Study Title:

Protocol ML29092: A Phase II Trial of the Efficacy and Safety of Tocilizumab for Treatment of Inflammation and Rejection in the Renal Allograft

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UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

SYNPOSIS

Study Title	Protocol ML29092: A Phase II Trial of the Efficacy and Safety of Tocilizumab for Treatment of Inflammation and Rejection in the Renal Allograft
Short Title	Tocilizumab for Renal Graft Inflammation and Rejection
Study Drug	Tocilizumab (ACTEMRA®)
Support Provided By	Genentech
Clinical Phase	Phase II
Sponsor Investigator	Flavio Vincenti
Sub-Investigators	Sindhu Chandran Zoltan Laszik
Research Coordinator	Niloufar Abdollahi
Accrual Objective	48
Study Design	Randomized open label clinical trial in which 48 renal transplant recipients with inflammation or acute rejection within the first year post-transplant will either receive standard of care immunosuppression or receive monthly Actemra (Tocilizumab) infusions for 6 months in addition to standard of care immunosuppression
Study Duration	It will take 12 months to enroll 48 patients. Actemra (Tocilizumab) will be administered for 6 months with an extended follow up period for each participant of 6 months for a total study duration of 24 months
Primary Endpoint	Primary outcome will be a 40% decrease in inflammation on repeat renal allograft biopsy at the end of treatment
Secondary Endpoint	Secondary outcomes are the change in urinary cytokines, development of donor specific anti-HLA antibody and the incidence of subsequent acute rejection

Protocol Version: 11.0

Date: 27 April 2016

LIST OF ABBREVIATIONS

AE	Adverse effect
AI	Allograft inflammation
AR	Acute rejection
CFR	Code of federal regulations
DMARD	Disease modifying anti-rheumatic drug
GFR	Glomerular filtration rate
IF/TA	Interstitial fibrosis and tubular atrophy
IL-6	Interleukin-6
MMF	Mycophenolate mofetil
MPA	Mycophenolic acid
REMS	Risk evaluation and mitigation strategy
SAE	Serious adverse event
SCI	Subclinical inflammation
SCR	Subclinical rejection
TCZ	Tocilizumab
ULN	Upper limit of normal

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1.0 INTRODUCTION

1.1 Background on Inflammation and Rejection in Kidney Transplants

Improved renal allograft survival over the past decades has been mostly driven by dramatic reductions in early acute rejections and first-year graft loss, accompanied by only very modest gains in long-term graft attrition (1, 2). A major contributor to graft loss is interstitial fibrosis and tubular atrophy (IF/TA) (3, 4), previously called chronic allograft nephropathy (CAN), which is the result of cumulative allograft damage of immunologic and non-immunologic origin. Studies of protocol biopsies have provided important clues on how early changes in graft histology relate to long-term graft survival. Early sequential post-transplant protocol biopsies show a rapid increase in the prevalence of IF/TA, to over 50% at one year in most studies, which constitutes nearly 2/3rds of the total fibrosis burden seen at 10 years (4-5). This means that the majority of IF/TA- a marker of previous injury and chronic damage- occurs early in the life of the kidney transplant. IF/TA on a 1-year biopsy is associated with inferior graft survival (6-7) and can be used as a surrogate marker of long-term survival (8-9).

The Banff 1997 classification (10), updated 2007 (11), of renal allograft pathology uses semi-quantitative lesion scoring and has proven to be reproducible and useful for the diagnosis, grading and management of acute rejection in kidney transplants (Appendix 1). “Acute T-cell-mediated rejection” is defined by a minimum threshold of i2 t2, i.e., interstitial inflammation (>25% of the cortex) and moderate tubulitis (> 4 mononuclear cells/ tubule). Inflammation which is insufficient to meet criteria for acute rejection is classified as “borderline change” or “suspicious” if there is tubulitis (t1, t2 or t3) with minor interstitial inflammation (i0 or i1) or interstitial inflammation (i2, i3) with mild (t1) tubulitis.

Early studies clearly established acute rejection (AR) as one of the strongest correlates of reduced allograft survival (12-14). Despite a decline in incidence rates of acute rejection (AR) in the modern era of immunosuppression, it is clear that AR remains a major risk factor for late graft loss. Even early episodes of acute rejection, such as those within the first year, have lasting impact on the graft. In a study (15) of 28,867 recipients of deceased donor kidney transplants between 1995 and 2005, AR anytime during the first post-transplant year was shown to confer risk (hazard ratio for graft survival to 1.35 for patients with rejection 0-90 days, 2.05 with rejection 91-180 days, and 2.74 with rejection 181-365 days post-transplant). These risks are seen in low immunologic risk populations as well. A study (16) of 797 living donor kidney transplant recipients from 1998-2010 found that 15.2% of recipients had AR diagnosed by protocol or clinical biopsies within the first year. In this analysis “borderline” changes were analyzed as an AR event. Compared to no-AR, all histologic types of AR (including borderline change) led to abnormal histology in 1 and 2 years protocol biopsies, including more fibrosis + inflammation (6.3% vs. 21.9%), moderate/severe fibrosis (7.7% vs. 13.5%) and transplant glomerulopathy (1.4% vs. 8.3%, all $p < 0.0001$). AR were associated with reduced graft survival (HR = 3.07). Finally, another study (17) of 270 patients found that all types of AR, including borderline change and Banff type 1 T-cell mediated rejection, shortened long-term graft survival. From these observations, it is clear that despite the remarkable success of modern immunosuppressive regimens in reducing the rates of incident AR and the effectiveness of available treatments for acute rejection, an episode of AR continues to have a

significant negative impact on graft outcome. Detailed follow up of allograft histology following AR, including even those episodes which are clinically and histologically mild, has shown that one-third of cases have residual inflammation and eventually develop a pattern of fibrosis + inflammation. Studies which identified AR as a strong predictor of death-censored graft survival (12, 14) found that most of that risk relates to a higher rate of late graft loss following the episode of rejection. These data indicate that conventional therapy of acute rejection, while improving graft function temporarily, may not be effective at preventing persistent inflammation and progressive fibrosis.

Importantly, the negative impact of AR on graft survival is not limited to those episodes which manifest clinically with elevations in serum creatinine. Subclinical rejection (SCR) is the presence of AR on routine biopsies in patients with stable kidney function. Subclinical inflammation (SCI) is a term that is often used to indicate the presence of inflammation on routine biopsies that is insufficient to meet criteria for acute rejection. SCI and SCR are common, reported in 11-44% of surveillance biopsies within the first year (18-20) and emerging data suggest that they are not benign.

It has been shown that immune-mediated injury, even if subclinical, precedes and/or worsens IF/TA. A study of 961 prospective protocol kidney biopsies (21) over 10 years from 119 diabetic recipients of a kidney-pancreas transplant and one kidney transplant alone found that SCR (including Banff borderline lesions) was a frequent finding early after transplantation (in 61 and 46% of biopsies at 1 and 3 months after transplant). If SCR persisted, it was not only associated with a higher degree of IF and TA but also resulted in significantly decreased renal function at 2 years after transplantation. Another study of 124 sequential protocol biopsies performed at 2, 3, and 5 years after transplantation in 46 patients who exhibited histologic evidence of CAN at 1 year found that the presence of SCR in association with CAN correlated significantly with histologic progression defined as an increased chronic allograft damage index (CADI) score of the follow-up biopsies (22). Furthermore, a group of patients who exhibited repeated SCR in the sequential follow-up biopsies had a lower creatinine clearance at 5 years after transplantation and worse long-term graft survival. In contrast, the absence of evidence of acute inflammation in association with CAN at any time point was associated with minimal deterioration in renal function or progression of renal lesions during the observation period.

