSZ, and HCQ, is permitted. Patients taking oral DMARDs must be on stable doses of DMARDs for at least 4 weeks prior to study drug initiation. Subjects are not required to be taking an oral DMARD. • Be seropositive for rheumatoid factor (RF) and/or anti-citrullinated cyclic (anti-CCP) antibody **Exclusion Criteria:** • Use of cyclophosphamide, penicillamine, cyclosporine A, tacrolimus or gold therapy is not permitted in the 6 months prior to enrollment. • Patients who are using or have used biologic agents or tofacitinib concomitantly or prior to this study. • History of active and/or chronic infection such as hepatitis, pneumonia, pyelonephritis, herpetic infections, or chronic skin infections and any active opportunistic infection, including but not limited to evidence of active cytomegalovirus, active *Pneumocystis carinii*, aspergillosis, histoplasmosis or atypical mycobacterium infection. • Active TB or evidence of latent TB (positive PPD skin test, positive Quantiferon TB-Gold test or a history of old or latent TB on chest x-ray) without adequate therapy for TB. • Pregnant or lactating women. • Patients with current signs or symptoms of uncontrolled renal, gastrointestinal, endocrine, pulmonary, cardiovascular, neurologic or cerebral disease. • Diagnosis of liver disease or elevated hepatic enzymes, as defined by ALT, AST or both > 1.5 x the upper limit of normal (ULN) or total bilirubin > ULN.

	• 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 e) Neutrophil count < 2,000 cells/μL • Major surgery (including joint surgery) within 8 weeks prior to screening or planned major surgery within 6 months following randomization. • Immunization with a live/attenuated vaccine within 2 months prior to baseline or 3 months of last study visit. • History of severe allergic or anaphylactic reactions to human, humanized, or murine monoclonal antibodies • 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 • Patients with reproductive potential not willing to use an effective method of contraception • History of alcohol, drug or chemical abuse with 1 year prior to screening
Study Duration	5 years
Study Agent/Intervention Description	Anti-TNF biologics (SQ) will be supplied by the subject's pharmacy. Tocilizumab and abatacept will be provided by the study; abatacept by Bristol-Myers Squibb and tocilizumab by Genentech. **Arm #1** (n=30): anti-TNF biologic (either etanercept, adalimumab,certolizumab or golimumab; selection based on discretion of treating physician and subject) **Arm #2** (n=30): SQ tocilizumab **Arm #3** (n=30): SQ abatacept 1.) **Etanercept:** 50 mg SQ qweek 2.) **Adalimumab:** 40 mg SQ q 2 weeks; increased to 40 mg SQ q 7 days at 3 months if CDAI > 2.8 and approved by primary rheumatologist 3.) **Certolizumab:** 400 mg SQ at baseline and at weeks 2 and 4 followed by either 200 mg SQ q 2 weeks or 400 mg SQ q 4 weeks; the dosing regimen for maintenance is at the discretion of the treating physician 4.) **Golimumab:** 50 mg SQ q month 5.) **Tocilizumab:** 162 mg SQ q 2 weeks for patients < 100 kg, increased to q week based on clinical response; or 162 mg SQ q week for patients ≥ 100 kg

	6.) **Abatacept:** SQ route: 125 mg SQ q week
Objectives	1.) To use a **randomized observation study design** as a means to evaluate the correlation between changes in disease activity and changes in B and T cell mechanistic studies following institution of a TNF antagonist, tocilizumab or abatacept. 2.) To use a **randomized observation study design** as a means to evaluate differences in the ***mechanisms of action*** of three clinically relevant treatment options (TNF antagonist vs. tocilizumab vs. abatacept) for rheumatoid arthritis patients with a moderate or high disease activity score (CDAI > 10), and an inadequate response to methotrexate and/or other oral DMARDs.
Endpoints	1.) Completion of at least 3 months of follow-up on stable doses of study medications. 2.) Comparisons of mechanistic study results a.) with changes in disease activity, b.) before initiation of therapy and following therapy and c.) between groups based on study drugs.

MAZERATI Study Design Schematic:

The MAZERATI study will occur according to the schematic below.



1. KEY ROLES

This is a single-site clinical trial occurring at the University of Pittsburgh within the University of Pittsburgh Medical Center (UPMC) Rheumatology Network.

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Genetech (funding of RACER and supply of tocilizumab)
Bristol Myers Squibb (supply of abatacept)

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1.1 Background Information

1.1.1 Description of the Study Agents

The medications to be evaluated are all approved by the FDA at the doses and in the combination(s) outlined in this protocol.

Overview of Anti-TNFα Biologics

There are currently five FDA-approved biologics that target tumor necrosis factor alpha (TNF), and all have a similar safety profile. Published post-marketing experience has drawn attention to TNF inhibitor associated infectious complications (*e.g.*, tuberculosis and other opportunistic infections) [1-6]; demyelination [7], vasculitis [8], lymphoma [6, 9-13], drug-induced systemic lupus erythematosus (SLE) [14, 15], and congestive heart failure [16]. Although there continues to be active research to determine the real relationships and severity of these reported adverse events and TNF inhibitors [17, 18], the U.S. Food and Drug Administration issued a black-box warning to doctors appearing in the product labeling of the anti-TNF drugs instructing them to screen and monitor potential patients carefully. All five of these agents inhibit TNF, but there are different mechanisms of action of these TNF antagonists.

Etanercept (Enbrel) was approved by the FDA in 1998 for treatment of RA. Etanercept is a fusion protein created by linking the human soluble TNF receptor 2 to the Fc domain of human IgG1. Acting as a decoy receptor, etanercept effectively neutralizes a fraction of TNFα in the body, thereby reducing the inflammatory response. The typical dose of etanercept is 50 mg administered subcutaneously every week.

Adalimumab (Humira) was the first fully human monoclonal antibody approved by the FDA in 2002 for the treatment of RA. Like infliximab and etanercept, adalimumab binds to TNFα, preventing it from activating TNF receptors [19]. The typical starting dose of adalimumab is 40 mg every 2 weeks administered subcutaneously, with an increase to 40 mg every week if adalimumab is ineffective at the 2 week dosing interval.

Certolizumab pegol (Cimzia) was approved by the FDA for treating RA in 2009 and approved for treating Crohn's disease in April 2008. The current approved dose for RA is 400 mg subcutaneously once monthly or 200 mg twice monthly. Certolizumab pegol is a recombinant, humanized Fab antibody fragment with specificity for human TNFα. It is conjugated to a ~40 kDa polyethylene glycol (PEG) to enhance plasma half-life. In contrast to infliximab and adalimumab, certolizumab pegol does not fix complement or cause antibody-dependent cell-mediated cytoxicity *in vitro*, as it does not contain an Fc region.

Golimumab (Simponi) is a fully human monoclonal antibody and was approved in 2009 for the treatment of RA. Golimumab is administered once-monthly subcutaneously at a dose of 50 mg.

Infliximab (Remicade) will not be used in this study due the need to adjust dose to achieve maximal efficacy.

Other Biologics

Tocilizumab (Actemra), delivered intravenously and subcutaneously, was approved in 2009 for the treatment of RA. Tocilizumab is a humanized monoclonal antibody targeting the interleukin-6 (IL-6) receptor and thereby blocking the activity of IL-6. Tocilizumab is typically administered initially at a monthly dose of 4 mg/kg and then increased to 8 mg/kg if not effective and no side-effects occur. A SQ route of tocilizumab administration has been approved for treatment of RA at 162 mg every other week for patients < 100 kg, increased to every week based on clinical response; or 162 mg per week for patients ≥ 100 kg. We will only use the subcutaneous administration for this study.

Abatacept (Orencia) modulates the immune response by inhibiting the costimulation of T cells via CD28. Abatacept is a fusion protein composed of the extracellular domain of CTLA-4 and an immunoglobulin Fc domain. Abatacept binds to the B7 protein on antigen presenting cells, thus preventing B7 from binding and activating CD28-mediated costimulation of T cells. The typical intravenous monthly dose of abatacept is 500-1000 mg depending on body weight. Abatacept is also approved for subcutaneous administration at a dose of 125 mg every week. We will only use the subcutaneous administration for this study.

1.1.2 Summary of Previous Pre-clinical Studies

The MAZERATI trial is a phase IV clinical trial. All of the therapies in the MAZERATI trial are FDA-approved and will be used for FDA-approved indications. The objective of the MAZERATI trial is to determine how best to utilize these therapies in humans, and no *pre-clinical* studies support that objective.

1.1.3 Summary of Relevant Clinical Studies

Although therapy with methotrexate is the current standard-of-care for RA patients initiating DMARD therapy, there is no clear consensus about how RA patients should be treated if there is an inadequate response to methotrexate. Many rheumatologists initiate therapy with a TNF antagonist in RA patients with an inadequate response to methotrexate but only about 50% of patients treated with a TNF antagonist or another biologic will respond to therapy [20] and there is currently no way to predict which patients will respond. Furthermore, there are two classes of biologic therapies (abatacept and tocilizumab) besides TNF antagonists approved for use in methotrexate inadequate responders. In addition, triple oral therapy with methotrexate, sulfasalazine and hydroxychloroquine may be equally effective at reducing disease activity in RA patients with an inadequate response to methotrexate [21, 22], but biologic therapies as opposed to triple oral therapy reduce the likelihood of developing bone erosions [21] and treatment with a biologic is perceived to work faster than oral therapy. The choice of a TNF antagonist, as opposed to abatacept or tocilizumab, for methotrexate inadequate responders likely occurs because TNF antagonists were first to market and occurs despite the fact that abatacept and tocilizumab appear to be at least as safe and effective as TNF antagonists [23-26]. In a head-to-head study of RA patients with an inadequate response to methotrexate treated with either the TNF antagonist adalimumab or subcutaneously administered abatacept, both biologics were equally efficacious and abatacept patients had fewer drug discontinuations due to adverse events [24, 25]. Likewise, a systematic review suggested that tocilizumab may be more efficacious than other biologics [27], and in a head-to-head comparison of monotherapy with adalimumab versus tocilizumab in RA patients intolerant or with an

inadequate response to methotrexate, tocilizumab therapy was more efficacious and had an equivalent number of side-effects [26]. *Therefore, it remains unclear which biologic therapy is most efficacious and safe in RA patients with an inadequate response to methotrexate and more importantly what is needed is a way to predict which RA patients will respond to a particular biologic therapy*.

1.1.4 Summary of Epidemiological Data

There are no published epidemiological data that bear on the question of which biologic therapy to select for the treatment of RA patients that have had an inadequate clinical response to methotrexate and/or other oral DMARDs.

1.2 Rationale

RA is a complex inflammatory disorder causing synovitis and joint destruction [28]. Biologics including TNF inhibitors (adalimumab, infliximab, certolizumab, golimumab, etanercept), anti-IL6R blocking drugs (tocilizumab), anti B cell (rituximab) and the T cell costimulation blocker CTLA4Ig (abatacept) have improved outcomes for many RA patients. However, around 40-50% of patients fail to respond to a given biologic therapy, and there are currently no biomarkers that predict response to aid clinicians in their treatment choices [20]. Therefore, there remains a great clinical need to understand the mechanisms by which different biologics target pathological immune responses in RA, and to develop simple bioassays to measure these responses. Autoreactive memory B cells and Th17 cells contribute to the pathogenesis of RA through production of antibodies and cytokines that activate monocytes and joint stromal cells [29]. Memory B cells and Th17 cells react to similar citrullinated joint proteins, and both populations have been shown to decrease in response to therapy with TNF inhibitors. However, interactions between these cells have not been interrogated in the same RA patients, and whether they are similarly affected by different biologic therapies is unknown. *The objective of this proposal is to determine the impact of different biologic therapies (tocilizumab, abatacept, and TNF inhibitors) on the frequency and function of autoreactive Th17 cells and autoreactive memory B cells in RA.*

Memory $CD4^+$ T cells bearing markers of both TfH (CXCR5) and Th17 (CCR6) cells have been suggested to contribute to inflammation in other autoimmune diseases including juvenile dermatomyositis [30] and Sjögren's syndrome [31]. The combined properties of TfH and Th17 cells position $CXCR5^+$Th17 cells to be superior mediators of both B cell activation and tissue inflammation, and our preliminary data indicate that both $CXCR5^+$Th17 cells and memory B cells are increased in the peripheral blood of patients with RA and decreased by TNF inhibitors. Our central hypothesis is that the activities of autoimmune $CXCR5^+$Th17 and memory B cells are linked in driving RA pathogenesis, and therefore successful therapies must directly or indirectly alter both of these populations. We have the unique opportunity to test this hypothesis by performing longitudinal analysis of peripheral blood mononuclear cells (PBMC) from RA patients with active disease initiating one of three biologic therapies with distinct targets: tocilizumab, abatacept or TNF inhibitor.

To date, we have a surprisingly poor mechanistic understanding of how IL-6, TNF and co-stimulation blockade ameliorate aberrant immune responses in RA [20, 32], and the reasons for variation in drug efficacy among patients remains unclear. There are no diagnostic or predictive parameters to guide informed decisions on the most appropriate therapy for each patient. This proposal will compare the mechanisms of action of tocilizumab, abatacept and TNF inhibitors on T and B cell populations in RA, and will test the predictive value of PBMC gene expression for these changes. This contribution will inform our understanding of how different therapies work in individual patients and will ultimately lead to better decisions about how to best use these drugs in clinical practice. These data will also advance our understanding of the complex immune mechanisms that mediate RA, since Th17 cells and B cells have typically been studied only in isolation or in animal models. Th17 cells and autoreactive B cells are common co-features of other autoimmune diseases including multiple sclerosis, systemic lupus erythematosus and Sjögren's syndrome, therefore the insights provided by this study will be broadly applicable.

1.3 Potential Risks and Benefits

1.3.1 Potential Risks

Known and Potential Risks of TNF antagonists
The most common side-effects associated with treatment with TNF antagonists are injection site reactions, including pain and rash; infections, headaches, and nausea. The major serious side-effects of treatment with TNF antagonists are serious infections, leucopenia, and lymphoma. It is recommended that all patients initiating TNF antagonist therapy be tested for PPD reactivity and/or with a Quantiferon TB-Gold test to assess for the presence of latent TB. We will follow the ACR recommendations for monitoring for toxicity during treatment with TNF antagonists [33, 34].

Known and Potential Risks of Tocilizumab
The most common adverse reactions associated with treatment with tocilizumab are upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased ALT, and injection site reactions. The major serious side-effect of treatment with tocilizumab is serious infections. We will follow the manufacturer's and ACR recommendations for monitoring for toxicity during treatment with tocilizumab [33, 34].

Known and Potential Risks of Abatacept
The most common side-effects associated with treatment with abatacept are headaches, upper respiratory tract infections, nasopharyngitis, and nausea. We will follow the ACR recommendations for monitoring for toxicity during treatment with abatacept [33, 34].

1.3.2 Potential Benefits

The therapies that are being offered to patients in this study are therapies that would typically be offered to RA patients as standard-of-care for patients at this stage of their disease. As such, it is expected that for many patients enrolled in this study that the therapies being offered to these patients will lower RA disease activity.

2. STUDY OBJECTIVES

2.1 Primary Objectives

To use a **randomized observation study design** as a means to evaluate the correlation between changes in disease activity and changes in B and T cell mechanistic studies following institution of a subcutaneously administered TNF antagonist, tocilizumab or abatacept.

To use a **randomized observation study design** as a means to evaluate differences in the ***mechanisms of action*** of three clinically relevant treatment options (TNF antagonist vs. tocilizumab vs. abatacept) for rheumatoid arthritis patients with a moderate or high disease activity score (CDAI > 10), and an inadequate response to methotrexate and/or other oral DMARDs.

The study agents are reviewed in **Section 1.1.1**. Details of dosing and administration of study agents are provided in **Section 5**.

The primary objectives of the MAZERATI study are covered in the following mechanistic specific aims:

AIM 1: Determine the longitudinal effects of blocking TNF, IL-6R and T cell costimulation on CXCR5+Th17 cells in RA: *Hypothesis: CXCR5^{+}Th17 cell frequency and function (cytokine production) are altered differently by each therapy correlating with clinical response and changes in autoantibody.* In **Aim 1a**, we will analyze freshly obtained PBMC by flow cytometry using well-established surface markers and intracellular cytokine staining to identify changes in T cell and B cell subsets over course of therapy in each individual. We will complement these *ex vivo* assays with *in vitro* stimulation assays in **Aim 1b**, to fully define cytokine responses in active RA and changes that occur with each therapy. These data will be correlated with serum autoantibody levels, as well as clinical disease activity over the 6-month trial period. In **Aim 1c**, we will use the highly sensitive and unbiased RNA-Seq approach to confirm observed T cell changes at the molecular level, and define novel gene expression signatures that correlate with response to each therapy.

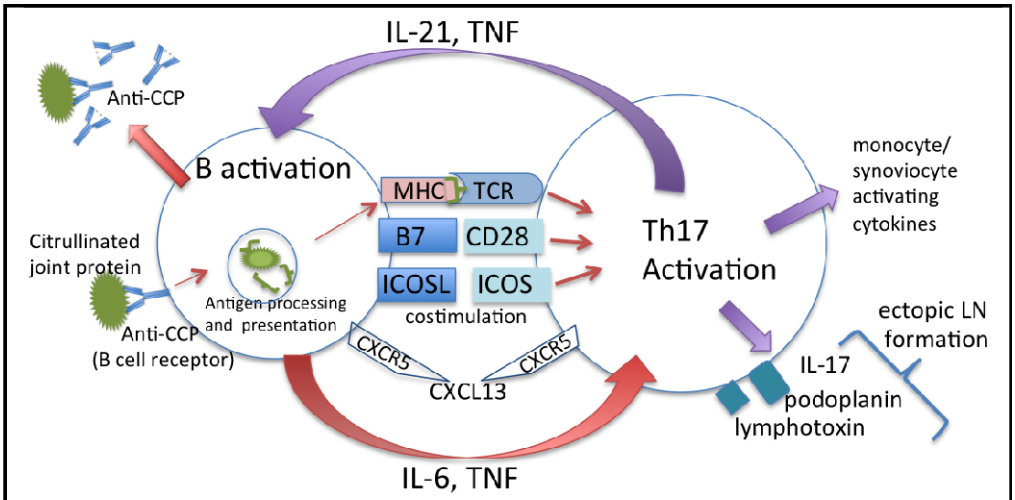

Fig. 1: Interactions between autoreactive B cells and CXCR5⁺Th17 cells drive activation of both subsets. *B cell take up self proteins bound to cell-surface expressed antibody, these are processed and presented on MHCII along with costimulatory molecules to activate autoreactive Th17 cells, drawn to the same locale by expression of CXCR5. Signals via ICOS, IL-6 and TNF promote proliferation and increased Th17 and TfH functions, including production of IL-21, IL-17 and TNF, that feedback to activate B cell expansion, differentiation and secretion of autoantibody that can trigger monocyte and complement activation in the joint.*

AIM 2: Define the pathogenic functions of CXCR5⁺Th17 cells on B cells and synovial fibroblasts in RA, and effect of different biologic therapies on these functions. *Hypothesis: CXCR5⁺Th17 cells are the most potent T activators of autoreactive B cells and synovial fibroblasts in RA.* CXCR5⁺Th17 cells have been shown to strongly induce antibody production in healthy donors, but their ability to activate autoantibody production in RA is unknown. Therefore, in **Aim 2a** we will compare the capacity of CXCR5⁺ and CXCR5⁻ T cell subsets from RA patients to promote antibody production and to direct isotype switching by B cells, and delineate the role of T cell produced cytokines in this process, using blocking antibodies. We will also assess the impact of biologic therapy on B cell activation over the course of therapy, and correlate these findings with serum antibody levels. Synovial fibroblasts are thought to drive cartilage and bone erosion in RA, and are a major downstream target of Th17 cytokines, including IL-17. In **Aim 2b** we will therefore perform parallel proof-of-concept experiments to assess the capacity of RA CXCR5⁺Th17 cells to activate RA synovial fibroblasts (as measured by cytokine and chemokine expression), and roles of IL-6, TNF and CD28 costimulation.

These data will for the first time determine the effects of tocilizumab, abatacept, and TNF inhibitors head-to-head in the same patient cohort, with a focus on the newly identified subset of $CXCR5^{+}Th17$ cells, and its relationship to memory B cells in the same patients. By analyzing longitudinal effects of these drugs in the same study, we have the unique opportunity to reveal therapy-specific differences in mechanisms of action and drug resistance, that will inspire future development of predictive biomarkers and ultimately lead to informed decisions on therapy choice.

2.2 Secondary Objectives

To use a randomized observation study design to evaluate the relative efficacy of three clinically relevant treatment options (anti-TNF *vs*. tocilizumab *vs*. abatacept) for RA in patients who have an inadequate response to methotrexate and/or other oral DMARDs. For these analyses, we will compare the change in CDAI before and after therapy between each of the three different treatment arms. Given the small number of patients, this study is not powered for efficacy and we will not perform inferential statistics with regard to efficacy.

2.3 Exploratory Objectives

To determine the effect of disease duration on the results of mechanistic studies and to determine the effect of clinical response on the results of the mechanistic studies. We will also establish the feasibility of a novel, low-cost trial design (randomized observation) for conducting comparative effectiveness studies in RA patients that mirrors real-world clinical practice, but includes randomization, blinded assessments, and fixed time points for assessment.

3. STUDY DESIGN

3.1 Description of the Study Design

Summary: MAZERATI is an open-label, assessor-blinded, randomized, observational study of 90 subjects to determine the mechanisms associated with treatment with a TNF inhibitor or non-TNF inhibitor biologic therapies (tocilizumab or abatacept) in the setting of an inadequate clinical response to methotrexate and/or other oral DMARDs in patients with RA. A summary of key study characteristics is provided in **Table 1**.

Table 1. Summary of the Key Characteristics of the MAZERATI trial.	
Phase:	IV
Study Arms:	3 arms, with 30 participants in each arm
Sites:	Single site; UPMC Rheumatology RACER Network
Population:	Participants will be diagnosed with rheumatoid arthritis and have a moderate to severe level of disease activity (CDAI > 10)
Clinic Location:	Out-patient rheumatology offices
Total Enrollment Time:	30 participants enrolled per year; total of 3 years for enrollment of 90 participants
Participation Duration:	6 months per participant
Study Agents:	See also Section 1.1.1; etanercept, adalimumab, certolizumab, golimumab, tocilizumab, and abatacept (all administered

	subcutaneously)

Randomization: 90 eligible subjects will be randomized in a 1:1:1 ratio to receive either a TNF antagonist, tocilizumab, or abatacept. Following screening, participants eligible for the study will be randomized to a TNF antagonist (specific one to be selected by the treating physician), tocilizumab, or abatacept. Subjects will be randomized on a password-protected web-based program on a computer. The costs for an anti-TNF drug will be the subject's responsibility. If insurance authorization is not obtained or available for the study drug, then we will work with the clinic staff to help the subject apply for assistance to pay for the medication from one of several foundations. If foundation financial assistance is not available, the subject will be referred to UPMC Social Services and/or a UPMC financial counselor to review their options for covering the cost of the drug. Finally, after every effort has been made to minimize costs to the subject, the subject may choose to pay out of pocket for the remaining expenses associated with the study drug,,If a patient chooses not to pay out-of-pocket, they may be prescribed another rheumatoid arthritis medication that their insurance will cover or continue on their current medications per the recommendation of their rheumatologist. In these cases, patients will be followed to study completion and included in analysis under the intent to treat principle.

Third party payors at this time feel that a TNF antagonist is the next line of treatment in RA patients who have failed MTX. Thus, they will not approve payment for abatacept or tocilizumab in this setting. This is despite current FDA approval for these two agents for this indication. Thus, the only way around this roadblock for this study was to seek free abatacept and tocilizumab from Bristol Myers Squibb and Genentech, respectively. We now have written approval for these agents from these two pharmaceutical companies.

Table 2. List of Specific Contraindications for the Use of MAZERATI Treatments

Study Drug	**Contraindications Specific to Given Study Drug***
TNF antagonist	Class III or IV congestive heart failure Past or current history of demyelinating neurological disorder Past or current history of lymphoma Past or current history of malignancy besides lymphoma within the past 5 years
Tocilizumab	Known hypersensitivity to tocilizumab
Abatacept	Severe chronic obstructive pulmonary disease (COPD)

* Additional contraindications related to all study drug treatments, such as a history of active or recurrent infection, are listed in the exclusion criteria for the study. If patients have any of these contraindications as part of screening they will not be eligible for this study.

Blinding: This study will utilize a partial blinding plan. The participant, the participant's physician, and the study coordinator will not be blinded to the participant's treatment assignment. Only the blinded assessor, who will perform a joint examination at fixed intervals, will be blinded to each participant's treatment.

3.2 Study Endpoints

3.2.1 Primary Endpoint

There will be no primary *efficacy* endpoints for the study. The primary endpoint of the study will be mechanistic comparisons within, between and including all the different treatment groups. The mechanistic comparisons will compare results from studies of samples 1.) within groups, before initiation of therapy and following therapy, between responders and non-responders within each group, and as a correlation between mechanistic results and disease activity, 2.) between groups, where groups are based on different study drugs, and 3.) including all treatment groups as a correlation between mechanistic results and disease activity.

3.2.2 Secondary Endpoints

Efficacy as measured by CDAI remission < 2.8;
Efficacy as measured by DAS remission with a DAS28-CRP < 2.6;
Efficacy as measured by ACR20, 50, and 70 response;
Adherence to drug regimen;
Reason for discontinuation of treatment (side effects, lack of efficacy, cost, patient compliance, *etc*.)

3.2.3 Exploratory Endpoints

None

3.2.4 Substudy Endpoints

None

4. STUDY POPULATION

Selection of Subjects

We will enroll RACER participants and other RA patients evaluated in UPMC rheumatology clinics with an inadequate response to methotrexate and/or other oral DMARDs. We will obtain a final sample of 90 (30 per treatment arm) participants that complete the 3-month study visit. “Inadequate response to methotrexate and/or other oral DMARDs” will be defined as RA patients having a Clinical Disease Activity Index (CDAI) > 10 after at least 3 months of treatment with methotrexate and/or other oral DMARDs. Treatment with methotrexate and/or other oral DMARDs must have occurred within the 1-year period prior to enrollment. If an RA patient is identified as an oral DMARD inadequate responder, s/he will be prescreened to confirm eligibility according to the inclusion and exclusion criteria.

4.1 Description of the Study Population

4.1.1 Participant Inclusion Criteria

To be eligible, patients must meet all of the following criteria:

- Must provide (sign) written informed consent to participate
- Diagnosis of RA by a physician as defined by the 1987 and/or 2010 ACR criteria.

- 18 years of age or older at the time of diagnosis of RA.
- RA Disease Activity CDAI > 10
- Patient age is greater than or equal to 18 yrs and less than or equal to 64 yrs.

- If using oral corticosteroids, must have been on stable dose (≤ 10 mg/day) for at least 2 weeks prior to study drug initiation.
- PPD and/or Quantiferon TB-Gold negative or if PPD and/or Quantiferon TB-Gold positive documentation of therapy with INH for at least 1 month prior to study initiation and negative chest x-ray.
- Must have been treated within the past year with methotrexate (MTX), leflunomide (LEF), hydroxychloroquine (HCQ) and/or sulfasalazine (SSZ) for ≥ 3 months.
- Prior or concurrent use of other oral DMARD therapy, including LEF, SSZ, and HCQ, is permitted. Patients taking oral DMARDs must be on stable doses of DMARDs for at least 4 weeks prior to study drug initiation. Subjects are not required to be taking an oral DMARD.
- Be seropositive for rheumatoid factor (RF) and/or anti-citrullinated cyclic (anti-CCP) antibody

4.1.2 Participant Exclusion Criteria

Patients meeting any of the exclusion criteria at baseline will be excluded from the study.

- Use of cyclophosphamide, penicillamine, cyclosporine A, tacrolimus or gold therapy is not permitted in the 6 months prior to enrollment.
- Patients who are using or have used biologic agents or tofacitinib concomitantly or prior to this study.
- History of active and/or chronic infection such as hepatitis, pneumonia, pyelonephritis, herpetic infections, or chronic skin infections and any active opportunistic infection, including but not limited to evidence of active cytomegalovirus, active *Pneumocystis carinii*, aspergillosis, histoplasmosis or atypical mycobacterium infection.
- Active TB or evidence of latent TB (positive PPD skin test, positive Quantiferon TB-Gold test or a history of old or latent TB on chest x-ray) without adequate therapy for TB.
- Pregnant or lactating women.
- Patients with current signs or symptoms of uncontrolled renal, gastrointestinal, endocrine, pulmonary, cardiovascular, neurologic or cerebral disease.
- Diagnosis of liver disease or elevated hepatic enzymes, as defined by ALT, AST or both > 1.5 x the upper limit of normal (ULN) or total bilirubin > ULN.
- 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
    e) Neutrophil count < 2,000 cells/µL
- Major surgery (including joint surgery) within 8 weeks prior to screening or planned major surgery within 6 months following randomization.
- Immunization with a live/attenuated vaccine within 2 months prior to baseline or 3 months of last study visit.
- History of severe allergic or anaphylactic reactions to human, humanized, or murine monoclonal antibodies

- 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
- Patients with reproductive potential not willing to use an effective method of contraception
- History of alcohol, drug or chemical abuse with 1 year prior to screening

4.2 Strategies for Recruitment and Retention

Enrollment

Subjects that are prescreened and meet the eligibility criteria for the study will be asked to consider participation in the study by her/his primary rheumatologist, and if the patient agrees, then written, informed consent will be sought and obtained by a clinical research coordinator. Two of the medications under investigation will be provided by the study. Tocilizumab and abatacept will be provided by Genentech and BMS, respectively. If patients are randomized to a TNF inhibitor, it will be paid for by the patient's insurance. Thus, for those randomized to a TNF inhibitor, screening will consist of obtaining preauthorization from the patient's insurance provider to ensure coverage of whatever TNF inhibitor the patient's attending physician orders. Based on the step-wise process described in **Section 3.1**, participants will be randomized to one arm of the study. The mechanism used for randomization will allow for even, unbiased distribution of patients into each arm of the study. A patient must take at least one dose of the assigned medication to be considered a study participant. Enrollment will continue until 90 participants have completed the 3-month study visit while receiving their originally randomized therapy and have not violated the protocol.

5. STUDY AGENTS

5.1 Study Agent Acquisition

General Statement on Study Agent Acquisition: The MAZERATI study is a blinded-assessor, randomized-observational study. Participants will be randomized to different RA therapies. Clinicians will provide a prescription for TNF inhibitors, within the guidelines of the MAZERATI protocol. For TNF inhibitors, participants will fill the prescription at their chosen pharmacy, and the pharmacist will use the labeling and provide materials as directed by their institution. Abatacept and tocilizumab prescriptions and orders will be handled by Dr. Moreland and the UPMC Investigational Drug Service (IDS). No placebo is utilized in this study. All study agents will be utilized in an open-label manner, within the guidelines of the MAZERATI clinical protocol, supplied in their standard form. The MAZERATI study utilizes board-certified, unblinded rheumatologists and open-label therapies administered with standard-of-care procedures; these study investigators are very familiar with the clinical management of these products. Descriptions of these study agents are provided below.