According to the Banff classification, the significance of sub-threshold inflammation seen on surveillance biopsies is unclear. However, even when the level of inflammation does not meet the threshold for acute cellular rejection, it has been shown to have the same molecular nature and similar impact on graft pathology and function as AR. A study of clinically stable renal allograft biopsies showed that histologic features of rejection were often accompanied by enhanced expression of pro-inflammatory gene transcripts, despite the absence of clinically overt graft dysfunction (23). In this study, biopsies with borderline change, i.e., those with inflammation which did not meet the threshold for acute rejection had a level of expression of inflammatory gene transcripts which was intermediate between that shown by histologically normal biopsies and those with AR. Another study which correlated renal function with routine histology, immunohistochemical analysis, and quantitative assessment of 72 relevant immune function gene transcripts found that a transcriptional profile indicative of activated TH1 type T cells, but not the magnitude or composition of the infiltrate, uniquely defined a functionally significant allograft rejection (24). Thus it appears that the immune response is qualitatively similar but quantitatively

reduced in SCI, indicating that SCI carries the same potential for allo-immune damage as clinical or subclinical AR. This is borne out by studies showing early SCI is associated with progression of IF/TA as well as worsened renal function. In a cohort of kidney transplant recipients treated with rapid steroid withdrawal who underwent sequential protocol biopsies, patients with SCI on their 1-month or 4-month biopsy had a higher risk of IF/TA score > 2 on the 1-year biopsy (18). In a protocol biopsy analysis of a subpopulation of the CONCEPT study, SCI was observed in 30.5% of patients with an evaluable biopsy at 1 year (20). At 30 months, SCI was associated with a significantly lower level of estimated glomerular filtration rate.

In addition, graft inflammation, with or without tubulitis, may not be benign or insignificant as previously considered, but is in fact associated with poor outcomes. A study of 124 biopsies for cause found that the sum of inflammation in atrophic and non-atrophic parenchyma (Banff "ti" or total i-score) showed stronger correlations with microarray-based gene sets representing major biological processes during allograft rejection than the Banff i-score, which only looks at inflammation in non-atrophic areas (25). In this study, the total-i score was also found to be a better predictor of graft survival than the Banff i-score. In another study, a decision tree analysis of the molecular changes in biopsies with acute cellular rejection, borderline and non-rejection showed that i-total >27% and tubulitis extent >3% matched the molecular diagnosis of acute cellular rejection in 85% of cases (26). This analysis indicated that the histologic assessment of rejection is more accurate when it relies primarily on interstitial inflammation, and that inflammation >27% (which by Banff 2007 classification is barely above the threshold of 25% for a score of i2), even when associated with rare tubulitis, is a marker of immune mediated injury. These findings are supported by studies showing that SCI occurring in association with IF/TA predicts progressive decline in kidney function and reduced graft survival. In a study of 151 living-donor recipients, the combination of fibrosis and inflammation in 1-year protocol biopsies was associated with reduced graft function and survival as well as a rejection-like gene expression signature, even among recipients with no clinical risk factors for poor outcomes (27). Similarly, a study of 1-year surveillance biopsies of 292 kidney transplant recipients found that the presence of fibrosis and inflammation predicted poorer survival whereas mild fibrosis alone did not. Importantly, the degree of inflammation associated with fibrosis generally did not qualify for the diagnosis of borderline rejection (6). Another study of 833 protocol and 306 indicated biopsies found that the only predictor of allograft function outcome was persistent inflammation in sequential biopsies (28). The investigators calculated the cumulative inflammatory burden by summing up the number of inflammatory infiltrates in sequential biopsies (at 1.5, 3, and 6 months after transplant) and found that the persistence of inflammation in sequential biopsy specimens regardless of its severity, localization, or cellular composition predicted creatinine clearance at 1 and 2 years. The study concluded that as detected by sequential biopsies, persistence of any inflammation including those infiltrates currently not considered by the Banff classification should be regarded as a morphological correlate of ongoing allograft damage. The appropriate clinical management for patients showing SCI on routine biopsies remains an area of uncertainty. The response (or lack) of SCI to treatment remains unclear, as studies that treated SCI have not clearly differentiated between the level or type of inflammation when looking at graft outcomes (54-58).

Cytokines play an important role in regulating alloimmune responses (29). Interleukin-6 (IL-6) is synthesized by T cells and macrophages upon immune challenge, and is further induced by the action of other cytokines (IL-1 and tumor necrosis factor), also generated in the context of an immune stimulus (30). Initially identified as a B-cell maturation factor (31, 32) IL-6 also serves as an immunoregulator of T cell growth and differentiation (33-35) and is critical for Th17 development. A subtype of Th cells, Th17 cells specifically secrete Il-17, which is responsible for neutrophil proliferation and migration, endothelial cell activation, and fibroblast activation and proliferation. Due to its strong anti-apoptotic properties, IL-6 can increase the effector/memory T-cell population (36) and has also been shown to skew Th cell differentiation toward a Th17 phenotype and to prevent the development of regulatory T cells (37).

The exact role of IL-6 and Th17 cells in solid organ transplantation has not been fully elucidated; however, there are now considerable data linking them to immune mediated injury. In a mouse skin transplantation model, IL-6 synergized with tumor necrosis factor-α to promote T-cell alloimmune responses and impaired the ability of regulatory T cells to suppress effector T-cell alloimmune responses (38). IL-6 along with interferon-c was found to be the major cytokine upregulated during allograft rejection in fully major histocompatibility complex (MHC)-mismatched mouse model of cardiac transplantation (39). In this model, neutralization of IL-6 by a monoclonal IL-6 antibody along with costimulation blockade inhibited rejection and facilitated allograft survival. IL-6 and Th17 have also been found to play a pathogenic role in the development of acute and chronic lung rejection (40, 41).

In renal transplant recipients, IL-6 expression in serum, urine and biopsy tissue is elevated during renal allograft rejection (42-48) and has been correlated with the degree of inflammatory cell infiltration (45, 46). Interestingly, the demonstration of the strongest immunostaining for IL-6 in atrophic tubular areas (45) and increase in soluble IL-6 receptor in urine 12 and 6 months before late graft failure (49), raises the possibility that IL-6 may play a significant role in mediating chronic graft injury a. A biopsy study of 40 stable renal allograft recipients 2-3 years after transplantation detected IL-6 transcripts in 18% and these were correlated with lymphocytic infiltrate, fibrosis, and tubular atrophy (50). Of the cytokines studies, IL-6 held the most consistent negative predictive value for histological injury. Epidemiologic studies also support a role for IL-6 in chronic rejection and potentially graft loss. A G/C single nucleotide polymorphism at position –174 within the 5’ flanking region of the IL-6 gene is known to be associated with differential plasma levels of IL-6 in healthy individuals (51). In kidney transplant recipients, the high IL-6 producer phenotype for this genetic polymorphism (GG or GC) has been associated with the production of donor-specific HLA antibodies post-transplantation (52) as well as reduced 5-year graft survival (53). These data collectively indicate that IL-6 plays a prominent role in immune mediated graft injury.

In summary, the varying combinations of interstitial inflammation and tubulitis in the renal allograft, whether clinically manifest or silent, whether designated acute rejection or borderline change or non-specific inflammation, appear to be part of the same spectrum of immune-mediated injury to the graft. Conventional immunosuppressive treatments and modifications have failed to eliminate immune-mediated injury and its negative impact on long-term graft outcome and have only made this injury more subtle and thus less easily recognizable both clinically and histologically. The Graft inflammation

and acute rejection and within the first year therefore represent the earliest stages of allogeneic immune injury, and an intervention at this stage, such as the inhibition of IL-6 which is a major cytokine regulator of T cells and the inflammatory alloresponse, has the potential to arrest or slow the development of IF/TA and improve long-term renal graft survival.

1.2 Tocilizumab Background

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

The elimination half-life of TCZ can be approximately 12.9 days. The TCZ exposures were stable over 2-years of treatment in the WA17823 study of 841 patients. The observed mean (± SD) C_{trough} at 8 mg/kg IV was 15.9 ± 12.0 µg/ml at week 24 and 19.9 ± 17.0 µg/ml at week 104. The observed mean (± SD) C_{trough} at 4 mg/kg was 1.02 ± 6.14 µg/ml at week 24 and 1.09 ± 2.77 µg/ml at week 104.

The Roche clinical development program in adult RA, comprised five pivotal Phase 3 trials and two open-label, long-term treatment extension studies. Further information on TCZ can be found in the Investigator's Brochure (IB).

1.3 Study Rationale

We performed a retrospective analysis of 380 consecutive 6-month surveillance kidney transplant biopsies performed at UCSF Medical Center between July 27, 2009 and May 9, 2011. These biopsies were scored by a single pathologist using the revised Banff 2007 classification. Multivariable Poisson regression with robust variance estimators was used to calculate relative risks of acute rejection and total inflammation. Multivariable linear regression was used to analyze associations with the estimated glomerular filtration rate (eGFR) by MDRD (Modification of Diet in Renal Disease) equation.

The analysis identified subclinical acute cellular rejection in 7.3% (n=28) of all surveillance biopsies; of these 5.5% (n=21) had Banff type 1a rejection. Subclinical inflammation (SCI) insufficient to meet criteria for acute rejection was found in 32% (n=122) of all surveillance biopsies. This included biospies with borderline change and non-specific inflammation. Both interstitial fibrosis (Banff ci-score) and tubular atrophy (Banff ct-score) were significantly associated with the presence of inflammation.

Table 1: Association of graft inflammation with interstitial fibrosis and tubular atrophy

	Without Inflammation (ti-score =0)	**With Inflammation (ti-score >0)**	**P value**
ci-score >0	14%	62%	<0.001
ct-score >0	53%	78%	<0.001

Inflammation was also found to be associated with lower eGFR by MDRD at 6 months and 12 months post-transplant in univariate analysis. This difference remained statistically significant at 6 months in a fully adjusted multivariate analysis.

Table 2: Association of graft inflammation with eGFR in univariate and multivariate analysis

	Without Inflammation (ti-score =0)	**With Inflammation (ti-score >0)**	**P value**
Total number	254	98	
Median MDRD eGFR at 6 months (ml/min/1.73 m^2)	67	60	<0.001
Median MDRD eGFR at 12 months (ml/min/1.73 m^2)	68	58	<0.001
FULLY ADJUSTED ANALYSIS			
	With Inflammation (ti-score >0)	**95% CI**	**P value**
Estimated difference in MDRD eGFR at 6 months (ml/min/1.73 m^2)	-7.0	(-10.8, -3.2)	0.0003
Estimated difference in MDRD eGFR at 12 months (ml/min/1.73 m^2)	-2.1	(-4.6, 0.31)	0.087 (NS)

Therefore, in this analysis, the presence of SCI and SCR was found to be significantly associated with both the development of chronicity and a decrease in graft function at 6 months.

Additionally, in 23 kidney transplant recipients who were found to have either inflammation or rejection on their 6-month protocol biopsy, a follow up biopsy was performed 6 months later, i.e., at 12 months post-transplantation. The 12-month biopsy found persistent inflammation in the majority. All patients with subclinical rejection had been treated with IV methylprednisolone pulse and intensification of baseline immunosuppression. Additionally, 2 had been treated with Thymoglobulin and 3 with IVIg. Patients with SCI on their initial biopsy received oral prednisone pulse (5 patients) or no specific treatment (5 patients).

Table 3: Evolution of graft inflammation found on 6-month surveillance biopsy

		12-MONTH BIOPSY		
6-MONTH BIOPSY		SCR	SCI	No inflammation or rejection
SCR	13	2	6	5
SCI	10	1	4	5

Overall, therefore, of these 23 patients, over half (56.5%) of those with SCR or SCI at 6 months were found to have persistent inflammation on a follow up biopsy at 12 months, indicating ongoing injury to graft despite conventional treatment.

It is not clear, therefore, that temporary intensification of the immunosuppression alters the course of the immune response to the graft. Additionally, these patients are all on dual or triple immunosuppressive therapy and any further increases in conventional immunosuppressive agents carry with them the risks of opportunistic infections and toxicities including BK virus infection and post-transplant lymphoproliferative disorder. Given the emergence of evidence supporting a key role for IL-6 and Th17 pathway in immune-mediated injury, we believe that targeting IL-6 or its signaling pathway can prove to be a useful clinical strategy to control inflammation and rejection in the graft and potentially facilitate improved long-term graft survival. Immune modulation via the administration of TCZ has the potential to suppress the immune response and alter the balance of the inflammatory cell infiltrate in the graft towards a regulatory rather than an effector phenotype. The advantages of intervening within the first year are that the renal allograft function is usually preserved and the injury is often acute and potentially reversible, so that the effect of immune modulation may be readily detected.

2.0 OBJECTIVES

To conduct a prospective randomized controlled study to examine the histologic and clinical outcomes in kidney transplant recipients with acute cellular rejection (Banff type 1a) or graft inflammation (Banff borderline change or mononuclear infiltrates in 10-50% of the cortical area without tubulitis) on kidney transplant biopsies within the first year post-transplant, who will be randomized to either continue their usual immunosuppression with or without pulse steroids (standard of care group) OR continue their usual immunosuppression with or without pulse steroids PLUS receive 4-weekly TCZ infusions (TCZ group) for 24 weeks.

2.1 Primary Objective

The primary objective is a 40% decrease in inflammation in the follow-up biopsies at the end of therapy.

2.2 Secondary Objective

The secondary objectives are to measure the effect of TCZ on

(a) Inflammatory urinary cytokines

(b) Renal allograft histologic biomarkers

(c) Development of donor specific anti-HLA antibody

(d) Incidence of acute rejection on biopsy at 6 and 12 months after study enrollment

3.0 STUDY DESIGN

3.1 Study Description

This is a prospective randomized controlled study of kidney transplant recipients with acute rejection or inflammation on kidney transplant biopsies within the first year post-transplant. AR for the purpose of this study is defined as Banff type 1a acute cellular rejection. Inflammation (AI) for the purpose of this study is defined as including Banff borderline change or 10-50% mononuclear inflammation (Banff i1-i2) without tubulitis.

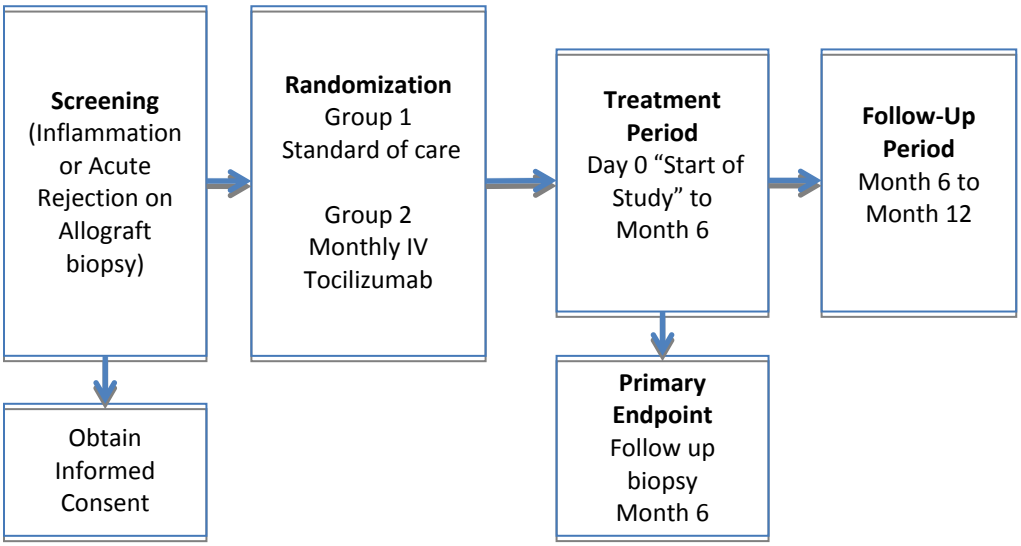
After enrollment, study participants subjects will be randomized to group 1 (standard of care group) or group 2 (TCZ group). Randomization will be stratified to ensure equal numbers of AR and AI in each group. Block randomization will be performed by the UCSF investigational pharmacy using computer-generated random numbers. The pathologist will be blinded to the randomization.

The study period will be 12 months (6 months of therapy plus 6 months of extended follow up- see Study Schema). Any episodes of infections, renal allograft dysfunctions, rejections or other clinical events during the study period will be treated per the usual standard of care.

All participants will be seen by the study investigator at monthly study visits during the treatment period and per usual standard of care in the follow up period. A focused history and physical exam will be performed, including queries for drug toxicities and signs/ symptom of infections. All participants will obtain laboratory tests at intervals of 4 weeks, consisting of a complete blood count, serum electrolytes, BUN and serum creatinine, fasting glucose, liver function tests and 12-hour trough tacrolimus levels. Lipid panels will be obtained at baseline, then every 3 months and at study termination. The outpatient electronic medical record will be queried twice weekly by the study coordinator for any new laboratory results on study participants. Laboratory data on all study participants will be reviewed weekly by the study PI.

The follow up surveillance biopsy will be performed at the end of therapy (6 months after study enrollment).