Dose regimen for biologic therapies

1.) Etanercept (50 mg SQ q week)

2.) Adalimumab (40 mg SQ q 2 weeks; increased to 40 mg SQ q 7 days at 3 months if CDAI > 2.8 and if acceptable with primary rheumatologist)

3.) Certolizumab (400 mg SQ at baseline and at weeks 2 and 4 followed by either 200 mg SQ q 2 weeks or 400 mg SQ q 4 weeks; the dosing regimen for maintenance is at the discretion of the treating physician)

4.) Golimumab (50 mg SQ q month)

5.) Tocilizumab (162 mg SQ q 2 weeks for patients < 100 kg, increased to q week based on clinical response; or 162 mg SQ q week for patients ≥ 100 kg)

6.) Abatacept (SQ route: 125 mg SQ q week)

Figure 1. Packaging Configurations for Etanercept.

5.1.1 Etanercept (Enbrel)

6.1.1.1 Formulation, Packaging, and Labeling

As stated in the **General Statement on Study Agent Acquisition** at the beginning of **Section 5.1**, etanercept (Enbrel) will be supplied by the participant's chosen pharmacy. Cost is the responsibility of the participant or the participant's third-party payer. No special labels or formulation are required in the MAZERATI study.

Enbrel® (etanercept) is supplied in prefilled syringes as a preservative-free, sterile solution for subcutaneous administration. The following packaging configurations are available.

Enbrel Single-use Prefilled SureClick Autoinjector: Enbrel is dispensed in a carton containing four prefilled SureClick Autoinjectors. Each prefilled SureClick Autoinjector is a single dose and contains a 1 mL prefilled syringe with a fixed 27 gauge ½ inch needle, providing 50 mg (1 mL) of Enbrel. The NDC number is 58406-445-04. See **Figure 1**.

Enbrel Single-use Prefilled Syringe: Enbrel is dispensed in a carton containing four prefilled syringes. Each prefilled syringe is a single dose and contains a 1 mL prefilled syringe with a fixed 27 gauge ½ inch needle, providing 50 mg (1 mL) of Enbrel. The NDC number is 58406-435-04. See **Figure 1**.

Storage and Stability: Do not use beyond the expiration date on the container. Enbrel must be refrigerated at 2 to 8° C (36 to 46° F). Do not freeze. Protect the prefilled syringe from exposure to light. Store in original carton until time of administration. Do not shake Enbrel at any time.

Summary for: Etanercept (Enbrel)	
Formulation:	Solution for subcutaneous injection
Labeling:	Routine labeling from participant's chosen pharmacy

Manufacturer Name:	Amgen and Pfizer, Inc.
Stability:	Enbrel must be refrigerated at 2 to 8° C (36 to 46° F); it should not be frozen. Enbrel is light-sensitive and should not be exposed to direct light.
Expiration Time:	Enbrel is supplied as a single-dose autoinjector or a single-dose prefilled syringe. It should not be used after the expiration date.

5.1.1.2 Preparation, Administration, Storage, and Dosage of Etanercept

As stated in the **General Statement on Study Agent Acquisition** at the beginning of **Section 5.1**, etanercept will be supplied by a participant's chosen pharmacy. Etanercept is supplied in prefilled, ready-to-use syringes as a preservative-free, sterile solution for subcutaneous administration. The recommended dose of etanercept for adult patients with rheumatoid arthritis is 50 mg in 1 mL administered every week. Participants will be encouraged to continue with etanercept for the full 6 months of randomization. Clinicians will monitor their patients and change study medications if desired by either the clinician or the participant, as this is a real-world study.

The prescribing physicians are board-certified rheumatologists, with experience prescribing and monitoring patients taking etanercept. In addition to counseling at the outpatient clinic and possibly at their pharmacy, patients will be instructed to read the full medication guide before taking etanercept. All participants will be tested for latent TB and hepatitis B and C prior to enrollment in the study, and all participants will be advised to consult their rheumatologist if they develop any signs of infection, including TB and hepatitis reactivation. Etanercept will be discontinued if a patient develops a serious infection or sepsis during treatment. Participants will be advised to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Latex-sensitive participants will be advised that the needle cap of the prefilled syringe contains latex. Participants will also be advised to report any signs of new or worsening medical conditions such as heart disease, neurological disease, autoimmune disorders, or symptoms suggestive of any cytopenia.

Etanercept can be supplied as either a single-dose autoinjector or single-dose syringe. There is no need for participants to thaw, dilute, mix, reconstitute, or prepare the solution. Participants will be counseled in the outpatient clinic on the proper way to administer the injection. The first injection will be performed under the supervision of a qualified health care professional. A puncture-resistant container for disposal of needles and syringes will be provided. Participants will be cautioned against reuse of these items. Specific, detailed instructions will be provided to participants by both their pharmacy and the nurse coordinators. The following are abridged instructions for administration of etanercept.

- Check and make sure the name ENBREL appears on the box and syringe/autoinjector label.
- Check the expiration date on the syringe/autoinjector label to make sure the date has not passed. Do not use a syringe/autoinjector if the date has passed.
- Have a special sharps (puncture proof) container nearby for disposing of the used syringe/autoinjector.

- Choose a site on the front of your thighs or your stomach area (abdomen) for administration.
- Wipe the site where etanercept (Enbrel) is to be injected with an alcohol prep (swab), using a circular motion. Do not touch this area again until you are ready to inject.
- Check the solution through the windows on the side of the syringe/autoinjector to make sure the liquid is clear and colorless. Do not use a syringe/autoinjector if the liquid is cloudy or discolored or has large particles in it. Do not use if frozen or if it was ever previously frozen.
- Check to make sure that the amount of liquid in the syringe/autoinjector is the same or close to the fill line seen through the window. If the syringe/autoinjector does not have the full amount of liquid, do not use that syringe/autoinjector.
- Inject the etanercept (Enbrel).

Participants should store etanercept in a refrigerator at 36 to 46ºF (2 to 8ºC) in the original container until it is used. It should be protected from light. Do not freeze etanercept or use previously frozen etanercept. Refrigerated etanercept remains stable to use until the expiration date printed on the prefilled syringe or autoinjector. If a participant will need to take etanercept outside of the home, such as when traveling, it must be stored in a cool carrier with an ice pack and protected from light. If etanercept freezes, do not use it, even after it has thawed. Do not use a autoinjector or prefilled syringe if the liquid is cloudy, discolored, or has large particles in it. Do not drop or crush etanerecept. For additional information or questions, coordinators or participants can call 1-888-4Enbrel (1-888-436-2735).

Summary for: Etanercept (Enbrel)	
Route:	Subcutaneous injection by trained participant
Dosing:	50mg
Duration:	Full 6 months of MAZERATI study
Frequency:	Every week
Expiration Time:	Follow expiration date on the packaging

5.1.1.3 Study Agent Accountability Procedures

If a participant is randomized to the anti-TNF arm of the study, then their treating rheumatologist can order any anti-TNF from the study agent list of anti-TNF therapies, provided that the patient has not had previous experience with any anti-TNF agent. As stated in the **General Statement on Study Agent Acquisition** at the beginning of **Section 5.1**, etanercept will be supplied by a participant's chosen pharmacy when a prescription is presented. These therapies will be used in an open-label manner, so frequency of product distribution and amount of product dispensed will be within open-label guidelines for each specific therapy (see specific dosing regimens in **Section 6.1**).

Participants will be provided with a sharps container for their spent etanercept syringes or autoinjectors. Participants will bring the sharps container to each study visit with a list of their unused etanercept syringes or autoinjectors. Coordinators will log the number of spent syringes or pens in the container to verify proper drug dosing. Used syringes or pens, expired etanercept, and unused etanercept will be returned to the study coordinators, who will dispose of it according to the appropriate regulations.

5.1.2 Adalimumab (Humira)

5.1.2.1 Formulation, Packaging, and Labeling

As stated in the **General Statement on Study Agent Acquisition** at the beginning of **Section 5.1**, adalimumab (Humira) will be supplied by a participant's chosen pharmacy. Cost is the responsibility of the participant or the participant's third-party payer. No special labels or formulation is required in the MAZERATI study.

Figure 2. Packaging Configurations for Adalimumab.

Humira® (adalimumab) is supplied in prefilled syringes as a preservative-free, sterile solution for subcutaneous administration. The following packaging configurations are available.

Humira Pen Carton: Humira is dispensed in a carton containing two alcohol preps and two dose trays. Each dose tray consists of a single-use pen, containing a 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 40 mg (0.8 mL) of Humira. The NDC number is 0074-4339-02. See **Figure 2**.

Prefilled Syringe Carton – 40 mg: Humira is dispensed in a carton containing two alcohol preps and two dose trays. Each dose tray consists of a single-dose, 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 40 mg (0.8 mL) of Humira. The NDC number is 0074-3799-02. See **Figure 2**.

Storage and Stability: Do not use beyond the expiration date on the container. Humira must be refrigerated at 2 to 8° C (36 to 46° F). Do not freeze. Protect the prefilled syringe from exposure to light. Store in original carton until time of administration.

Summary for: Adalimumab (Humira)	
Formulation:	Solution for subcutaneous injection
Labeling:	Routine labeling from participant's chosen pharmacy
Manufacturer Name:	Abbott Laboratories
Stability:	Humira must be refrigerated at 2 to 8° C (36 to 46° F); it should not be frozen. Humira is light-sensitive and should not be exposed to direct light.
Expiration Time:	Humira is supplied as a single-dose pen or a single-dose syringe. It should not be used after the expiration date.

5.1.2.2 Preparation, Administration, Storage, and Dosage of Adalimumab

As stated in the **General Statement on Study Agent Acquisition** at the beginning of **Section 5.1**, adalimumab will be supplied by a participant's chosen pharmacy. Adalimumab is supplied in prefilled, ready-to-use syringes as a preservative-free, sterile solution for subcutaneous administration. The recommended dose of adalimumab for adult patients with rheumatoid

arthritis is 40 mg in 0.8 mL administered every other week. In rheumatoid arthritis, some patients not taking concomitant methotrexate may derive additional benefit from increasing the dosing frequency of adalimumab to 40 mg every week. Clinicians will be permitted to order the appropriate dose and frequency for their patients. Participants will be encouraged to continue with adalimumab for the full 6 months of randomization. Clinicians will monitor their patients and change study medications if desired by either the clinician or the participant, as this is a real-world study.

The prescribing physicians are board-certified rheumatologists, with experience prescribing and monitoring patients taking adalimumab. In addition to counseling at the outpatient clinic and possibly at their pharmacy, patients will be instructed to read the full medication guide before taking adalimumab. All participants will be tested for latent TB and hepatitis B and C prior to enrollment in the study, and all participants will be advised to consult their rheumatologist if they develop any signs of infection, including TB and hepatitis reactivation. Adalimumab will be discontinued if a patient develops a serious infection or sepsis during treatment. Participants will be advised to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Latex-sensitive participants will be advised that the needle cap of the prefilled syringe contains latex. Participants will also be advised to report any signs of new or worsening medical conditions such as heart disease, neurological disease, autoimmune disorders, or symptoms suggestive of any cytopenia.

Adalimumab can be supplied as either a single-dose pen or single-dose syringe. There is no need for participants to thaw, dilute, mix, reconstitute, or prepare the solution. Participants will be counseled in the outpatient clinic on the proper way to administer the injection. The first injection will be performed under the supervision of a qualified health care professional. A puncture-resistant container for disposal of needles and syringes will be provided. Participants will be cautioned against reuse of these items. Specific, detailed instructions will be provided to participants by both their pharmacy and the nurse coordinators. The following are abridged instructions for administration of adalimumab.

- Check and make sure the name HUMIRA appears on the dose tray and syringe/pen label.
- Check the expiration date on the dose tray label and the syringe/pen label to make sure the date has not passed. Do not use a syringe/pen if the date has passed.
- Have a special sharps (puncture proof) container nearby for disposing of the used syringe/pen.
- Choose a site on the front of your thighs or your stomach area (abdomen) for administration.
- Wipe the site where adalimumab (Humira) is to be injected with an alcohol prep (swab), using a circular motion. Do not touch this area again until you are ready to inject.
- Check the solution through the windows on the side of the syringe/pen to make sure the liquid is clear and colorless. Do not use a syringe/pen if the liquid is cloudy or discolored or has flakes or particles in it. Do not use if frozen or if it was ever previously frozen.
- Check to make sure that the amount of liquid in the syringe/pen is the same or close to the fill line seen through the window. If the syringe/pen does not have the full amount of liquid, do not use that syringe/pen.
- Inject the adalimumab (Humira).

Participants should store adalimumab in a refrigerator at 36 to 46ºF (2 to 8ºC) in the original container until it is used. It should be protected from light. Do not freeze adalimumab or use previously frozen adalimumab. Refrigerated adalimumab remains stable to use until the expiration date printed on the prefilled syringe or pen. If a participant will need to take adalimumab outside of the home, such as when traveling, it must be stored in a cool carrier with an ice pack and protected from light. If adalimumab freezes, do not use it, even after it has thawed. Do not use a pen or prefilled syringe if the liquid is cloudy, discolored, or has flakes or particles in it. Do not drop or crush HUMIRA. The prefilled syringe is glass. For additional information or questions, coordinators or participants can call 1-800-4HUMIRA (448-6472).

Summary for: Adalimumab (Humira)	
Route:	Subcutaneous injection by trained participant
Dosing:	40mg
Duration:	Full 6 months of MAZERATI study
Frequency:	Every week or every other week
Expiration Time:	Follow expiration date on the packaging

5.1.2.3 Study Agent Accountability Procedures

If a participant is randomized to the anti-TNF arm of the study, then their treating rheumatologist can order any anti-TNF from the study agent list of anti-TNF therapies, provided that the patient has not had previous experience with any anti-TNF agent. As stated in the **General Statement on Study Agent Acquisition** at the beginning of **Section 5.1**, adalimumab will be supplied by a participant's chosen pharmacy when a prescription is presented. These therapies will be used in an open-label manner, so frequency of product distribution and amount of product dispensed will be within open-label guidelines for each specific therapy (see specific dosing regimens in **Section 5.1**).

Participants will be provided with a sharps container for their spent adalimumab syringes or pens. Participants will bring the sharps container to each study visit with a list of their unused adalimumab syringes or pens. Coordinators will log the number of spent syringes or pens in the container to verify proper drug dosing. Used syringes or pens, expired adalimumab, and unused adalimumab will be returned to the study coordinators, who will dispose of it according to the appropriate regulations.

Figure 3. Packaging Configurations for Golimumab.

5.1.3 Golimumab (Simponi)

5.1.3.1 Formulation, Packaging, and Labeling

As stated in the **General Statement on Study Agent Acquisition** at the beginning of **Section 5.1**, golimumab (Simponi) will be supplied by a participant's chosen pharmacy. Cost is the

responsibility of the participant or the participant's third-party payer. No special labels or formulation is required in the MAZERATI study.

Simponi (golimumab) is supplied in prefilled syringes as a sterile solution for subcutaneous administration. The following packaging configurations are available. Each golimumab (Simponi) prefilled autoinjector or prefilled syringe is packaged in a light-blocking, cardboard outer carton.

Prefilled SmartJect Autoinjector: Golimumab prefilled SmartJect Autoinjectors are dispensed with one autoinjector per box. Each single dose SmartJect autoinjector contains a prefilled glass syringe (27 gauge, ½ inch) providing 50 mg of golimumab (Simponi) per 0.5 mL of solution. The NDC number is 57894-070-02. See **Figure 3**.