3.1.1 Study Schema



3.2 Rationale for Study Design and Dose

At UCSF Medical Center, transplant kidney biopsies are performed for cause (e.g, for renal graft dysfunction) or for surveillance (kidney transplant surveillance biopsies at 6 months post-transplant in all patients, and at 3-6 months following previous biopsies showing acute rejection or graft inflammation). Currently we perform 30-40 renal allograft biopsies per month. All kidney transplant biopsies are obtained under real-time ultrasound guidance using a 16-gauge automated biopsy needle. Two cores are generally obtained. All biopsies are read by UCSF Renal Pathology and are interpreted using the Banff 1997 criteria (updated 2007). C4d staining (for the diagnosis of acute antibody-mediated rejection) is done on all biopsies. Patients with biopsies showing AR or AI on surveillance or for-cause biopsies undergo repeat surveillance biopsies 3-6 months later. Patients with AR, whether clinical or subclinical, are usually treated with IV steroids. Due to uncertainty regarding the benefits of treatment in general and lack of data supporting the efficacy of increasing usual immunosuppressive agents, patients with AI (borderline change or nonspecific inflammation) are not currently treated with any specific therapy. Therefore, these patients who receive the standard of care treatment (steroids and/or continuation of their maintenance immunosuppressive regimen) form an ideal group in which to test the efficacy of treatment with TCZ. Based on available literature and our preliminary data, over 12 months approximately 90-100 patients will fulfill entry criteria and with a 50% enrollment rate, 50 patients are likely to consent to the trial.

The currently recommended dose of TCZ for adult patients with rheumatoid arthritis (the FDA approved indication) is 8 mg/kg given once every four weeks as an IV infusion. Given the accumulated efficacy and safety data for this dose, we will plan to use the same dose in kidney transplant recipients in this study.

3.3 Outcome Measures

Evaluation of response to TCZ therapy will be primarily based on histologic assessments as described below.

Semiquantative assessment of inflammation on kidney transplant biopsies for each subject at baseline and at 6 months follow-up will be performed using the Banff "i" and "t" scores. In addition, more precise estimates of the inflammation will be obtained using computer assisted image analysis to determine the inflammatory cell density per sq.mm in the renal cortex (glomeruli excluded) of baseline and follow-up biopsies which will include LCA, CD4, CD18, CD20, CD68, FoxP3, and T-bet. Results will be expressed as % of the cortex with inflammatory cells and the number of cells per sq mm of cortex. The % value for any variable (inflammation or fibrosis) on the qualifying biopsy will be taken as the baseline, and the increase or decrease in the variable at follow-up biopsy calculated = (% value at follow up minus % value at baseline)/ (% value at baseline).

In addition, we will perform quantitative in situ hybridization for IL-6 mRNA and protein expression on paraffin sections. Frozen or paraffin sections of the kidney biopsy will be stained (by immunofluorescence/ immunohistochemistry) for downstream IL-6 mediated inflammatory response genes (SAA2 and CRP), Janus kinase (JAK) and signal transducer and activator of transcription 3 (STAT3). We have recently validated an in situ hybridization analysis in biopsies of renal allografts. The IL6 signal is present with inflammation and tubulitis (acute cell mediated rejection) but is absent in acute or chronic antibody medicated rejection. The use of this assay may further validate the therapeutic effect of blockade of the IL-6 pathway.

For the measurement of urinary cytokines, urine samples will be collected from enrolled patients on day 0 and monthly till the end of the study at 12 months post-enrollment. The sample will be divided into supernatant and cell pellets prior to banking so that soluble mediators and gene expression by cellular sediments can be analyzed separately. The urine cell pellets will be analyzed using qRT-PCR for the presence of inflammatory mediators. We will use a combination of multiplex Luminex and ELISA to measure urinary protein in the supernatant, with focus on inflammatory mediators that are likely made by infiltrating leukocytes or induced by local inflammation and proteins that are reflective of kidney function, using a customized multiplex Luminex assay to profile inflammatory mediators reported to be altered in rejection or subclinical inflammation. Molecules to be profiled include CXCL-9 and CXCL-10, both of which have been reported to be elevated in the urine of patients with graft inflammation. PCR primers for these genes are available from Qiagen and a SYBR Green-based real-time PCR assay will be used to quantify the transcripts.

3.3.1 Primary Outcome Measure

The primary outcome measure will a 40% decrease in inflammation between kidney biopsies at baseline and 6 months later as measured by a composite endpoint of either a 1-point reduction in the Banff "i" or "t" scores or by computer-assisted quantitative image analysis of the percentage of renal cortex infiltrated with interstitial LCA (leukocyte common antigen)-positive cells.

3.3.2 Secondary Outcome Measures

(a) Change in the quantity and fraction of macrophages (CD68 positive cells) and regulatory T cells (FoxP3 positive cells) in the inflammatory infiltrate, as measured by computer-assisted quantitative image analysis, at baseline and 6 months follow-up.

(b) Change in the level of urinary cytokines CXCL-9 and CXCL-10 (also known as IP-10) at baseline and 6 months follow up.

(c) Change in the expression of intragraft IL6 (by in-situ hybridization).

(d) Incidence of de novo donor specific anti-HLA antibody between baseline and 6 months follow up.

(e) Incidence of clinical acute T-cell mediated rejections, defined as Banff type 1A acute rejection or greater, on biopsies performed for elevated serum creatinine between enrollment and 6 months follow up.

(f) Incidence of opportunistic infections, including bacterial urinary tract infections, pneumonia, sepsis and TB; viral infections with CMV, EBV, or BK virus; and any systemic fungal infections between enrollment and 6 months follow up.

(g) Estimated GFR by MDRD at 6 months and 12 months following enrollment.

(h) Death or graft loss at 6 months and 12 months following enrollment

3.4 End of Study

The study period will be a total of 12 months, including study drug administration for 6 months and an extended follow up period of 6 months for each participant after therapy is completed.

4.0 STUDY POPULATION

4.1 Overview

The target population includes kidney transplant recipients with stable kidney function at 6 months post-transplantation who are incidentally found to have acute rejection or graft inflammation on a biopsy within the first year post-transplant.

AR for the purpose of this study is defined as Banff type 1a acute cellular rejection.

AI for the purpose of this study is defined as including Banff borderline change or 10-50% total parenchymal mononuclear inflammation (Banff i1-i2) without tubulitis.

4.2 Inclusion Criteria

- All kidney transplant recipients with AR or AI (as defined above) on kidney transplant biopsy within the first year post-transplant.
- Maintenance immunosuppression regimens containing tacrolimus and MMF with or without prednisone.
- Ability to provide written informed consent for the study.
- Men and women of reproductive potential must agree to use an acceptable method of birth control during treatment and for six months after completion of treatment.

4.3 Exclusion Criteria

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

General:

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

Excluded Previous or Concomitant Therapy:

- Treatment with any investigational agent within 4 weeks (or 5 half-lives of the investigational drug, whichever is longer) of screening.
- Immunization with a live/attenuated vaccine within 4 weeks prior to baseline.
- Previous treatment with TCZ (an exception to this criterion may be granted for single dose exposure upon application to the sponsor on a case-by-case basis).
- Current treatment with other biological disease-modifying anti-rheumatic drug (bDMARD)
- Any previous treatment with alkylating agents such as chlorambucil, or with total lymphoid irradiation.

Exclusions for General Safety:

- Acute antibody mediated rejection or severe acute cellular rejection defined as exceeding Banff type 1a rejection on the qualifying biopsy or requiring therapy with Thymoglobulin.
- History of BK virus infection that is currently active (defined as detectable BK viremia >1000 copies/ml within 1 month prior to the biopsy).
- History of severe allergic or anaphylactic reactions to human, humanized or murine monoclonal antibodies.
- Evidence of serious uncontrolled concomitant cardiovascular, nervous system, pulmonary (including obstructive pulmonary disease), renal, hepatic, or endocrine (include uncontrolled diabetes mellitus) disease.
- History of diverticulitis, diverticulosis requiring antibiotic treatment or chronic ulcerative lower GI disease such as Crohn's disease, ulcerative colitis or other symptomatic lower GI conditions that might predispose to perforations.

- History of pre-existing CNS demyelination
- Current liver disease as determined by principal investigator unless related to primary disease under investigation.
- Known active current or history of recurrent bacterial, viral, fungal, mycobacterial or other infections (including but not limited to tuberculosis and atypical mycobacterial disease, Hepatitis B and C, and herpes zoster, but excluding fungal infections of nail beds).
- Any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks of screening or oral antibiotics within 2 weeks prior to screening.
- Active TB requiring treatment within the previous 3 years. Patients should be screened for latent TB and, if positive, treated following local practice guidelines prior to initiating TCZ. A negative screen for latent TB within the previous 2 years will be considered acceptable. Patients treated for tuberculosis with no recurrence in 3 years are permitted.
- Primary or secondary immunodeficiency (history of or currently active) unless related to kidney transplant immunosuppressive medications.
- Evidence of active malignant disease, malignancies diagnosed within the previous 10 years (including hematological malignancies and solid tumors, except basal and squamous cell carcinoma of the skin or carcinoma in situ of the cervix uteri that has been excised and cured), or breast cancer diagnosed within the previous 20 years.
- Pregnant women or nursing (breast feeding) mothers.
- Patients with reproductive potential not willing to use an effective method of contraception.
- History of alcohol, drug or chemical abuse within 1 year prior to screening.
- Patients with lack of peripheral venous access.

Laboratory Exclusion criteria (at screening):

- Serum creatinine > 1.6 mg/dL (141 µmol/L) in female patients and > 1.9 mg/dL (168 µmol/L) in male patients. Patients with serum creatinine values exceeding limits may be eligible for the study if their estimated glomerular filtration rates (GFR) are >30 ml/min/1.73 m^2.
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1.5 times upper limit of normal (ULN)
- Total Bilirubin > 1.5 times ULN
- Platelet count < 100 x 10^9/L (100,000/mm^3)
- Hemoglobin < 85 g/L (8.5 g/dL; 5.3 mmol/L)
- White Blood Cells < 3.0 x 10^9/L (3000/mm^3)
- Absolute Neutrophil Count < 2.0 x 10^9/L (2000/mm^3)
- BK virus quantitative DNA PCR (plasma) >1000 copies/ml

4.4 Immunization during TCZ therapy

Live/attenuated vaccines should not be given within 4 weeks prior to baseline and during the study as clinical safety has not been established. Because IL-6 inhibition may interfere with the normal immune response to new antigens, patients should be brought up to date on all recommended vaccinations, except for live vaccines, prior to initiation of therapy with TCZ.

4.5 Criteria for Premature Withdrawal

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

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

When applicable, patients will be informed of circumstances under which their participation may be terminated by the investigator without the patient's consent. The investigator may withdraw patients from the study in the event of intercurrent illness, adverse events, treatment failure, lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits), or any reason where it is felt by the investigator that it is in the best interest of the patient to be terminated from the study. The reason(s) for withdrawal will be documented and explained to the patient.

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

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

5.0 TREATMENT PLAN

Phase II clinical trial of TCZ plus standard of care vs. standard of care alone for kidney transplant recipients with AR or AI noted on kidney biopsy within the first year post-transplant.

After enrollment, subjects will be randomized to group 1 (standard of care group) or group 2 (TCZ group. Randomization will be stratified to include equal numbers of participants with AR and AI in each group. Block randomization will be performed by the UCSF investigational pharmacy using computer-generated random numbers. The pathologist will be blinded to the randomization.

In Group 1 (standard of care group):

- Participants with AI will continue their usual immunosuppression and not receive any specific intervention.

- Participants with AR will receive IV methylprednisolone pulse (500 mg IV daily for 3 doses) followed by oral prednisone taper over 2 weeks down to 5 mg prednisone per day in addition to continuing their usual immunosuppression

In Group 2 (TCZ group):

Participants will receive TCZ 8 mg/kg intravenously at four-week intervals for a total of 6 doses in addition to the standard of care described for group 1. This means that:

- Participants with AI will receive TCZ 8 mg/kg intravenously at four-week intervals for a total of 6 doses in addition to continuing their usual immunosuppression
- Participants with AR will receive TCZ 8 mg/kg intravenously at four-week intervals for a total of 6 doses. In addition, they will receive IV steroids and oral prednisone taper identical to SCR participants in group 1 and continue their usual immunosuppressive regimen.

Usual maintenance immunosuppression regimen is defined as follows:

- Recipients who are already receiving prednisone will continue it at 5 mg/day.

  Recipients on prednisone-free regimens will remain prednisone-free (if they have SCI) or start maintenance prednisone after pulse steroids (if they have SCR).

- Mycophenolate mofetil (MMF) dosing will be maintained or adjusted per standard of care to dose ranging from 500-3000 mg daily.
- Tacrolimus dosing will be maintained or adjusted to aim for trough levels of 4-10 mcg/L.

Although we believe that it is extremely unlikely that the addition of TCZ to standard post-transplant immunosuppression will increase the probability of fibrosis, we nevertheless used a two-tailed alternative hypothesis and set alpha at 0.05. Based on a review of the relevant literature and our previous experience, we anticipate that 50% of study participants randomized to group 1 (standard of care group) will manifest persistent inflammation at 12 months compared with 10% of study participants randomized to group 2 (TCZ group). We will have 83% power to detect an effect of this magnitude, i.e., a 40% absolute difference between groups with a sample size of 24 per group, or a total N=48.

Currently we perform 6-month surveillance biopsies of about 20-30 renal allografts per month. Based on available literature and our preliminary data, approximately 7-10 patients per month will have AR or AI on their biopsies. We aim to enroll 4-6 patients per month, so the period of recruitment will be approximately 12 months to accrue 48 patients. The study period will be 12 months (6 months of therapy + 6 months of follow up) so that total duration will be 24 months from the enrollment of the first subject.

This research study protocol allows the subject to receive up to 6 infusions of TCZ. Even if the treatment is shown to be of benefit, additional infusions of TCZ beyond that allowed in the protocol cannot be given to the subject while she/he is participating in this study.

6.0 STUDY MEDICATION

6.1 Tocilizumab

Tocilizumab (ACTEMRA®) is a recombinant humanized anti-human IL-6 receptor monoclonal antibody of the immunoglobulin IgG1κ (gamma 1, kappa) subclass with a typical H2L2 polypeptide structure. Each light chain and heavy chain consists of 214 and 448 amino acids, respectively. The four polypeptide chains are linked intra- and inter-molecularly by disulfide bonds. TCZ has a molecular weight of approximately 148 kDa.

TCZ is supplied as a sterile, preservative-free solution for intravenous (IV) infusion at a concentration of 20 mg/mL. TCZ is a colorless to pale yellow liquid, with a pH of about 6.5. Single-use vials are available containing 80 mg/4 mL, 200 mg/10 mL, or 400 mg/20 mL of TCZ. Injectable solutions of TCZ are formulated in an aqueous solution containing disodium phosphate dodecahydrate and sodium dihydrogen phosphate dehydrate (as a 15 mmol/L phosphate buffer), polysorbate 80 (0.5 mg/mL), and sucrose (50 mg/mL).

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

6.1.1 Tocilizumab Dosage and Administration

The recommended dose of TCZ for adult patients is 8 mg/kg given once every four weeks as an IV infusion. TCZ is currently approved for use alone or in combination with methotrexate and/or other disease modifying anti-rheumatic drugs.

TCZ will be diluted to 100 mL by a healthcare professional with sterile 0.9%w/v sodium chloride solution using aseptic technique. TCZ will be administered as an IV infusion over 1 hour. For individuals whose body weight is more than 100 kg, the maximum dose per infusion will not exceed 800 mg.

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

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

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

Given the rarity of infusion reactions, subjects may be monitored per discretion of the investigator for 30 minutes after the first infusion. They do not need monitoring after subsequent infusions.

6.1.2 Tocilizumab Storage

TCZ will not be used after the expiry date (EXP) shown on the pack.

For vials: Vials will be stored between 2ºC – 8ºC, will not freeze. The container will be kept in the outer carton in order to protect from light.

For prepared infusion solution: The prepared infusion solution of TCZ is physically and chemically stable in 0.9% w/v sodium chloride solution at 30ºC for 24 hours. From a microbiological point of view, the prepared infusion will be used immediately. If not used immediately, in-use storage times and conditions will not be longer than 24 hours at 2ºC – 8ºC, unless dilution has taken place in controlled and validated aseptic conditions.

6.1.3 Tocilizumab Overdosage

There are limited data available on overdoses with 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, the patient will be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions will receive appropriate symptomatic treatment.

6.2 Other Study Drugs

All study participants will be on standard post-transplant maintenance immunosuppression containing tacrolimus, MMF/ MPA, with or without prednisone. Study subjects will continue their maintenance immunosuppression as usual (if they have AI) or receive a pulse of IV methylprednisolone at 500 mg daily for 3 days (if they have AR). Subjects who are already receiving prednisone will continue it at 5 mg/day. Subjects on prednisone-free regimens will remain prednisone-free (if they have AI) or start maintenance prednisone after the pulse of IV methylprednisolone is completed (if they have AR). MMF or MPA doses will be continued as per standard of care with doses ranging from 500-3000 mg daily, with tacrolimus dosing adjusted to aim for trough levels of 4-10 mcg/L. All prescribers in the study will be required to enroll in the Mycophenolate REMS program as noted below in Section 7.2.2.