Prefilled Syringe: Golimumab prefilled syringes are dispensed with one syringe per box. Each single dose prefilled glass syringe (27 gauge, ½ inch) contains 50 mg of golimumab (Simponi) per 0.5 mL of solution. The NDC number is 57894-070-01. See **Figure 3**.

Storage and Stability: Do not use beyond the expiration date on the container. Golimumab must be refrigerated at 2 to 8° C (36 to 46° F). Do not freeze. Do not shake golimumab. Protect the prefilled syringe from exposure to light. Store in the original carton until the time of administration.

Summary for: Golimumab (Simponi)	
Formulation:	Solution for subcutaneous injection
Labeling:	Routine labeling from participant's chosen pharmacy
Manufacturer Name:	Centocor Ortho Biotech, Inc.
Stability:	Simponi must be refrigerated at 2 to 8° C (36 to 46° F); it should not be frozen. Simponi is light-sensitive and should not be exposed to direct light.
Expiration Time:	Simponi is supplied as a single-dose autoinjector or a single-dose prefilled syringe. It should not be used after the expiration date.

5.1.3.2 Preparation, Administration, Storage, and Dosage of Golimumab

As stated in the **General Statement on Study Agent Acquisition** at the beginning of **Section 5.1**, golimumab will be supplied by a participant's chosen pharmacy. Golimumab is supplied in prefilled, ready-to-use syringes as a preservative-free, sterile solution for subcutaneous administration. The recommended dose of golimumab for adult patients with rheumatoid arthritis is 50 mg in 0.5 mL administered every month. Participants will be encouraged to continue with golimumab for the full 6 months of randomization. Clinicians will monitor their patients and change study medications if desired by either the clinician or the participant, as this is a real-world study.

The prescribing physicians are board-certified rheumatologists, with experience prescribing and monitoring patients taking golimumab. In addition to counseling at the outpatient clinic and possibly at their pharmacy, patients will be instructed to read the full medication guide before taking golimumab. All participants will be tested for latent TB and hepatitis B and C prior to enrollment in the study, and all participants will be advised to consult their rheumatologist if they

develop any signs of infection, including TB and hepatitis reactivation. Golimumab will be discontinued if a patient develops a serious infection or sepsis during treatment. Participants will be advised to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Latex-sensitive participants will be advised that the needle cap of the prefilled syringe contains latex. Participants will also be advised to report any signs of new or worsening medical conditions such as heart disease, neurological disease, autoimmune disorders, or symptoms suggestive of any cytopenia.

Golimumab can be supplied as either a single-dose autoinjector or single-dose syringe. There is no need for participants to thaw, dilute, mix, reconstitute, or prepare the solution. Participants will be counseled in the outpatient clinic on the proper way to administer the injection. The first injection will be performed under the supervision of a qualified health care professional. A puncture-resistant container for disposal of needles and syringes will be provided. Participants will be cautioned against reuse of these items. Specific, detailed instructions will be provided to participants by both their pharmacy and the nurse coordinators. The following are abridged instructions for administration of golimumab.

- Check and make sure the name SIMPONI appears on the box and syringe/autoinjector label.
- Check the expiration date on the box label and the syringe/autoinjector label to make sure the date has not passed. Do not use a syringe/pen if the date has passed.
- Allow golimumab to warm up for 30 minutes prior to use. Do this by leaving the syringe/autoinjector sit out at room temperature for 30 minutes where children can't reach it. Never warm up golimumab any other way.
- Have a special sharps (puncture proof) container nearby for disposing of the used syringe/pen.
- Choose a site on the front of your thighs or your stomach area (abdomen) for administration.
- Wipe the site where golimumab (Simponi) is to be injected with an alcohol prep (swab), using a circular motion. Do not touch this area again until you are ready to inject.
- Check the solution through the windows on the side of the syringe/autoinjector to make sure the liquid is clear and colorless. Do not use a syringe/autoinjector if the liquid is cloudy or discolored or has large particles in it. Do not use if frozen or if it was ever previously frozen.
- Check to make sure that the amount of liquid in the syringe/autoinjector is the same or close to the fill line seen through the window. If the syringe/autoinjector does not have the full amount of liquid, do not use that syringe/pen.
- Inject the golimumab (Simponi).

Participants should store golimumab in a refrigerator at 36 to 46ºF (2 to 8ºC) in the original container until it is used. It should be protected from light. Do not freeze golimumab or use previously frozen golimumab. Refrigerated golimumab remains stable to use until the expiration date printed on the prefilled syringe or pen. If a participant will need to take golimumab outside of the home, such as when traveling, it must be stored in a cool carrier with an ice pack and protected from light. If golimumab freezes, it should not be used, even after it has thawed. Do not use a autoinjector or prefilled syringe if the liquid is cloudy, discolored, or has large particles in it. Do not drop or crush Simponi. The prefilled syringe is glass. For additional information or questions, coordinators or participants can call 1-800-457-6399.

Summary for: Golimumab (Simponi)

Route:	Subcutaneous injection by trained participant
Dosing:	50mg
Duration:	Full 6 months of MAZERATI study
Frequency:	Every month
Expiration Time:	Follow expiration date on the packaging

5.1.3.3 Study Agent Accountability Procedures

If a participant is randomized to the anti-TNF arm of the study, then their treating rheumatologist can order any anti-TNF from the study agent list of anti-TNF therapies, provided that the patient has not had previous experience with any anti-TNF agent. As stated in the **General Statement on Study Agent Acquisition** at the beginning of **Section 5.1**, golimumab will be supplied by a participant's chosen pharmacy when a prescription is presented. These therapies will be used in an open-label manner, so frequency of product distribution and amount of product dispensed will be within open-label guidelines for each specific therapy. See **Section 5.1** for detailed dosing information for each therapy.

Participants will be provided with a sharps container for their spent golimumab syringes or autoinjectors. Participants will bring the sharps container to each study visit with a list of their unused golimumab syringes or autoinjectors. Coordinators will log the number of spent syringes or autoinjectors in the container to verify proper drug dosing. Used syringes or autoinjectors, expired golimumab, and unused golimumab will be returned to the study coordinators, who will dispose of it according to the appropriate regulations.

5.1.4 Certolizumab pegol (Cimzia)

Figure 4. Packaging Configurations for

Certolizumab Pegol.

5.1.4.1 Formulation, Packaging, and Labeling

As stated in the **General Statement on Study Agent Acquisition** at the beginning of **Section 5.1**, certolizumab pegol (Cimzia) will be supplied by a participant's chosen pharmacy. Cost is the responsibility of the participant or the participant's third-party payer. No special labels or formulation is required in the MAZERATI study.

Cimzia (certolizumab) is supplied in prefilled glass syringes as a sterile solution for subcutaneous administration. Only 1 packaging configuration is available. Each certolizumab (Cimzia) prefilled syringe is packaged in a light-blocking, cardboard outer carton.

Prefilled Syringe: Certolizumab prefilled syringes are dispensed with two syringes per box. Each single dose prefilled glass syringe (25 gauge, ½ inch) contains 200 mg of certolizumab (Cimzia) per 1.0 mL of solution. The NDC number is 50474-710-79. See **Figure 4**.

Storage and Stability: Do not use beyond the expiration date on the container. Certolizumab must be refrigerated at 2 to 8° C (36 to 46° F). Do not freeze. Protect the prefilled syringe from exposure to light. Store in the original carton until the time of administration.

5.1.4.2 Preparation, Administration, Storage, and Dosage of Certolizumab Pegol

As stated in the **General Statement on Study Agent Acquisition** at the beginning of **Section 5.1**, certolizumab will be supplied by a participant's chosen pharmacy. Certolizumab is supplied in prefilled, ready-to-use syringes as a sterile solution for subcutaneous administration. The recommended dose of certolizumab for adult patients with rheumatoid arthritis is 400 mg at baseline and at weeks 2 and 4, followed by either 200 mg every 2 weeks or 400 mg every 4 weeks. The dosing regimen for maintenance is at the discretion of the treating physician. Participants will be encouraged to continue with infliximab for the full 6 months of randomization. Clinicians will monitor their patients and change study medications if desired by either the clinician or the participant, as this is a real-world study.

The prescribing physicians are board-certified rheumatologists, with experience prescribing and monitoring patients taking certolizumab. In addition to counseling at the outpatient clinic and possibly at their pharmacy, patients will be instructed to read the full medication guide before taking certolizumab. All participants will be tested for latent TB and hepatitis B and C prior to enrollment in the study, and all participants will be advised to consult their rheumatologist if they develop any signs of infection, including TB and hepatitis reactivation. Certolizumab will be discontinued if a patient develops a serious infection or sepsis during treatment. Participants will be advised to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Participants will also be advised to report any signs of new or worsening medical conditions such as heart disease, neurological disease, autoimmune disorders, or symptoms suggestive of any cytopenia.

Certolizumab is supplied as a single-dose syringe. There is no need for participants to thaw, dilute, mix, reconstitute, or prepare the solution. Participants will be counseled in the outpatient clinic on the proper way to administer the injection. The first injection will be performed under the supervision of a qualified health care professional. A puncture-resistant container for disposal of needles and syringes will be provided. Participants will be cautioned against reuse of these items. Specific, detailed instructions will be provided to participants by both their

pharmacy and the nurse coordinators. The following are abridged instructions for administration of certolizumab.

- Check and make sure the name CIMZIA appears on the box and syringe label.
- Check the expiration date on the box label and the syringe label to make sure the date has not passed. Do not use a syringe if the date has passed.
- Allow certolizumab to warm up for 30 minutes prior to use. Do this by leaving the syringe sit out at room temperature for 30 minutes where children can't reach it. Never warm up certolizumab any other way.
- Have a special sharps (puncture proof) container nearby for disposing of the used syringe/pen.
- Choose a site on the front of your thighs or your stomach area (abdomen) for administration.
- Wipe the site where certolizumab (Cimzia) is to be injected with an alcohol prep (swab), using a circular motion. Do not touch this area again until you are ready to inject. Alcohol swabs are provided in the certolizumab injection kit.
- Check the solution through the windows on the side of the syringe to make sure the liquid is clear and colorless. Do not use a syringe if the liquid is cloudy or discolored or has large particles in it. Do not use if frozen or if it was ever previously frozen.
- Check to make sure that the amount of liquid in the syringe is the same or close to the fill line seen through the window. If the syringe does not have the full amount of liquid, do not use that syringe.
- Inject the certolizumab (Cimzia).

Participants should store certolizumab in a refrigerator at 36 to 46ºF (2 to 8ºC) in the original container until it is used. It should be protected from light. Do not freeze certolizumab or use previously frozen certolizumab. Refrigerated certolizumab remains stable to use until the expiration date printed on the prefilled syringe. If a participant will need to take certolizumab outside of the home, such as when traveling, it must be stored in a cool carrier with an ice pack and protected from light. If certolizumab freezes, it should not be used, even after it has thawed. Do not use a prefilled syringe if the liquid is cloudy, discolored, or has large particles in it. Do not drop or crush certolizumab. The prefilled syringe is glass. For additional information or questions, coordinators or participants can call 1-866-489-1899.

Summary for: Certolizumab (Cimzia)	
Route:	Subcutaneous injection by trained participant
Dosing:	400mg loading dose, then 200 or 400mg as warranted
Duration:	Full 6 months of MAZERATI study
Frequency:	Every month or twice monthly as warranted
Expiration Time:	Follow expiration date on the packaging

5.1.4.3 Study Agent Accountability Procedures

Certolizumab pegol will be supplied by a participant's chosen pharmacy when a prescription is presented for prefilled syringes or by a UPMC pharmacist at an outpatient rheumatology clinic when the rheumatologist or participant decide against self-injection of certolizumab pegol. If a participant is randomized to the anti-TNF arm of the study, then their treating rheumatologist can order any anti-TNF from the study agent list of anti-TNF therapies provided that the patient has not had previous experience with any anti-TNF agent. These therapies will be used in an

open-label manner, so frequency of product distribution and amount of product dispensed will be within open-label guidelines for each specific therapy.

For participants choosing to self-inject, we will provide a sharps container for their spent certolizumab pegol syringes. Participants will bring the sharps container to each study visit with a list of their unused certolizumab pegol syringes. Coordinators will log the number of spent syringes in the container to verify proper drug dosing. Used syringes, expired certolizumab pegol, and unused certolizumab pegol will be returned to the study coordinators, who will dispose of it according to the appropriate regulations. When the rheumatologist or participant elects against self-injection, then the certolizumab pegol will be reconstituted and prepared by a trained medical professional and administered according to standard operating procedure in that clinic. In these cases, the dosing will be recorded and monitored from the participant's electronic medical records.

5.1.5 Tocilizumab (Actemra)

5.1.5.1 Formulation, Packaging, and Labeling

As stated in the **General Statement on Study Agent Acquisition** at the beginning of **Section 5.1**, tocilizumab (Actemra) will be supplied by the study from Genentech. No special labels or formulation is required in the MAZERATI study.

Pre-filled syringe: Actemra (tocilizumab) is supplied as a sterile preservative-free liquid solution in a single-use prefilled syringe, providing 162 mg per 0.9mL. The NDC number is 50242-138-01. See **Figure 5**.

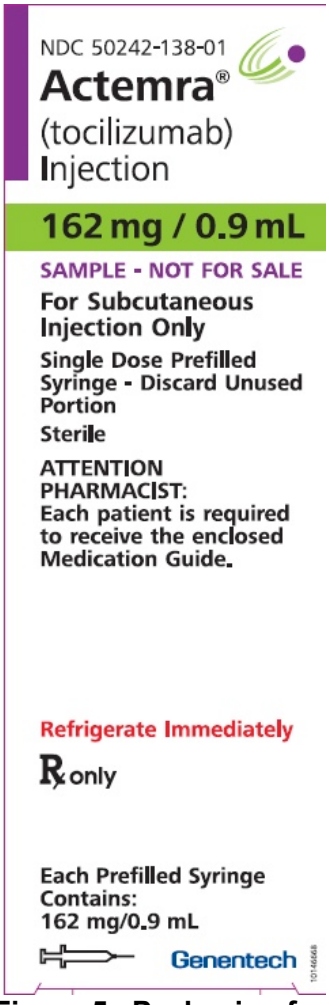

Figure 5. Packaging for tocilizumab.

Storage and Stability: Do not use beyond the expiration date on the container. Tocilizumab solution must be refrigerated at 2 to 8° C (36 to 46° F). Do not freeze tocilizumab. Store in the original package to protect from light and keep syringes dry. Patients will be instructed to perform a visual inspection of the medication before use. If visibly opaque particles, discoloration or other foreign particles are observed, the solution should not be used.

5.1.5.2 Preparation, Administration, Storage, and Dosage of Tocilizumab

As stated in the **General Statement on Study Agent Acquisition** at the beginning of **Section 5.1**, tocilizumab will be handled by the UPMC Investigational Drug Service. Tocilizumab is supplied as a sterile preservative-free liquid solution in a single-use prefilled syringe. The recommended dose of tocilizumab for adult patients with rheumatoid arthritis is 162 mg delivered subcutaneously every other week for patients < 100 kg, increased to weekly if CDAI > 2.8 and if not opposed by the treating physician. The dose change is determined by the treating physician based on clinical response. For adult patients ≥ 100 kg, the recommended dose is 162 mg delivered

subcutaneously every week, Participants will be encouraged to continue with tocilizumab for the full 6 months of randomization. Clinicians will monitor their patients and change study medications, if desired by either the clinician or the participant, as this is a real-world study.

The prescribing physicians are board-certified rheumatologists, with experience prescribing and monitoring patients taking tocilizumab. In addition to counseling at the outpatient clinic and possibly at a UPMC infusion center, patients will be instructed to read the full medication guide before receiving tocilizumab. Unless previously done, all participants will be tested for latent TB and hepatitis B and C prior to enrollment in the study, and all participants will be advised to consult their rheumatologist if they develop any signs of infection, including TB and hepatitis reactivation. Tocilizumab will be discontinued if a patient develops a serious infection or sepsis during treatment. Other reasons for discontinuing tocilizumab include: hypersensitivity/anaphalaxis, elevated AST, thrombocytopenia and low absolute neutrophil count. Participants will be advised to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Participants will also be advised to report any signs of new or worsening medical conditions such as heart disease, neurological disease, autoimmune disorders, or symptoms suggestive of any cytopenia.

Tocilizumab can be administered subcutaneously by trained clinical personnel or can be self-administered. Participants will be counseled in the outpatient clinic on the proper way to administer the injection. The first injection will be performed under the supervision of a qualified health care professional. A puncture-resistant container for disposal of needles and syringes will be provided. Participants will be cautioned against reuse of these items. Specific, detailed instructions will be provided to participants by the nurse coordinators. For additional information or questions, coordinators or participants can call 1-866-681-3261.

Summary for: Tocilizumab (Actemra)	
Route:	Subcutaneous injection by trained participant
Dosing:	162 mg every other week initially for participants < 100 kg, escalated up to every week if warranted; or 162 mg every week for participants ≥ 100 kg
Duration:	Full 6 months of MAZERATI study
Frequency:	Every other week or every week
Expiration Time:	Follow expiration date on the syringe

5.1.5.3 Study Agent Accountability Procedures

Tocilizumab will be used under the guidance and supervision of a physician and will be administered as subcutaneous injection. Tocilizumab will be used in an open-label manner, so frequency of product distribution and amount of product dispensed will be within open-label guidelines.

For participants choosing to self-inject, we will provide a sharps container for their spent syringes. Participants will bring the sharps container to each study visit with a list of their unused syringes. Coordinators will log the number of spent syringes in the container to verify proper drug dosing. Used syringes, expired tocilizumab, and unused tocilizumab will be returned to the study coordinators, who will dispose of it according to the appropriate regulations. This research study protocol allows the subject to receive up to 30 injections of TCZ. Even if the treatment is shown to be of benefit, additional injections of TCZ beyond that allowed in the protocol cannot be given to the subject while she/he is participating in the study.

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.

5.1.5.4 Dose Modification & Toxicity Management

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.

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 5.1.2) 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.

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

ANC (cells/mm^3)	Action
> 1000	Maintain dose.
500 – 1000	Hold tocilizumab dosing. When ANC increases to > 1000, 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	Hold tocilizumab dosing. When platelet count increases to > 100,000, 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)	Hold 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 8 weeks after the last SC 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 for RA, including TCZ.

Drug Interaction

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (eg, IL-6) during chronic inflammation. Therefore, it is expected that for molecules that antagonize cytokine activity, such as TCZ, the formation of CYP450 enzymes could be normalized. When starting or stopping therapy with TCZ, patients taking medications which are individually dose-adjusted and metabolized via CYP450, 3A4, 1A2, or 2C9 (e.g. atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, ciclosporin, or benzodiazepines) should be monitored as doses may need to be adjusted to maintain their therapeutic effect. Given its long elimination half-life (t1/2), the effect of TCZ on CYP450 enzyme activity may persist for several weeks after stopping therapy.

5.1.6 Abatacept (Orencia)

5.1.6.1 Formulation, Packaging, and Labeling

As stated in the **General Statement on Study Agent Acquisition** at the beginning of **Section 5.1**, abatacept (Orencia) will be supplied by the study. No special labels or formulation is required in the MAZERATI study.

Prefilled Syringe: Abatacept prefilled syringes are dispensed with four syringes per box. Each single dose prefilled glass syringe (29 gauge, ½ inch) contains 125 mg of abatacept (Orencia) per 1.0 mL of solution. The NDC number is 0003-2188-31. See **Figure 6**.

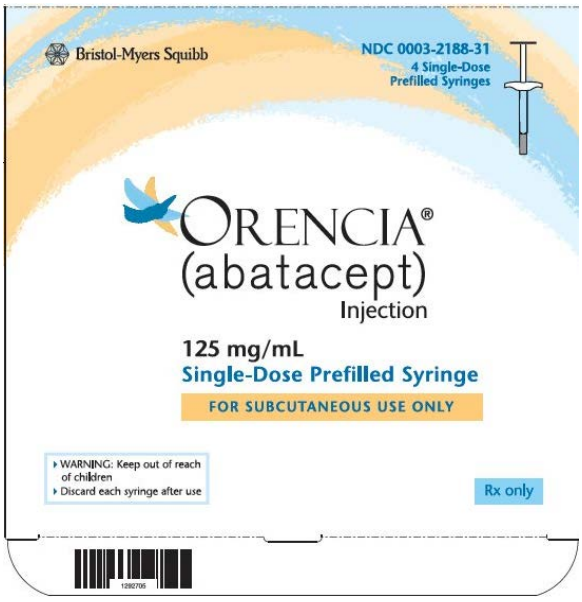

Figure 6. Packaging for SQ Abatacept.

SQ dose: 125 mg SQ q week.

Storage and Stability: Do not use beyond the expiration date on the container. Abatacept solution must be refrigerated at 2 to 8° C (36 to 46° F). Do not allow to freeze. Store in the original package to protect from light until time of use.

5.1.6.2 Preparation, Administration, Storage, and Dosage of Abatacept (as per package insert)

As stated in the **General Statement on Study Agent Acquisition** at the beginning of **Section 5.1**, abatacept will be supplied by the study when abatacept is chosen. The process for SQ abatacept is described in this section. The recommended dose of SQ abatacept for adult patients with RA is 125 mg every week delivered subcutaneously. Participants will be encouraged to continue with abatacept for the full 6 months of randomization. Clinicians will

monitor their patients and change study medications, if desired by either the clinician or the participant, as this is a real-world study.

The prescribing physicians are board-certified rheumatologists, with experience prescribing and monitoring patients taking abatacept. In addition to counseling at the outpatient clinic, patients will be instructed to read the full medication guide before receiving abatacept. All participants will be tested for latent TB and hepatitis B and C prior to enrollment in the study, and all participants will be advised to consult their rheumatologist if they develop any signs of infection, including TB and hepatitis reactivation. Abatacept will be discontinued if a patient develops a serious infection or sepsis during treatment. Participants will be advised to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Participants will also be advised to report any signs of new or worsening medical conditions such as heart disease, neurological disease, autoimmune disorders, or symptoms suggestive of any cytopenia.

Patients will receive appropriate counseling in the outpatient clinic on administration of the drug and safety, as detailed for the other self-administered SQ biologics in previous sections. For additional information or questions, coordinators or participants can call 1-877-920-8039.

Summary for: SQ Abatacept (Orencia)	
Route:	Subcutaneous administration by trained participant
Dosing:	125 mg SQ q week
Duration:	Full 6 months of MAZERATI study
Frequency:	Every week
Expiration Time:	Follow expiration date on the packaging

5.1.6.3 Study Agent Accountability Procedures

SQ abatacept will be supplied by the study; it has been donated by Bristol Myers Squibb. Abatacept will be used in an open-label manner, so frequency of product distribution and amount of product dispensed will be within open-label guidelines for each specific therapy.

We will provide a sharps container for spent abatacept syringes. Participants will bring the sharps container to each study visit with a list of their unused abatacept syringes. Coordinators will log the number of spent syringes in the container to verify proper drug dosing. Used syringes, expired abatacept, and unused abatacept will be returned to the study coordinators, who will dispose of it according to the appropriate regulations.

5.2 Assessment of Participant Compliance with Study Agents

As detailed throughout Section 5.1 and its sub-sections, participant compliance will be assessed for each study agent. For agents administered subcutaneously, participants will be provided with a sharps container and instructed to place all used or expired syringes in the sharps container. During each study visit, the study coordinator will examine the sharps container and record the number of used and expired syringes in the study log. Participants will also be queried regarding their self-administration of the study agents. The recorded count and the participant responses will serve as the means to assess participant compliance of subcutaneously delivered agents.

5.3 Concomitant Medications and Procedures

5.3.1 Permitted concurrent medications:

Methotrexate

In the United States, methotrexate has become the drug of choice for patients with early, moderate-to-severe RA [33-37]. Methotrexate is typically used in doses between 15 and 25 mg/week. Methotrexate is a DMARD and is a folate antagonist that inhibits cell proliferation and has anti-inflammatory properties possibly mediated by effects on adenosine signaling. The toxicities of methotrexate are well known and guidelines for monitoring have been published [33, 34]. The methotrexate *vs*. etanercept trial [38] and BeST studies [39] established that higher doses of methotrexate (20 mg/week) can be safely administered. In standard clinical practice, methotrexate is routinely co-administered with the study's biologic drugs.

Leflunomide

The FDA approved leflunomide (Arava) in 1998 as a DMARD for treatment of RA and psoriatic arthritis. Leflunomide is administered orally and works by blocking pyrimidine biosynthesis (inhibits dihydroorotate dehydrogenase). By blocking *de novo* pyrimidine biosynthesis, leflunomide inhibits cell proliferation and has anti-inflammatory properties, likely as a result of decreased cell numbers (Product Information: Arava. Hoechst Marion Roussel, US, 98). It is generally administered at 20 mg/day without a loading dose. Leflunomide has been used successfully in combination with NSAIDs (*e.g.*, aspirin) and/or low-dose corticosteroids, and is sometimes used in conjunction with MTX due to synergistic effects of the combination, although side-effects sometimes limit the utility of this combination [40]. The toxicities of leflunomide are well known and guidelines for monitoring have been published [33, 34]. In standard clinical practice, leflunomide is routinely co-administered with the study's biologic drugs.

Hydroxychloroquine

Hydroxychloroquine is approved by the FDA for treating RA, SLE, and malaria. Overall, hydroxychloroquine has a very favorable safety profile with retinal toxicity being the most serious, but uncommon side-effect [41, 42]. The American Academy of Ophthalmology [42] acknowledges there is minimal risk of toxicity for individuals using less than 6.5 mg/kg/day (300 or 400 mg/day) of hydroxychloroquine for less than 7 years. Annual ophthalmologic screening, especially after the first 7 years of usage is recommended [33, 34]. In standard clinical practice, hydroxychloroquine is routinely co-administered with the study's biologic drugs.

Sulfasalazine

Sulfasalazine has been used as monotherapy and in combination with other DMARDs. Myelosuppression is the primary toxicity reported requiring routine monitoring with a CBC [33, 34]. The standard dose of sulfasalazine used in clinical practice and in published clinical trials is 2 gm/day in divided doses [43-45]. In clinical practice, the starting dose is 500 mg twice daily and increased to 1000 mg twice daily after 6 weeks if no intolerance or toxicity is noted. The maximum dose for the treatment of RA is typically 3,000 mg/day in divided doses. In standard clinical practice, sulfasalazine is routinely co-administered with the study's biologic drugs.

Oral Corticosteroids

We will allow use of a low-dose (≤ 10 mg/day) of oral corticosteroids (prednisone or prednisolone) at study entry in MAZERATI. The clinical benefits and adverse effects of low-dose steroids in RA patients have been well documented [46-50]. If receiving oral steroids, a stable dose (≥ 2 weeks) of prednisone will be required at study entry.

5.3.2 Medication changes and monitoring for toxicity for DMARDs and steroids

The primary rheumatologist will provide ongoing treatment for each patient enrolled in this study. They will monitor for toxicities.

If a patient has active disease that requires an increase in DMARD, or change of DMARD, they will no longer be considered part of the analysis for mechanistic studies. We will continue to monitor the patient for the 6-month period of the study for toxicity of medications.

Regarding corticosteroid, doses of prednisone (≤10 mg/day) are allowed at entry. Doctors may decrease the dose if disease activity has improved or adverse events required a lower dose of steroids. We will allow two increases in steroids over the 6-month study. These could include a one week oral prednisone boost, or a Medrol dose pack. We will record all changes in steroid dose from baseline. If more than two transient increases in steroids are needed, then the patient will not be considered evaluable for the mechanistic studies.

5.4 Precautionary and Prohibited Medications and Procedures

5.4.1 Prohibited Medications and Procedures

MAZERATI is a phase IV clinical trial. All medications will be dispensed by practicing rheumatologists familiar with these therapies and their side effects and contraindications. All therapies will be used in an open-label manner according to FDA-approved guidelines. The participants and the rheumatologists will not be blinded to the therapies, which will allow proper clinical management of these participants, including standard-of-care toxicity monitoring.

Participants will be randomized to a treatment arm, and will be considered an active participant if they take at least one dose of the randomized drug. Additionally, to be considered study participants, MAZERATI subjects must maintain their baseline prednisone and oral DMARD medications until they have received their first dose of randomized medication. During the first 3 months of therapy, patients and their physicians will be permitted to taper but not increase corticosteroids. Adjustments of study medication or DMARDs will not be permitted except as described above during the first 3 months of the study.

Specifically, MAZERATI participants will not be permitted to take more than one biologic at a time. Participants will be asked to avoid unnecessary or routine vaccinations while they are participating in the study as vaccination may affect the mechanistic studies. Participants randomized to etanercept will be cautioned to avoid taking cyclophosphamide due to a higher incidence of non-cutaneous solid malignancies in patients receiving both therapies. Participants randomized to tocilizumab, who are already taking a cytochrome P-450 (CYP450) substrate for another condition, will be

monitored for the therapeutic effect of their CYP450 therapy, with dose adjustment as needed.

5.4.2 Precautionary Medications and Procedures

MAZERATI is a phase IV clinical trial. All medications will be dispensed by practicing rheumatologists familiar with these therapies and their side effects and contraindications. All therapies will be used in an open-label manner according to FDA-approved guidelines. The participants and the rheumatologists will not be blinded to the therapies, which will allow proper clinical management of these participants, including standard-of-care toxicity monitoring.

Precautionary medications presented in the product brochures for the MAZERATI therapies are similar to the prohibited medications and procedures presented in **Section 5.4.1**. Participants will not be prescribed more than one biologic at one time and will be cautioned against taking other biologics for other diseases. Hepatosplenic T-cell lymphoma has been reported in adolescents and young adults receiving TNF blockers for Crohn's disease or ulcerative colitis, with concomitant use of azathioprine or mercaptopurine. As a result, clinicians must carefully assess the risk *vs*. benefit of using TNF blockers, azathioprine, and/or mercaptopurine in adolescents and young adults, especially for the treatment of Crohn's disease or ulcerative colitis. Participants will be cautioned against receiving vaccines while also receiving these immune-modulatory therapies and will be asked to receive any necessary vaccines at least 2 months prior to enrollment in the MAZERATI study. Switching between DMARDs will not be permitted during the 6 months of this study. Participants will be monitored for signs of chronic and serious infections, such as hepatitis, TB, *etc*.

5.5 Prophylactic Medications and Procedures

All participants receiving MTX will also be prescribed folic acid supplements due to MTX's known depletion of folic acid levels. There will be no other prophylactic medications or procedures in the MAZERATI study.

5.6 Rescue Medications

Participants enrolling in MAZERATI must be on stable doses of oral steroids (*e.g*., prednisone) for 2 or more weeks at entry, but steroids can be tapered after initiation of the study drug at the discretion of the treating physician. During the first 3 months of the study, prednisone can't be increased and intra-articular and/or intra-muscular injections of corticosteroids will not be permitted. After the 3-month study visit, addition of steroids or other oral DMARDS is permitted at the discretion of the treating physician.