7.0 DOSE MODIFICATION/TOXICITY MANAGEMENT

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

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, blood pressure, and laboratory measurements at 1-monthly intervals. Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study.

7.1 Tocilizumab

Kidney Function and Acute Rejection

Significant nephrotoxicity has not been demonstrated in clinical trials of TCZ to date. However, the effect on kidney transplant function and the development of acute rejection is unknown. Kidney function will be monitored closely in study participants. If there is a suspicion for acute rejection, kidney biopsy will be performed as per usual standard of care and at the discretion of the PI. Patients who develop acute rejection will be withdrawn from the study.

Opportunistic Infections and Serious Infections

The most commonly reported infections (5% to 8% of patients) in clinical studies of rheumatoid arthritis were upper respiratory tract infections and nasopharyngitis. In the 24 week, controlled clinical studies, the rate of serious infections in the TCZ monotherapy group was 3.6 per 100 patient-years compared to 1.5 per 100 patient-years in the methotrexate group. The most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Among opportunistic infections, tuberculosis, cryptococcus, aspergillosis, candidiasis, and pneumocystosis have been reported with TCZ. TCZ will not be administered in patients with active infection. The effects of TCZ on CRP, neutrophils, and the signs and symptoms of infection will be considered when evaluating a patient for a potential infection. Vigilance for timely detection of serious infection will be maintained for kidney transplant recipients receiving TCZ as signs and symptoms of acute inflammation may be lessened due to concomitant immunosuppressive therapy. Patients will 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 will be interrupted and the patient will be withdrawn from the study.

Gastrointestinal Perforations

During the 24 week, controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100 patient-years with TCZ therapy. Reports of gastrointestinal perforation were primarily reported as complications of diverticulitis including generalized purulent peritonitis, lower GI perforation, fistula and abscess. Patients with known history or uncontrolled GI disease such as diverticulitis or inflammatory bowel disease are excluded from participation. Patients will be made aware of the symptomatology potentially indicative of diverticular disease, and will be instructed to alert their healthcare provider as soon as possible if these symptoms arise. Patients who develop GI perforations will be withdrawn from the study.

Demyelinating Disorders

The impact of treatment with TCZ on demyelinating disorders is not known; multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies of rheumatoid arthritis. Patients with known CNS demyelinating disorders will be excluded from participation. All subjects will be closely monitored for signs and symptoms potentially indicative of central demyelinating disorders. Treatment with TCZ will be interrupted during assessment of a potential demyelination event and if confirmed, patient will be withdrawn from the study.

Hematologic Abnormalities and Bleeding Events

Decreases in neutrophil and platelet counts have been observed following treatment with TCZ in combination with MTX.

In the 24 week, controlled clinical studies, decreases in neutrophil counts <1000/mm^3 occurred in 1.8% and 3.4% of patients in the 4 mg/kg and 8 mg/kg TCZ plus DMARD group, respectively, compared to 0.1% of patients in the placebo plus DMARD group. Approximately half of the instances of ANC <1000/mm^3 occurred within 8 weeks of starting therapy. In the same studies, decreases in platelet counts <100,000/mm^3 occurred in 1.3% and 1.7% of patients on 4 mg/kg and 8 mg/kg TCZ plus DMARD, respectively, compared to 0.5% of patients on placebo plus DMARD, without associated bleeding events. It is possible that there may be an increased risk of neutropenia and thrombocytopenia in kidney transplant recipients who are concurrently receiving MMF/ MPA, a known myelosuppressive agent.

The risk mitigation strategies for neutropenia and thrombocytopenia are summarized in Tables 4 and 5, respectively.

Table 4 : Neutropenia risk mitigation

ANC (cells/mm^3)	Action
> 1000	Maintain dose.
500 – 1000	Interrupt TCZ dosing. When ANC increases to > 1000, resume TCZ at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
< 500	Discontinue TCZ.

ANC = absolute neutrophil count

Patients withdrawn from TCZ treatment due to a reduced neutrophil count will be monitored for signs of infection, with treatment as deemed appropriate by the PI, and will 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 PI), a hematology referral will be considered.

Table 5: Thrombocytopenia risk mitigation

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

Patients withdrawn from TCZ treatment due to a reduced platelet count will 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 PI), a hematology referral will be considered.

Elevated Liver Enzymes and Hepatic Events

Treatment with TCZ was associated with a higher incidence of transaminase elevations in clinical studies in rheumatoid arthritis, particularly when it was used in combination with DMARDs. Mild elevations (up to 3X ULN) of ALT and AST were common, seen in 36% and 22% respectively of patients receiving TCZ monotherapy, and especially frequent when TCZ 8 mg/kg was used in combination with DMARDs (48% and 41% respectively compared to 23% and 17% with placebo + DMARDs). Severe elevations of ALT and AST (to >5X ULN) were seen in 1.5% and 0.2% receiving TCZ 8 mg/kg plus DMARDs vs. 0.3% and <0.1% in the group receiving placebo plus DMARDs. These elevations did not result in apparent permanent or clinically evident hepatic injury in clinical trials. The effects on ALT and AST when TCZ is used in combination with tacrolimus and mycophenolate mofetil/ mycophenolic acid are not known.

Table 6: Risk mitigation for abnormal liver enzymes

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

Patients withdrawn from TCZ treatment due to elevated liver function tests will 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 PI), an ultrasound and/or liver biopsy will be considered.

Cardiovascular Events and Elevated Lipids

Increases in lipid parameters (total cholesterol, LDL, HDL, triglycerides) were observed at 6 weeks following initiation of TCZ in the controlled 24 week clinical trials and remained stable thereafter. Mean increased in LDL, HDL and LDL/HDL ratio at week 24 in the TCZ 8 mg/kg plus DMARD group were 20 mg/dl, 5 mg/dl and 0.15 respectively. Elevated lipids responded to lipid lowering agents. Patients with kidney disease have an increased risk for cardiovascular disorders; therefore, risk factors for cardiovascular disease (e. g., hypertension, hyperlipidemia) will be managed as part of their standard of care.

Malignancies

Exposure-adjusted incidence of malignancies was similar in the TCZ groups (1.32 events per 100 patient-years) and in the placebo plus DMARD group (1.37 events per 100 patient-years). There is a known increased incidence of malignancies associated with post-kidney transplant immunosuppression. Although no imbalance of malignancies was observed in controlled clinical trials of TCZ, malignancies may become a concern when it is used concomitantly with post-kidney transplant immunosuppression. TCZ will 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).

Infusion Reactions, Hypersensitivity or Anaphylaxis:

An infusion/dose reaction is defined as an adverse event occurring during and within 24 hours after the infusion or subcutaneous injection of TCZ. This may include hypersensitivity reactions or anaphylactic reactions. In the 24 week, controlled clinical studies, infusion reactions were reported in 8% and 7% of patients in the 4 mg/kg and 8 mg/kgTTCZ plus DMARD group, respectively, compared to 5% of patients in the placebo plus DMARD group. The most frequently reported event for both doses during the infusion was hypertension (1% for both doses), while the most frequently reported event occurring within 24 hours of finishing an infusion were headache (1% for both doses) and skin reactions (1% for both doses), including rash, pruritus and urticaria. These events were not treatment limiting. Hypersensitivity reactions requiring treatment discontinuation, including anaphylaxis, associated with TCZ were reported in 0.1% (3 out of 2644) in the 24 week, controlled trials and in 0.2% (8 out of 4009) in the all-exposure population. These reactions were generally observed during the second to fourth infusion of TCZ.

Signs of a possible hypersensitivity reaction include but are not limited to: fever, chills, pruritus, urticaria, angioedema, skin rash, cardiopulmonary reactions, including chest pain, dyspnea, hypotension or hypertension.

Healthcare professionals administering TCZ infusions will 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. Study subjects will be

instructed to seek medical attention if they experience symptoms of a hypersensitivity reaction outside of the clinic.

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

Viral Reactivation

Viral reactivation has been reported with immunosuppressive biologic therapies and cases of herpes zoster exacerbation were observed in clinical studies with TCZ. No cases of Hepatitis B reactivation were observed in the trials; however patients who screened positive for hepatitis were excluded. Reactivation of viral and other serious infections (e.g. EBV or TB) has been observed with standard post-transplant immunosuppression and patients will be monitored carefully during the study for this event.