6. STUDY PROCEDURES/EVALUATIONS

6.1 Clinical Evaluations

<u>Assessments of Efficacy</u>

All information needed to compute the CDAI and the DAS28-CRP will be obtained at baseline and at the 1-month, 3-month, and 6-month study visits. A physician global assessment of RA disease activity and patient measurements as outlined below will also be obtained at each study visit. Information from these assessments will be used to determine the number of subjects:

Achieving a CDAI remission < 2.8;
Achieving a DAS remission with a DAS28-CRP < 2.6;
Achieving a ACR20, 50, and 70 response

Joint Assessments

Prior to initiating therapy (baseline), participants will undergo a standardized 28-joint examination by a trained, blinded assessor as described (93). The blinded assessor will also perform treatment-blinded assessments following treatment initiation at 1-, 3-, and 6- month visits. Clinicians can establish any schedule as necessary for office visits, provided that 1-, 3-, and 6-month treatment-blinded joint examinations are included among the scheduled visits.

Patient assessment of disease activity

Participants will complete self-assessments that include a RAPID-3, SF-12, WPAI, and visual analog scale measurements of RA global disease activity and pain.

6.2 Laboratory Evaluations

6.2.1 Clinical and Research Laboratory Evaluations and Specimen Collection

C-reactive Protein Measurements

C-reactive protein (CRP) levels will be measured in a clinical laboratory at the University of Pittsburgh Medical Center using nephelometry. CRP levels will be used to calculate the DAS28-CRP.

Mechanistic assessments

Participants will provide a blood sample totaling 60 ml (6 x 10-ml heparin tubes for PBMC isolation) for the mechanistic studies.

Tocilizumab-specific assessment (Arm 2 participants only)

Anti-TCZ antibodies, TCZ levels and sIL6-R are to be drawn and stored at baseline for all patients receiving tocilizumab, but analyzed only for patients who experience anaphylaxis, serious hypersensitivity, or discontinuation of study treatment (tocilizumab) due to hypersensitivity (serious or non-serious). For patients who meet any of these criteria, additional immunogenicity samples will be collected at the time of the event, and then again at least 6 weeks after the last SC dose of tocilizumab.

Immunogenicity assays: samples will undergo screening to test for anti-TCZ antibody and if positive, a confirmatory test will be run. If confirmed, an IgE test will be run.

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

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

Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the National Institutes of Health.

All infectious specimens will be transported using packaging mandated in the Code of Federal Regulations, 42 CFR Part 72. Where applicable, especially for future studies, refer to individual carrier guidelines, *e.g.*, Federal Express, for specific instructions.

6.2.2 Specimen Preparation, Handling and Shipping

All potentially infectious specimens will be transported using packaging mandated in the Code of Federal Regulations, 42 CFR Part 72. Where applicable, especially for future studies, refer to individual carrier guidelines, *e.g.*, Federal Express, for specific instructions. Since this is a single-site study in the UPMC Rheumatology Network, we will use the usual, approved local courier of biospecimens.

Instructions for Specimen Storage

After centrifugation, serum will be carefully removed from the serum separator tubes and aliquoted into appropriately-sized aliquots. These serum aliquots will be labeled in a de-identified way and stored long-term in ultralow temperature freezers (-80°C). PBMCs will be purified over Ficoll gradients and resuspended in specialized freezing media with dimethyl sulfoxide (DMSO). Subsequently, PBMC aliquots will be prepared and frozen in a controlled manner to liquid nitrogen temperatures.

Specimen Shipment Preparation, Handling and Storage

As detailed in the section on biohazard containment, biospecimens will be handled according to the current recommendations of the Centers for Disease Control and Prevention and the National Institutes of Health. All biospecimens will be transported using packaging mandated in the Code of Federal Regulations, 42 CFR Part 72. Where applicable, especially for future studies, refer to individual carrier guidelines, *e.g.*, Federal Express, for specific instructions. Biospecimens will be stored in a de-identified manner, in locked ultralow freezers and liquid nitrogen storage units. All temperature-controlled devices have alarms and auto-dialers in the event of power or equipment failure.

For tocilizumab-specific samples (Anti-TCZ antibodies, TCZ levels and sIL6-R), sample logistics and handling will be managed by Covance Laboratories.

6.3 Substudies

It is not anticipated that substudies will be a part of the MAZERATI protocol, but if a substudy is necessary, then we follow the approved guidelines. Future ancillary studies using banked biospecimens will be approved by Drs. Moreland and McGeachy, following the NIH guidelines for the sharing of research resources.

7. STUDY SCHEDULE (SEE APPENDIX A)

7.1 Screening

7.1.1 Evaluations and Procedures

Screening and enrollment in the MAZERATI study can occur as long as one month prior to the baseline visit or the same day as baseline. It is expected that time will be required, after the screening visit, but prior to the baseline visit, to secure authorization for subjects randomized to TNF inhibitor therapy.

At the MAZERATI screening visit, the following MAZERATI-specific screening, enrollment, and randomization procedures will be performed:

1. Obtain written, informed consent
2. Urine pregnancy test (if applicable, *i.e.*, pre-menopausal women without a history of hysterectomy, bilateral oophorectomy, and/or tubal ligation)
3. Radiograph of chest[^] and PPD skin test or Quantiferon TB-Gold test[£]
4. Hepatitis B surface antigen[¥] & hepatitis C antibodies[¥]
5. Medical history
6. Collect patient demographics and RA medication history
7. Assess likelihood of insurance approval for a TNF antagonist
8. Assess for RF and CCP autoantibody status
9. Randomize the patients to one of the three treatment arms based on the randomization scheme described in **Section 3.1**.

[^]Chest x-rays taken 1 year prior to screening with no evidence of malignancy or active infection are accepted.
[¥]The window for Hep B and Hep C screening is 1 year prior to screening. Documentation of results must be included in the patient's study chart.
[£]PPD skin test or Quantiferon TB-Gold results taken up to 1 year prior to screening are accepted if no risk of exposure has occurred, *e.g.*, travel outside of US or contact with TB+ individuals.

7.1.2 Instructions for Completing the Screening Visit

Written informed consent MUST be obtained prior to any study-specific procedures being performed. A copy of the Informed Consent should be given to the participant, and the original is placed in the medical record (as per institutional guidelines). Participants should be allowed

to read the full consent document and to have their questions answered prior to their signing the informed consent.

Potential participants will be randomized to one of the three treatment arms as described in Section 3.1. Between the screening and the baseline visit, the participants' health insurance must be contacted for approval for TNF inhibitor therapy.

Medical History

Each participant must provide information related to RA disease duration and past and current use of medications related to arthritis treatment. Other demographic information related to education level, income, smoking history and comorbidities will also be asked.

Treating Physician: Clinical Laboratory Tests

All participant clinical laboratory test results, obtained at the discretion of the treating physician primarily for the assessment of drug toxicity must be reviewed, evaluated, and signed off by a licensed M.D., D.O., Physician's Assistant or nurse practitioner. Screening visit labs MUST be reviewed prior to the Participant's enrollment in the study and baseline visit. Recommended evaluations include:

- Hematology: complete blood count (CBC) with differential and platelet count
- Serum chemistries: total bilirubin, SGOT (AST), and SGPT (ALT)
- Lipid panel

Patient Assessments

The Patient Demographics and RA Medication History forms will be completed at the screening visit.

7.2 Enrollment/Baseline

After the screening visit, the study coordinator and the treating clinician will review the potential participant's screening data. All entry criteria must be met for the patient to continue in the MAZERATI study. If the patient continues to meet the entry criteria, then the patient will be randomized to one of the three treatment arms based on the randomization scheme description in Section 3.1. The clinic nurse will secure approval for the participants randomized to treatment Arm 1 from the patient's insurance company. Once standard-of-care clinical labs have been evaluated and insurance approval received, then the patient can return for the baseline visit. At the baseline visit, baseline labs and forms must be completed. During the baseline visit, clinical personnel will instruct participants on the proper administration of the randomized therapy and participants will receive their first dose of study medication. All standard-of-care procedures relevant to each therapy must be used. MAZERATI is a phase IV clinical trial, with therapies used in an open-label manner, and the treating physician, study coordinator, and participants are not blinded to the randomized therapy; MAZERATI participants

will be provided all relevant standard-of-care. The screening visit and the baseline visit can occur on the same day, but can occur no more than 30 days apart.

All assessments listed in Section 7.3 (Follow-Up) will be performed at the baseline visit prior to administration of the randomized therapy. This includes Patient Questionnaires, Blinded Assessor Assessments, Laboratory Tests, and Adverse Events assessment.

7.3 Follow-up

Follow-up visits will occur 1 month (3-5 weeks), 3 months (10-14 weeks), and 6 months (22-30 weeks) after the baseline visit (study drug initiation). At each follow-up visit the following assessments may be performed:

Patient Questionnaires

Patient questionnaires, consisting of the following assessments:
Modified Health Assessment Questionnaire (mdHAQ as part of RAPID3)
Patient's Assessment of Arthritis Pain (VAS)
Patient's Global Assessment of Disease Activity (VAS)
SF-12 (quality of life survey)
WPAI (work-productivity survey)
PROMIS 29

Blinded Assessor Arthritis Assessments

Arthritis assessments, consisting of blinded assessments, must be performed at all study visits by a blinded assessor that is different from the patient's physician. The blinded assessor's examination will be used to calculate a DAS28-CRP and the CDAI and will consist of the following:

28 joint count assessment of joint tenderness
28-joint count assessment of joint swelling
Assessor's Global Assessment of Disease Activity (VAS)

Treating Physician: Clinical Laboratory Tests

All participant clinical laboratory test results, obtained at the discretion of the treating physician primarily for the assessment of drug toxicity must be reviewed, evaluated, and signed off by a licensed M.D., D.O., Physician's Assistant or nurse practitioner. RACER screening visit labs MUST be reviewed prior to the Participant's enrollment in the study and baseline visit.

Laboratory Tests

A blood sample will be obtained from all subjects for determination of a high sensitivity C-reactive protein (hsCRP). The hsCRP will be used to determine the DAS28-CRP for subjects at each study visit.

Mechanistic Study Blood samples

Blood samples will be obtained at the baseline visit and at each follow-up visit for the mechanistic studies described in Section 6.2.1.

Adverse Events Data Collection Form

Information related to any adverse events will be collected on a data collection form at each follow-up visit. The treating rheumatologists will determine the level of seriousness of all adverse events and if they impart any change in therapy.

7.4 Final Study Visit

The final study visit will occur at the 6-month follow-up. The assessments described in the previous section (Section 7.3) will be performed at the final study visit.

7.5 Early Termination Visit

For subjects that discontinue therapy at any point in the study, these subjects will be asked to continue assessments as outlined in the study protocol. For subjects that discontinue therapy and refuse or cannot complete study protocol assessments, these subjects will be evaluated by their treating physician and by the blinded assessor at an early termination visit. This visit will be scheduled as soon as possible after study drug discontinuation or where possible, participants will be asked to continue study drug until after the early termination visit. At the early termination visit, the information collected in Section 7.3 for each follow-up visit will be collected. If the early termination visit occurs within the time window for a follow-up visit, then this visit will also be used in the analysis as a follow-up visit as long as the patient is evaluated within one dosing interval of their assigned therapy. For example, data collected from a study participant in the 23rd week of the study treated with etanercept who discontinues therapy and is evaluated within one week of their last injection will be included in the analysis of 6 month follow-up data.

7.6 Pregnancy Visit

The MAZERATI study uses drugs (*e.g.*, MTX and LEF) are contraindicated in pregnant patients, so no pregnant patients will be involved in the study. Pregnant or lactating females will be excluded from the MAZERATI trial, and urine pregnancy tests will be performed during the screening visit when appropriate. Female patients will be counseled regarding the pregnancy risks of all medications and advised to use appropriate contraception with their partners during the use of these therapies. In the event that a female participant does become pregnant, they will be referred to high-risk obstetrics for follow-up and terminated from the MAZERATI study.

7.7 Unscheduled Visits

Unscheduled visits related to the treatment of rheumatoid arthritis will be monitored by the study coordinators. Any unscheduled study visits that relate to the safety of the study drugs or to

changes in patient disease activity that may alter the outcome of the MAZERATI study will be monitored for collection of adverse events and for their potential effects on study participation.

8. ASSESSMENT OF SAFETY

MAZERATI is a phase IV clinical trial, and safety parameters are not a primary objective for this study.

8.1 Specification of Safety Parameters

The study drugs, etanercept, adalimumab, infliximab, certolizumab, golimumab, tocilizumab, and abatacept are approved by the FDA for treating RA and will only be used in approved ways and for approved indications. The known adverse events of each of the study drugs are well-defined and included in the package inserts for each medication. No primary safety endpoints will be used to address the goals of the current study. Anticipated adverse events will not be reported to the IRB as part of the MAZERATI study. However, ***unanticipated*** adverse events (AEs and SAEs as defined in Sections 8.2 and 8.3) and other unanticipated problems will be recorded at each study visit in accordance with the University of Pittsburgh IRB policies and procedures and sponsor requirements for the duration of each subject's participation in the study. The University of Pittsburgh IRB policies and procedures related to management of reportable events can be found at: http://www.irb.pitt.edu/pandp/default.aspx

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

8.2 Definition of an Adverse Event (AE)

Adverse Event (or Adverse Experience)

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 rheumatoid arthritis 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.

8.3 Definition of a Serious Adverse Event (SAE)

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). Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, the development of drug dependency or drug abuse, or drug induced liver injury (DILI).

8.4 Methods and Timing for Assessing, Recording, and Analyzing, Managing Safety Parameters

8.4.1 Methods and Timing for Assessment

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), Genentech, Inc. (per Genentech Inc., requirements), and Bristol Myers Squibb as outlined in section 8.6.2, in accordance with CFR 312.32 (IND Safety Reports).

8.4.1.1 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.

8.4.2 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 study drug (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 study drug, 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 study drug; and/or the AE abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.

No
Evidence exists that the AE has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to study drug 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 Inserts or current Investigator Brochures.

Unexpected adverse events are those not listed in the Package Inserts (P.I.) or current Investigator Brochures (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.

8.5 Procedures for Eliciting, Recording, and Reporting Adverse Events

8.5.1 Eliciting Adverse Events
A consistent methodology for eliciting AEs at all subject evaluation time-points should be adopted. To prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more of these events, but rather non-directive questions should be used to elicit information. 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?"

8.5.2 Specific Instructions for Recording Adverse Events

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

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.

Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 8.4.1.1), 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”.

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”).

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.

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.

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 study drug 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.

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.

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 8.7).

8.6 Reporting of Serious Adverse Events

8.6.1 Reporting of Serious Adverse Events Associated with Tocilizumab (Arm 2 only)

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, along with the fax cover sheet (Appendix B) immediately upon completion to Genentech Drug Safety 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 a quarterly report 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

8.6.2 Reporting of Serious Adverse Events Associated with Abatacept (Arm 3 only)

All SAEs whether related or unrelated to abatacept, and all pregnancies must to be reported to Bristol Myers Squibb (by the investigator or designee) within 24hours of being made aware of the event. SAEs related to abatacept must be reported to Bristol Myers Squibb (BMS) within 1 business day of becoming aware of the event. AEs related to abatacept must be reported within 7 business days of becoming aware of the event.

All SAEs should be reported via confirmed facsimile (fax) transmission, or scanned and reported via electronic mail to:

SAE Email Address: Worldwide.Safety@BMS.com

SAE Fax Number: 609-818-3804

8.7 AEs of Special Interest (AESIs)

8.7.1 AESIs for Tocilizumab (Arm 2) Only

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 8.6 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.