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) will be monitored as doses may need to be adjusted to maintain their therapeutic effect. In particular, attention will be paid to the levels of tacrolimus, a CYP3A4 substrate, and doses will be adjusted as needed to maintain levels of 4-10 mcg/L. Given long elimination half-life (t1/2) of TCZ, the effect on CYP450 enzyme activity may persist for several weeks after stopping therapy.

Reproductive Issues

Adequate and well-controlled studies with TCZ have not been conducted in pregnant women. All females of reproductive potential will be required to use acceptable contraception for the duration of the study. All females of reproductive potential will screened for pregnancy prior to enrollment and before infusion of every dose of TCZ. If pregnancy is discovered, participants will be terminated from the study. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to TCZ during pregnancy. The study investigator will register any pregnant patients and pregnant women will be encouraged to register themselves by calling 1-877-311-8972.

7.2 Other Study Drugs

7.2.1 Post-transplant maintenance immunosuppression

The standard post-transplant immunosuppressive regimen which the subjects have been on prior to enrollment in the study will be continued during the study. Enrollment will include all kidney transplant recipients with graft inflammation who are on maintenance immunosuppressive regimens containing tacrolimus, mycophenolate mofetil/ mycophenolic acid with or without prednisone. At UCSF, typically about 30% of kidney transplant recipients are maintained on prednisone free immunosuppression. Therefore, some study subjects will be on prednisone (5 mg daily) at the time of enrollment and others will not be on prednisone. Those who are on prednisone will remain on it and those who are not on prednisone will remain prednisone free (if they have AI) or receive pulse IV methylprednisolone and start maintenance prednisone (if they have AR). During randomization, we will aim to keep the proportion of patients on prednisone equal in both arms. As with standard post-transplant care, all participants will undergo a physical exam, medical interview and laboratory testing (complete blood count, serum electrolytes, BUN and serum creatinine, fasting glucose, liver function tests and 12-hour trough tacrolimus levels) every month and they will be queried and examined for known drug toxicities and signs/ symptom of infections. Doses of tacrolimus, MMF/ MPA acid and prednisone will be modified if needed to address toxicity or infectious concerns.

6.2.2 Mycophenolate REMS

All prescribers participating in the study will be required to enroll in the FDA Mycophenolate REMS (risk evaluation and mitigation strategy) program. Of note, all study participants will already have been on a maintenance regimen containing MMF/MPA and will not be started on it as part of the study.

Use of MMF/MPA during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations. Females of reproductive potential will be made aware of these risks and will be counseled regarding pregnancy prevention and planning. All females must be willing to use acceptable contraception during the entire period of the study. Patients will be made aware that MMF/MPA reduces blood levels of the hormones in the oral contraceptive pill and could theoretically reduce its effectiveness. Urine pregnancy test is part of the screening laboratory tests and will be repeated at each follow-up visit. Results of all pregnancy tests will be discussed with the patient.

For those females who are discovered to be pregnant either at study screening or enrollment or during the study and who are on MMF/MPA or within 6 weeks of discontinuing therapy, the study investigators will report the pregnancy to the Mycophenolate Pregnancy registry (1-800-617-8191) and strongly encourage the patient to enroll in the pregnancy registry. When appropriate, pregnant patients will be switched to alternative immunosuppression with less potential for embryofetal toxicity after a discussion of maternal and fetal risks and benefits.

8.0 CRITERIA FOR SUBJECT DISCONTINUATION

8.1 Tocilizumab-Specific Criteria

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

- Anaphylaxis or hypersensitivity reaction or requires an interruption of the study drug because of symptoms of anaphylaxis or hypersensitivity (TCZ will 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

8.2 General Criteria

- Biopsy proven acute rejection during the study
- Serious infection including but not limited to sepsis, BK viremia (>10,000 copies/m/L), CMV infection, EBV infection, TB, or systemic fungal infections during the study
- Inability of subject to comply with study requirements
- Determination by the investigator that it is no longer safe for the subject to continue therapy

9.0 STOPPING RULES

9.1 Ongoing Review

The progress of the study will be monitored by a two-member DSMB, which includes 2 transplant surgeons (Dr. Ryutaro Hirose and Dr. Chris Freise). The DSMB will be chartered to perform independent oversight for the trial through regular review of enrollment and safety information provided in tables, listings and figures generated from the clinical database. If the trial is suspended for any reason they will monitor the reassessment and potential restarting of the trial.

The DSMB will have the authority to suspend the trial. The trial will be suspended if the board determines that the risks to study participants exceed the originally described risks and/or that modifications to the protocol are needed to minimize the risks. The DSMB will receive safety data at least every 6 months following treatment of first subject. The DSMB will be informed immediately if a criterion for stopping the trial is met. The DSMB will also be informed if the principal investigator or co-investigator judges at any time that a review of safety experience is warranted.

9.2 Stopping Rule Guidance

The following will lead to suspension of enrollment and to review:

- Any unexpected death or death from opportunistic infection in the TCZ patients
- Any event which in the opinion of the clinical investigators merits review prior to further enrollment
- Graft loss due to thrombosis in the TCZ patients

If any of these criteria are met, the principal investigator and sub-investigators will conduct a review of all safety data and a report will be provided to the DSMB, IRB, and FDA. Enrollment will not resume until these agencies approve reopening the enrollment.

10.0 CLINICAL AND LABORATORY EVALUATIONS

All participants will have 12 months of monitoring (6 month of therapy plus extended follow up for 6 months) as outlined in the schedule of assessments. Any episodes of infections, renal allograft dysfunctions, rejections or other clinical events during the study period will be treated per the usual standard of care.

Physical Exam: All participants will be seen by the study PI or co-investigator at monthly study visits during treatment and per usual standard of care in the extended follow up period. A focused history and physical exam will be performed, including queries for drug toxicities and signs/ symptom of infections.

Laboratory testing: All participants will obtain laboratory tests at intervals of 4 weeks, consisting of a complete blood count, serum electrolytes, BUN and serum creatinine, fasting glucose, and 12-hour trough tacrolimus levels. Liver function tests (total bilirubin, AST and ALT) will be monitored monthly while on therapy and every 3 months in the follow up period. Lipid parameters (total cholesterol, LDL, triglycerides, HDL) will be assessed once 4-8 weeks after the initiation of TCZ therapy, and then every 3 months till the end of the study. For females of reproductive potential, urine pregnancy tests will be obtained at screening and every follow up study visit. The outpatient electronic medical record will be queried once weekly by the study coordinator for any new laboratory results on study participants. Laboratory data on all study participants will be reviewed weekly by the study PI.

Safety Monitoring: Any episodes of infections, renal allograft dysfunctions, rejections or other clinical events during the study period will be recorded. These episodes will be treated per the usual standard of care. An interim analysis will be performed once 50% of subjects are enrolled to capture any excess adverse events.

10.1 Visit windows

All scheduled study visits must occur within the time limits specified in Table 7. Visits that occur outside of the specified windows will be considered protocol deviations.

Table 7

VISIT	WINDOW
Visit -1	Day -28 to day 0
Visit 0	No window
Visit 1 through 5	±3 days
Visit 6	± 5 days
Visit 7-12	± 7 days

10.2 Schedule of Assessments

Part 1: First 6 months (On therapy)

Time from enrollment →	Screening (Variable)	Baseline (Day 0)- At enrollment	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Visit number	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Kidney Biopsy	**X**							**X**
Inclusion/ Exclusion criteria	**X**							
IV methylprednisolone pulse		**X**						
Tocilizumab infusion in group 2 only		**X**	**X**	**X**	**X**	**X**	**X**	
Physical Exam	**X**	**X**	**X***	**X***	**X***	**X***	**X***	**X***
Safety Monitoring		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Laboratory Tests								
CBC with differential, chem-10, tacrolimus levels	**X**		**X**	**X**	**X**	**X**	**X**	**X**
LFT, BK virus PCR	**X**		**X**	**X**	**X**	**X**	**X**	**X**
Lipid panel	**X**		**X**		**X**			**X**
Regulatory T cells		**X**			**X**			**X**
Donor specific antibody		**X**						**X**
PK/PD, Immunogenicity/Anti-TCZ testing in group 2 only		**X**			**X**			**X¶**
Urine pregnancy test	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Urine cytokines		**X**	**X**	**X**	**X**	**X**	**X**	**X**

*In group 2 only. Physical exam frequency can be per usual standard of care in group 1
¶Or at termination of therapy