8.7.2 AESIs for Abatacept (Arm 3) Only

Adverse events of special interest are considered **serious** must to be reported by the Investigator to Bristol Myers Squibb within 24 hours after learning of the event**. SAEs** of special interest for this study include the following:

Cancer

Overdose

Pregnancy

Drug-induced liver injury, defined as:

a) AT (ALT or AST) elevation > 3 times ULN, and

b) Total bilirubin > 2 time ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase), and

c) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

8.8 Modification of Study Agent(s)/Intervention(s) for a Participant

8.8.1 Dose/Schedule Modifications for a Participant

MAZERATI is a phase IV clinical trial. All medications will be dispensed by practicing rheumatologists familiar with these therapies and their dosage scheduling. All therapies will be used in an open-label manner according to FDA-approved guidelines. The participants and the rheumatologists will not be blinded to the therapies, which will allow proper clinical management of these participants, including standard-of-care toxicity monitoring. Treating rheumatologists will be permitted to prescribe each treatment within that treatment's specific FDA-approved dosing and scheduling, and non-approved dose and schedule modifications will not be permitted for any participants.

8.9 Halting Rules for the Protocol

MAZERATI is a phase IV clinical trial. All medications will be dispensed by practicing rheumatologists familiar with these therapies and their dosage scheduling. All therapies will be used in an open-label manner according to FDA-approved guidelines. The participants and the rheumatologists will not be blinded to the therapies, which will allow proper clinical management of these participants, including standard-of-care toxicity monitoring. Treating rheumatologists will be permitted to prescribe each treatment within that treatment's specific FDA-approved dosing and scheduling, and non-approved dose and schedule modifications will not be permitted for any participants. There are no plans to halt MAZERATI after enrollment begins.

8.10 Stopping Rules for an Individual Participant/Cohort

Discontinuation of Study Therapy

Protocol-specified requirements for the treatment of participants, including regimens for investigational or concomitant medications, as well as, restrictions for disallowed medications, will be discontinued for any individual participant under the following conditions:

- At the request of the participant;
- The participant's health, safety, and/or well-being is threatened;
- For any participant who experiences any of the following:
    - Suspicion of a serious bacterial or opportunistic infection requiring hospitalization or parenteral treatment;
    - Development of any of the exclusion criteria; or
    - Toxicities to the assigned study drug as per **Section 1.3**.
- Per the study sponsor Genentech, tocilizumab-specific criteria for discontinuation includes the following:
    - 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/mm3) < 50,000
    - ANC (cells/mm3) < 500

Finally, protocol-specified treatment requirements will be discontinued as a natural consequence in participants who are withdrawn from the study.

Procedures for Discontinuation of Study Therapy

Participants who discontinue study treatment prematurely due to their concerns or the concerns of their treating rheumatologist will be given appropriate care under medical supervision. Participants who discontinue study treatment for any reason will be encouraged to complete all remaining scheduled follow-up visits. If the participant elects not to complete these visits, participants will be asked to complete an end-of-study evaluation, which includes the treatment-blinded, standardized joint assessment planned for the end-of-treatment study visit (6 month).

8.11 Premature Withdrawal of a Participant

When a participant is withdrawn from the study, protocol-specified treatment requirements are discontinued, and study-related visits, exams, procedures, assessments, tests, and data

collection are terminated. Individual participants will be withdrawn from the protocol under any of the following conditions:

- The subject withdraws consent;
- The investigator or participant's clinician believes it is in the best interest of the participant; or
- The study is terminated.

9. CLINICAL MONITORING STRUCTURE

9.1 Site Monitoring Plan

The MAZERATI study will occur at a single site: the UPMC Rheumatology Network in Pittsburgh, PA. The University of Pittsburgh has and maintains all required federal assurances for human participant research. We will submit to the standard institutional and governmental audits as required. In Section 9.2, we describe our safety monitoring plan. Site monitoring will be a part of the regular and usual safety monitoring plan. Dr. Moreland will have the final responsibility for monitoring the treating physicians and study personnel and will have discretion to recommend actions regarding study conduct and continuation as a consequence of any planned or unplanned monitoring activity. Participants in MAZERATI are treated by their primary rheumatologist, and both of those parties are unblinded to the therapy.

9.2 Safety Monitoring Plan

The biologic medications that will be used in this study are currently FDA-approved for the treatment of RA patients that are refractory to therapy with MTX. As such the biologic medications used in this study are consistent with the normal standard-of-care for patients at this stage of RA. Therefore, rather than convening a Data and Safety Monitoring Board, we will implement a Data and Safety Monitoring Plan (DSMP). The DSMP will review accumulating data at least every 6 months during planned DSMP Data Review Meetings that will include Drs. Moreland and McGeachy, and the coordinators working on the project. Data for the planned safety reviews will include, at a minimum, a listing of all unanticipated problems during the trial and assessment of the relatedness of each to MAZERATI. DSMP members will also review study progress, adverse events and outcome data, external factors, relevant information, procedures in place to protect participant privacy and confidentiality, and the conduct of the various study members for compliance with the protocol.

In addition to the pre-scheduled data reviews and planned safety monitoring, it may be necessary to have *ad hoc* reviews or emergency meetings related to Data and Safety Monitoring.

Dr. Moreland will have discretion to recommend actions regarding study conduct and continuation as a consequence of any planned or unplanned monitoring activity.

<u>Routine EDC Review</u>

The EDC will generate reports that compile all newly submitted and accumulated unanticipated problems. A subsequent review of periodic reports will be performed by the PI.

10. STATISTICAL CONSIDERATIONS

10.1 Overview and Study Objectives

The MAZERATI study is designed to test hypotheses related to the effects of TNF antagonists, tocilizumab and abatacept on B cell and T cell function in RA patients. We believe that these studies will 1.) determine the pathogenic pathways regulating B and T cell function in RA patients, 2) provide a means to understand clinical responsiveness to different RA medications and 3.) provide a mechanistic basis to understand the relative merits of combination therapy directed at different pathogenic pathways. Therefore, the MAZERATI study is primarily powered to answer questions related to the mechanistic specific aims of this protocol.

10.2 Study Population

Analysis Populations

Three analysis populations, the Safety (SAF) population, Intent-to-Treat (ITT) Population, and the Per Protocol (PP) Population, will be defined for this study. Each subject's status with respect to each analysis population will be established at a blinded data review meeting prior to initiating the statistical analyses and reasons for excluding subjects from analysis populations will be documented.

Safety Population
The SAF population includes all subjects who receive at least one dose of study treatment. The Safety population will be used for all safety analyses when related to unanticipated adverse events and problems.

Intent-to-Treat Population
The ITT population will include all randomized subjects. Subjects, who for whatever reason do not complete their assigned therapy, will be included in the ITT population in the groups to which they were randomized. One set of secondary outcome measures will be based on analyses of the ITT population and the PP population described below.

Per Protocol Population
For the purposes of the mechanistic studies and the primary outcome analyses, the PP population will be defined as those subjects who complete all visits and receive the study drug as scheduled up to Month 3. For the purposes of the efficacy analyses and secondary outcome analyses, the PP will be defined as those subjects who receive at least one dose of study drug, whether they complete all visits or not.

10.3 Description of the Analyses

Primary Analysis Statistical Considerations

For statistical analyses, we will compare the baseline characteristics across the three treatment groups. For continuous characteristics (disease duration, disease activity/DAS28, CRP, erythrocyte sedimentation rate) an analysis of variance, either parametric or nonparametric, as

appropriate, will be used. For discrete characteristics (sex, race, smoking) a chi-square test will be used. We will determine if the frequencies or changes in the frequencies of T and B cell populations, within treatments and among treatments, correlate with disease activity or changes in disease activity as measured by the CDAI and DAS28-CRP using Spearman's rank correlation coefficients. The analysis of correlations between changes in frequencies of T and B cell populations with changes in disease activity will represent the primary outcome analysis. For the secondary mechanistic statistical analyses, we will determine whether there are longitudinal changes in T and B cell populations, within treatments and between treatments, using a linear mixed effect model with random intercept to assess the effects of treatment over time. Baseline levels of T and B cell populations will be included as a covariate in the mixed effect model, along with the main effect treatment, as fixed effects. Time and disease activity (as measured by the CDAI and DAS28-CRP) will also be included as fixed effects. The differential effect of treatment by time will be investigated by including a treatment by time interaction in the mixed effect model. All assumptions of the model, such as normality of residuals, will be assessed. If assumptions are violated, transformations will be utilized, such as ranking the post baseline values of the T and B cell population frequencies and analyzing the ranked scores in the mixed effects model. Additional main effects will be included for baseline characteristics, which were not balanced by random assignment. If significant treatment effects are identified, pairwise post-hoc comparisons will be conducted maintaining the overall type I error of 0.05. All analyses will be conducted using the Per Protocol (PP) population of subjects.

Together, these data will provide a comprehensive analysis of the common and unique cellular, molecular and genetic changes that are mediated by TNF inhibitors, tocilizumab and abatacept in RA. These data will pave the way for more effective patient therapy, including rationalizing the use of biologics other than TNF inhibitors as first-line therapies after methotrexate failure.

Efficacy Analysis

Primary Efficacy Analysis

Given the limited sample size of the study, there will be no primary efficacy analysis. The study is powered to meet primary endpoints based on the mechanistic studies.

Secondary Efficacy Analyses

For the secondary efficacy analyses we will compare the following measures of disease activity and other measurements of efficacy between subjects receiving a TNF antagonist, tocilizumab or abatacept.

Continuous variables
1.) Efficacy as measured by change in CDAI from baseline
2.) Efficacy as measured by change in DAS28-CRP from baseline
3.) Efficacy as measured by ACR20, 50 and 70 response

Discrete variables
1.) Efficacy as measured by CDAI remission < 2.8
2.) Efficacy as measured by DAS remission with a DAS28-CRP < 2.6

3.) Adherence to drug regimen for 6 months
4.) Reason for discontinuation of treatment (side effects, lack of efficacy, or other (cost, patient compliance, etc.))

The main secondary efficacy analysis of change in CDAI score from Baseline to Month 6 will be performed on the PP and ITT populations. A longitudinal data analysis based on a mixed model repeated measures method will be used to test for a treatment effect between treatment groups (TNF antagonist vs. abatacept vs. tocilizumab) with the change in CDAI score from Baseline at each follow-up time-point (1, 3 and 6 months) as the dependent variable. Terms in the model will include treatment group, month, treatment group by month, original TNF inhibitor failure group (etanercept, adalimumab, infliximab, certolizumab or golimumab), any DMARDs used at the start of the study, and clinic. Additional covariates will include those characteristics not balanced through random assignment. A similar analytic plan will be utilized for other continuous variables (DAS28-CRP, ACR 20/50/70 response, EULAR response and average corticosteroid dose). The approach for discrete secondary variables will utilize mixed effects models, though the link function will be modified based on the type of discrete variable (e.g., logit link for binary, Poisson like for count).

The fit of all models will be assessed. If the models do not adequately fit, transformed data will be investigated. If an adequate transformation cannot be identified, nonparametric approaches will be investigated.

The CDAI is a calculated measure based on the following: sum of number of swollen joints, number of tender joints, patient's global disease activity (PGA) (on a scale of 0 -10) and physician's global disease activity (PGA) (on a scale of 0 -10).

The DAS28-CRP is a calculated measure based on the following: number of swollen joints, number of tender joints, CRP, and patient's global disease activity (PGA) measured on a Visual Analogue Scale (VAS): DAS28-4(CRP) = 0.56*sqrt(tender28) + 0.28*sqrt(swollen28) + 0.36*ln(CRP+1) + 0.014*PGA + 0.96

For the discrete efficacy-related variables, we will perform comparisons between the different treatments using contingency tables and two-tailed *chi* square tests. Corrections for multiple testing will not be made since all of these analyses are exploratory.

Safety Analysis

All safety analyses will be performed using the Safety population. The safety analysis is done for unanticipated problems or adverse events.

Unanticipated AEs including changes in laboratory values will be graded according to the NCI CTCAE (http://ctep.cancer.gov/reporting/ctc.html). The frequency of unanticipated AEs will be summarized by system organ class, preferred term, severity (grade), and relationship to study treatment. For each of these summaries, participants will be counted at most once within each organ class or preferred term at the greatest severity. For these summaries, relationship to study treatment will be categorized as either treatment related (unlikely, possibly, probably, or definitely related to study medication) or unrelated. Similar analyses will be performed for unanticipated SAEs. The proportion of treatment-related adverse events of Grade 3 or higher will also be reported for each treatment group. In an exploratory fashion, chi-square tests, or Fisher's exact test when appropriate, will be conducted to compare the rate of each

unanticipated AE in the treatment groups. These comparisons and associated p-values are considered exploratory and, especially given the number of tests conducted, will be interpreted with care.

Laboratory parameters will be summarized both overall and by treatment group using appropriate descriptive statistics. For quantitative safety parameters, change from the last pre-randomization assessment to the final visit assessment will be summarized overall and by treatment group. For qualitative parameters, descriptive information on shifts in pre- to post-randomization findings will be provided. In addition, abnormal and clinically significant abnormalities will be summarized and listed separately.

10.4 Measures to Minimize Bias

Enrollment will be available to any patient with RA within the UPMC Rheumatology Network, meeting the entry criteria. Upon successful screening, the participants will be randomized to one of the three treatment arms. The treating rheumatologist, the participant, and the study coordinators will NOT be blinded or masked to the participant's drug treatment. Participants will be randomized using the randomization methods described in Section 3.1. This is a real-world study, so treating rheumatologists will be permitted to restrict some of the treatment options for their participants who are randomized to the anti-TNF group (Arm 1). The UPMC Rheumatology Network is a large network with more than 44,000 rheumatology outpatient visits each year. Based upon planning meetings with the rheumatologists in this network, we don't expect a large number of randomization restrictions. We will enroll enough patients to enter adequate numbers of subjects as outlined. The disease activity assessments will be handled by fully-trained, blinded assessor.

10.5 Appropriate Methods and Timing for Analyzing Outcome Measures

Definition of Subject Completion

A subject is considered to have completed the study if he/she has completed the 6-month study visit. For the purposes of the secondary endpoint analyses, a subject's results will be considered eligible for analysis if the subject receives their first dose of study medication. For subjects that do not complete all study visits but are eligible for analysis because they received their first dose of study drug, non-mechanistic outcome analyses will be based on the last observation carried forward. Mechanistic study outcome analyses will only be conducted on the 90 subjects that complete the 6-month study visit. Secondary efficacy study outcome analyses will be conducted on all subjects that receive the first dose of study drug.

10.6 Study Hypotheses

See section 2.1

10.7 Sample Size Considerations

For the power analysis and sample size estimates, we based our primary estimates on the analyses described in Aim 1a, which focus on within treatment analyses of responsiveness to therapy following therapy with TNF antagonists, tocilizumab, or abatacept by analyzing the correlation between changes in T and B cell populations with changes in disease activity as measured by the DAS28-CRP and CDAI. These sample size estimates were based on using Spearman's rank correlation coefficients and an alpha of 0.05 and a beta of 0.2 (80% power) (**Table 4**). The estimates in **Table 4** suggest that about 20 subjects per treatment arm will provide enough subjects for a correlation analysis within treatments to achieve a correlation of at least 0.5 if a correlation exists between changes in T and B cell populations and changes in disease activity following treatment with TNF antagonists, tocilizumab, or abatacept. However, because we aim to assess immunological changes that occur in responders to each therapy, and estimate a 60% response rate, we will enroll 30 patients per treatment arm to gain around 20 responders per group.

Table 4: Sample size estimates for correlation analysis of changes in mechanistic studies with changes in disease activity

Correlation coefficient (rho)	Number / treatment arm
0.30	67
0.40	37
0.50	23
0.55	19
0.60	16
0.70	11

For the other aims, with no adjustments for multiple comparisons, there is at least 80% power to detect an effect size of 0.30. For the other aims, an effect size of 0.30 is likely to result in statistically significant differences between groups based on prior published studies by others and by our group.

10.8 Maintenance of Trial Treatment Randomization Codes

Dr. Wisniewski and the data management team (Epidemiology Data Center – EDC) will program the randomization. The randomization process is described in detail in section 3.1. The randomization codes will be maintained in the database, in a secure area inaccessible to the blinded assessors. The treating rheumatologist, the participant, and the study coordinators will NOT be blinded or masked to the participant's drug treatment. The blinded assessor of disease activity WILL be blinded to the treatment options.

10.9 Participant Enrollment and Follow-Up

While a potential patient-participant is in the clinic with their treating physician, they will be approached by the treating physician for potential enrollment in the MAZERATI study. If the patient agrees to discuss the study further, then a study coordinator will discuss the MAZERATI study. The details of the study will be discussed and the informed consent will be presented. The patient will be provided plenty of time to ask questions and to review the consent and study documents. MAZERATI is a standard-of-care, randomized observation study, so patients will continue to be seen by the treating rheumatologists according to the appropriate standard-of-care. Specific MAZERATI follow-up will occur at 1, 3 and 6 months and at other times

(unscheduled visits) at the discretion of a participant's treating physician. Where possible follow-up visits will be coordinated with visits to the treating physician.

10.10 Planned Interim Analyses (if applicable)

Interim Analysis
An interim analysis will not be performed. An interim analysis will likely be of limited value given the limited size of the MAZERATI study and given the low likelihood of significant unanticipated adverse events from the FDA approved medications that will be studied in this protocol.

10.11 Safety Review

MAZERATI is a phase IV clinical trial. All medications will be dispensed by practicing rheumatologists familiar with these therapies and their side effects and contraindications. All therapies will be used in an open-label manner according to FDA-approved guidelines. The participants and the rheumatologists will not be blinded to the therapies, which will allow proper clinical management of these participants, including standard-of-care toxicity monitoring as appropriate. Unanticipated events will be collected but safety outcomes will not be a part of this study.

10.12 Immunogenicity or Efficacy Review

MAZERATI is a phase IV clinical trial. All medications will be dispensed by practicing rheumatologists familiar with these therapies and their side effects and contraindications. All therapies will be used in an open-label manner according to FDA-approved guidelines. The participants and the rheumatologists will not be blinded to the therapies, which will allow proper clinical management of these participants, including standard-of-care toxicity monitoring as appropriate. Some of the biologic therapies are recognized as potentially immunogenic, but the treating physicians are aware of these precautions. The primary outcome of the MAZERATI study is mechanistic, and the study is not powered for efficacy. Nevertheless, Dr. Moreland will monitor the safety of the study on a regular basis.

10.13 Final Analysis Plan

The statistical analysis plans for the study are described in detail in **Section 10.3**.

11. QUALITY CONTROL AND QUALITY ASSURANCE

MAZERATI is a single-site clinical trial, occurring within the UPMC Rheumatology Network. Within this network, each clinic has similar standard operating procedures (SOPs) for quality management. Dr. Moreland and Dr. Wisniewski will be responsible for monitoring and assuring quality of the data collected, and will designate a MAZERATI study monitor for this purpose. Data will be evaluated for compliance with protocol and accuracy in relation to source documents. The study will be conducted in accordance with procedures identified in this protocol and the MAZERATI standard operating procedures as presented in the MAZERATI MOP.

Following written standard operating procedures, the study monitor will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. The treating physicians will provide direct access to all trial-related source data and documents and reports for the purpose of monitoring and auditing by the study monitor and for inspection by local and regulatory authorities. The statistical manager and data manager will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated biweekly to the study coordinators for clarification and resolution.

The training of new and future study coordinators and staff will be done by the lead MAZERATI coordinator and the study monitor, under the supervision of Dr. Moreland.

12. ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 Institutional Review Board/Ethics Committee

The University of Pittsburgh holds a current Federal Wide Assurance issued by the Office of Human Research Protection (OHRP) at the Department of Health and Human Services (DHHS) and will provide for the review and approval of this protocol and associated informed consent documents. Any amendments to the protocol or consent materials must be approved before they are placed into use.

The investigators will inform the IRB of serious or unexpected AEs that might occur during the study and are likely to affect the safety of the subjects, or the conduct of the study. The investigators will comply fully with all IRB requirements for reporting AEs, protocol or consent form changes, as well as any new information pertaining to the use of the study medication that might affect the conduct of the study.

The study will be conducted according to Good Clinical Practice (GCP) guidelines, U.S. 21 CFR Part 50 – Protection of Human Subjects, and Part 56 – Institutional Review Boards.

Compliance with Good Clinical Practices
This trial will be conducted in compliance with the protocol, current GCPs recommended by the International Conference on Harmonization (ICH) and the applicable regulatory requirements for the University of Pittsburgh. These include the tenets of the Declaration of Helsinki and review and approval by the IRB.

Study drugs will be used in an open-label manner and patients will receive the usual counseling on study medications from their physician. Laboratory monitoring will also be performed according to the physician's judgment. Since this study uses standard-of-care surveillance and open-label therapies, the potential risks to the participants are minimized.

12.2 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the participants and their families.

Consent forms describing in detail the therapies, procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting the study agent. Consent forms will be IRB approved, and the participant will be asked to read and review the document. Upon reviewing the document, the study coordinator will explain the research study to the participant and answer any questions that may arise. The participants will sign the informed consent document prior to any procedures being done specifically for the study. The participants will have sufficient opportunity to discuss the study and process the information in the consent process prior to agreeing to participate. The participants may withdraw consent at any time throughout the course of the trial.

The principles of informed consent in the current edition of the Declaration of Helsinki, as well as compliance with all IRB requirements, will be implemented in the MAZERATI study, before any protocol-specified procedures are carried out. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

After completion, an unsigned copy of the consent form will be given to the subject for her/his records. Paper and electronic versions of this form are identical in appearance. If the consent form is recorded electronically on the PC tablet, it will be saved to a secure location on the UPMC server, separate from study data. If consent is recorded using a paper form, it will be kept in a locked file drawer, in the coordinators' locked office. Both electronic and paper consent forms will be available for inspection by regulatory authorities, both federal and institutional.

12.2.1 Assent or Informed Consent Process (in Case of a Minor)

The MAZERATI trial is a trial for adults with RA. No children will be recruited for this trial. This study is designed to investigate adults with RA. Juvenile chronic arthritis is thought by many to be pathogenetically different from adult-onset RA. Therefore, children will not be studied in the trial, but information gained could be used in an independent fashion for potential, future studies in children.

12.3 Exclusion of Women, Minorities, and Children (Special Populations)

This study will not involve fetuses, neonates, pregnant women, prisoners, institutionalized individuals, or others who may be considered vulnerable populations. Fetuses and neonates will not be included since the study is for patients with uncontrolled adult rheumatoid arthritis. Several of the study therapies are contraindicated in pregnant females, so they will be excluded. Prisoners, institutionalized individuals, and others will be excluded as well.

All participants will be carefully evaluated to select patients that meet entry criteria and will be capable of signing an IRB-approved consent form, which will include the risks and benefits of the study.

12.4 Participant Confidentiality

Every effort will be made to protect the subject's privacy and information will be handled in a confidential manner. Participants involved in MAZERATI will not be identified by name, but with

a specific code that will protect their identity. Electronic files that link the subjects name to the code number will be stored in a password protected secure server, and only the study staff will have access to them. Paper-based files will be kept in a locked file cabinet, within a locked office. Data will be published in aggregate format only, without the possibility of identifying individual participants.

12.5 Study Discontinuation

MAZERATI is a phase IV clinical trial. All medications will be dispensed by practicing rheumatologists familiar with these therapies and their side effects and contraindications. All therapies will be used in an open-label manner according to FDA-approved guidelines. The participants and the rheumatologists will not be blinded to the therapies, which will allow proper clinical management of these participants, including standard-of-care toxicity monitoring. All of the randomized arms of the MAZERATI study are equally potential interventions for patients with the entry criteria of the MAZERATI study. In the event that MAZERATI is discontinued, then participants will continue standard care with their treating rheumatologists.

13. DATA HANDLING AND RECORD KEEPING

13.1 Data Management Responsibilities

Accurate records to ensure the conduct of the study is fully documented will be maintained and the period of retention will be consistent with National Institutes of Health (NIH) requirements.

Data will be collected using the subject's screening or enrollment number to ensure the strictest confidence. The Data Management group (EDC), headed by Dr. Steve Wisniewski, will not collect personally identifying information such as the subject's name or social security number.

Personally identifying information as well as demographic information such as race, ethnicity, and birth date are collected in a database, which is housed in a separate location, with access limited to the PI and research coordinators to protect patients from access that could reveal personally identifying information about any subject in the trial.

Research coordinators and research specialists (lab personnel) will verify the completeness, consistency and accuracy of documented clinical data.

13.2 Data Capture Methods

Data will be obtained from a variety of sources including, but not limited to laboratory notebooks, automated instrument output files, clinical subject charts (EMR) and electronically collected patient and physician questionnaires and joint examination findings. Data from these source materials will be transmitted to the EDC via one of two mechanisms. Data collected electronically in Dr. Moreland's laboratory will be transferred electronically directly from the laboratory to the EDC using standard secure data transfer procedures. Data collected in the clinical sites will be transmitted to the EDC using a secure wireless data entry system. Clinical site personnel use tablet PCs to enter data into electronic CRFs (e-CRFs); each CRF page is submitted to the secure UPMC server electronically as the page is completed. The central database, which resides on the UPMC server, is backed up nightly. At any time, authorized site personnel may log in to the wireless data entry system, review and correct previously entered

data, or key additional data. The data will be further validated per the study data validation plan via a series of computerized and manual edit checks, and all relevant data queries will be raised and resolved on an ongoing basis. Complete, clean data will be frozen to prevent further inadvertent modifications. All discrepancies will be reviewed and any resulting queries will be resolved with the research coordinators and amended in the database. All elements of data entry (i.e., time, date, verbatim text, and the person performing the data entry) will be recorded in an electronic audit trail to allow all data changes in the database to be monitored and maintained in accordance with federal regulations.

13.3 Types of Data

The MAZERATI study will collect safety data, laboratory data, mechanistic data, and outcome measures data. Since this is a phase IV clinical trial, safety data will not be collected in a separate database, but will be monitored within the MAZERATI database to monitor AEs and SAEs. The laboratory data collected will be a hsCRP for calculation of the DAS28-CRP. The percentage of various leukocyte isoforms will be collected as part of the mechanistic data. Various patient, rheumatologist, and blinded assessor questionnaires will be collected as part of the outcomes measures for quality-of-life. Standardized joint counts by the participant's physician and by the blinded assessor will be collected as well for the DAS28-CRP.

13.4 Source documents and Access to Source Data/Documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH-GCP, regulatory and institutional requirements for the protection of confidentiality of participants. Each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

13.5 Timing/Reports

MAZERATI is a phase IV clinical trial. All medications will be dispensed by practicing rheumatologists familiar with these therapies and their side effects and contraindications. All therapies will be used in an open-label manner according to FDA-approved guidelines. The participants and the rheumatologists will not be blinded to the therapies, which will allow proper clinical management of these participants, including standard-of-care toxicity monitoring. The data safety-monitoring plan is described in detail in Section 9. Dr. Moreland, the rheumatologist who is also PI of this study will hold weekly meetings with the study coordinators to review the safety data and MAZERATI reports described in Section 9. During these meetings, any data

which has the potential to stop a participant from continuing is monitored and evaluated. Rheumatologists will be required to sign off on all toxicity monitoring lab results in the timeframe compatible with standard-of-care. Meeting agendas and notes will be stored by the PIs for at least 7 years after the close of MAZERATI.

13.6 Study Records Retention

Study records consist of electronic and paper records generated as a result of the MAZERATI study. These records must be retained for a minimum of three years after the use of the last biospecimen from the study. The principal investigator (Moreland) must give concurrence for the destruction of study records.

13.7 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practice (GCP), or Manual of Procedures requirements. The noncompliance may be either on the part of the participant, the investigator, or the study staff. As a result of deviations, corrective actions are to be implemented promptly. In general, deviations to the MAZERATI clinical protocol are not allowed, except when required for the health and safety of the participants.

These practices are consistent with Good Clinical Practice (GCP ICH E6) Sections:

Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3

Quality Assurance and Quality Control, section 5.1.1

Noncompliance, sections 5.20.1, and 5.20.2

It is the responsibility of the site to use continuous vigilance to identify and report deviations according to the guidelines of the MAZERATI principal investigators, UPITT, UPMC, and the NIH.

The PI will be responsible for the conduct of the trial and for verifying adherence to the protocol as well as adherence to all IRB requirements. All protocol deviations will be reported to the IRB, PI and EDC per the instructions in the Manual of Operations.

14. PUBLICATION POLICY

Following completion of the MAZERATI study, the investigators will publish the results of this research in scientific journals. The International Committee of Medical Journal Editors (ICMJE) member journals has adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. MAZERATI will be registered at this site prior to its commencement.

A Publications Committee will be formed to review all requests for the use of data derived from this clinical trial. The Publications Committee will be chosen during the first 6 months of funding. The Publication Committee will be charged with maintaining publication and authorship policies. Final authorship determinations will be made by the Publication Committee in consultation with Drs. Moreland, McGeachy, Hwang and Wisniewski in accordance with ICMJE guidelines.

Publication of the results of this trial will be governed by NIAMS publication policies. Any presentation, abstract, or manuscript will be made available for review by the NIAMS supporters prior to its submission.

Drs. Moreland and McGeachy will maintain control of all MAZERATI-generated biospecimens and will decide on the scientific merit of any future sub-studies. They will adhere to the letter and the spirit of the prevailing NIH and NIAMS guidelines on the sharing of research resources produced from federally-funded research.

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STUDY VISIT	Screening- ≤30 days	Enrollment/Randomization ≤30 days	Baseline Day 0	1 month (3-5 wks)	3 months (10-14 wks)	6 months (22-30 wks)	Unscheduled visit	Early termination
VISIT #	0	0	1	2	3	4	UT	ET
Informed consent	X							
Confirm eligibility	X							
Randomization		X						
Insurance approval[1]		X						
Receive first dose of study drug[2]			X					
Research Laboratory								
Research blood samples			X	X	X	X		X
PK-PD/Immunogenicity samples[4]			X					
Safety Evaluations								
Quantiferon TB-Gold Test[6] or PPD/CXR[6]	X							
Assessments								
Patient questionnaires	X		X	X	X	X		X
CDAI exam by physician	X		X	X	X	X		X
Blinded joint exam for CDAI/DAS 28			X	X	X	X		X
Drug accountability/ Compliance monitoring				X	X	X		X
AE monitoring			X	X	X	X	X	X
Assess RF and/or CCP autoantibody status	X							
Clinical lab review								
CBC/diff/plt/ANC	X			X	X	X	X[7]	X
Liver function tests (ALT/AST/ T. bili)	X			X[5]	X[5]	X[5]	X[7]	X[5]
Lipid profile	X			X[5]	X[5]	X[5]	X[7]	X[5]
HepBsAg and HepCAb[6]	X							
Urine pregnancy[3]	X							

[1] TNF (Arm 1) Only
[2] counseling and training to be provided as standard of care in the outpatient clinic
[3] women of childbearing potential (WOCBP)
[4] Only required for TCZ (Arm 2) at baseline, at time of hypersensitivity/anaphylaxis event (if applicable), and at 6 weeks post-event (if applicable)
[5] Only required for TCZ (Arm 2) patients (per TCZ packaging)
[6]Results within one year of screening may be used (PPD/Quantiferon TB-Gold test may be used if no risk of exposure has occurred, e.g. travel outside the US or contact with TB infected individuals)
[7]To be completed at the discretion of the treating MD.

Appendix B – Genentech Safety Reporting Fax Cover Sheet

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET
Investigator Sponsored Trials

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

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

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

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

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

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

PAGE 1 OF ___