Part 2: 6-12 months (extended follow-up period)

Time from enrollment →	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Visit number	7	8	9	10	11	12
Physical Exam*			**X**			**X**
Safety Monitoring			**X**			**X**
CBC with differential, chem-10, tacrolimus levels	**X**	**X**	**X**	**X**	**X**	**X**
LFT, lipid panel			**X**			**X**
Urine pregnancy test			**X**			**X**

*Or per usual standard of care

10.3 Pre-Treatment Evaluations in both groups

The following evaluations will be performed within 1 month prior to the date of each patient's initial treatment with TCZ:

- Pregnancy test (serum or urine) for women of childbearing potential.
- Medical history and documentation of the rationale for treatment of the patient's disease with TCZ.
- Physical examination, including vital signs, blood pressure, performance status and toxicity assessment.
- Hematology: complete blood count (CBC) with differential and platelet count.
- Serum Chemistries: BUN, creatinine, electrolytes (Na, K, Cl, CO2, Ca, Mg, Phos), fasting glucose, total bilirubin, SGOT(AST), and SGPT (ALT)
- Tacrolimus trough level
- Lipid Panel (total cholesterol, triglycerides, LDL, HDL)
- Serum BK virus quantitative PCR

10.3.1 Evaluations During Treatment in group 2 (TCZ group)

Baseline (prior to 1st dose):

- Anti-TCZ antibody testing
- PK/ PD
- Pregnancy test (serum or urine) for women of childbearing potential
- Regulatory T cell count
- Donor specific anti-HLA antibody

Every month:

- Pregnancy test (serum or urine) for women of childbearing potential.
- Physical examination, including vital signs, blood pressure, performance status and toxicity assessment.
- Hematology: complete blood count (CBC) with differential and platelet count.
- Serum Chemistries: BUN, creatinine, electrolytes (Na, K, Cl, CO2, Ca, Mg, Phos), fasting glucose, total bilirubin, SGOT(AST), and SGPT (ALT)
- Tacrolimus trough level

Every 3 months:

- Serum BK virus quantitative PCR
- Regulatory T cell count

At 1 month, 3 months and then every 3 months:

- Lipid Panel

At 6 months:

- Donor specific anti-HLA antibody

All patients will provide samples for anti-TCZ antibody testing as described in the Schedule of Assessments (baseline, 12 weeks and at termination of therapy). In addition, samples for PK/PD will be tested for each time point when an anti-TCZ antibody test is done. All patients experiencing events related to serious hypersensitivity or anaphylactic reactions that cause the patient to be withdrawn from TCZ treatment will need to have anti-TCZ and PK/PD testing at time of event, and also 6 weeks after the last dose for anti-TCZ and PK/PD testing. All samples collected for immunogenicity assays will be tested using a screening assay and, if positive, by a confirmation assay to determine specificity. If the confirmation assay is positive, a neutralizing assay will be performed to test for the ability to inhibit the activity of TCZ. Reports of the results of these analyses will be provided by Genentech to the investigator for patients testing positive for anti-TCZ antibodies. Samples will be shipped as described in Appendix B.

10.3.2 Evaluations During Treatment In Group 1(Standard of Care group)

Baseline (within 1 month after randomization):

- Donor specific anti-HLA antibody
- Regulatory T cell count

Every month:

- Hematology: complete blood count (CBC) with differential and platelet count.
- Serum Chemistries: BUN, creatinine, electrolytes (Na, K, Cl, CO2, Ca, Mg, Phos), fasting glucose, total bilirubin, SGOT(AST), and SGPT (ALT)
- Tacrolimus trough level

Every 3 months:

- Serum BK virus quantitative PCR
- Regulatory T cell count

At 6 months

- Donor specific anti-HLA antibody

Per usual standard of care:

- Pregnancy test (serum or urine) for women of childbearing potential.
- Physical examination, including vital signs, blood pressure, and performance status.

10.4 Post-Treatment Evaluations in both groups

Subjects will continue to obtain monitoring for an additional 6 months after therapy is completed. This will include:

- Medical interview and physical examination every 3 months or per usual standard of care.
- Pregnancy test (serum or urine) for women of childbearing potential at every study visit
- Complete blood count (with differential and platelet count) every month
- Serum chemistries: BUN, creatinine, electrolytes (Na, K, Cl, CO2, BUN, creatinine, Ca, Mg, Phos), fasting glucose every month
- Tacrolimus trough levels every month
- Total bilirubin, AST and ALT every 3 months
- Lipid panel every 3 months

11.0 REPORTING OF ADVERSE EVENTS

11.1 Adverse Event and Reporting Definitions

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

Additionally, an AE can be any of the following:

Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)

Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.

Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram, x-ray) that is associated with symptoms or leads to a change in TCZ or concomitant treatment or discontinuation from TCZ.

In the event of an adverse event, the first concern will be for the safety of the subject. Investigators are required to report to Genentech Drug Safety any **serious adverse event**, and non-serious adverse events of special interest, whether **expected** or **unexpected**, and whether or not considered related to the TCZ.

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

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

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

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

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

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

Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. 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 theTCZ (see following guidance), and actions taken.

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

Yes

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

No

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

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

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

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

Eliciting Adverse Events

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

"How have you felt since your last clinical visit?"

"Have you had any new or changed health problems since you were last here?"

Specific Instructions for Recording Adverse Events

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

a. Diagnosis vs. Signs and Symptoms

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

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 5.1.2), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death". This includes death attributed to progression of underlying disease.

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

c. Preexisting Medical Conditions

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

d. Hospitalizations for Medical or Surgical Procedures

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

Hospitalizations for the following reasons do not require reporting:

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

e. Pregnancy

If a female subject becomes pregnant while receiving investigational therapy or within 90 days after the last dose ofTCZ, a report will 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, will always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to TCZ will be reported as an SAE. A Clinical Trial Pregnancy Reporting Form will be completed by the sponsor within 24 hours after learning of the pregnancy Pregnancy should not be recorded on the Adverse Event CRF. The sponsor will counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the will should continue until conclusion of the pregnancy.

Abortions

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

Congenital Anomalies/Birth Defects

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

f. Post-Study Adverse Events

The investigator will expeditiously report any SAE or non-serious AESI occurring after a subject has completed or discontinued study participation if attributed to priorTCZ exposure regardless of how

much time has elapsed since study participation. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this will be reported as an SAE. All unrelated SAEs must be reported during the study and up to 3 months after the last dose ofTCZ, even if the study has been closed.

g. Reconciliation

The sponsor agrees to conduct reconciliation for the product. Genentech and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange monthly line listings of cases received by the other party. If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.

11.2 Reporting of Serious Adverse Events Associated with Tocilizumab

Immediate Reporting Requirements

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

SAEs.

Non-serious and serious AEs of special interest.

All Non-Serious Adverse Events originating from the Study will be forwarded in a quarterly report to Genentech.

Pregnancies.

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

New signs or symptoms or a change in the diagnosis.

Significant new diagnostic test results.

Change in causality based on new information.

Change in the event's outcome, including recovery.

Additional narrative information on the clinical course of the event.

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

All serious adverse events (SAEs) for which there is a reasonable possibility the experience may have been caused by TCZ (this applies to both expected and unexpected events) should be recorded on a MedWatch 3500A Form and faxed to:

Genentech Drug Safety

Tel: (888) 835-2555

Fax: (650) 225-4682 or (650) 225-5288

This must be reported to Genentech within 24 hours.

AND:

Principal Investigator: Flavio Vincenti, M.D.

Telephone: 415-353-1322

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AND:

IRB Contact information:

UCSF-Committee on Human Research

Telephone: 415-476-1814

Fax: 415-502-1347

E-mail: chr@ucsf.edu

MedWatch 3500A Reporting Guidelines:

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

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

Follow-up information:

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

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

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the subject for whom and adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above.

11.3 Actemra Events of Special Interest

Adverse events of special interest (non-serious and serious) are required to be reported by the Investigator to Genentech Drug Safety within 24 hours after learning of the event (see Section 11.2 for reporting instructions**). Non-serious and serious AEs** of special interest for this study include the following:

Infections including all opportunistic infections and non-serious infections as defined by those treated with IV anti-infectives

Myocardial infarction/acute coronary syndrome.

GI perforation and related events.

Malignancies.

Hypersensitivity reactions.

Demyelinating disorders.

Stroke.

Bleeding events.

Hepatic events.

Guided questionnaires have been prepared for the AEs of special interest.

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

11.4 Study Close Out

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

Clinical Operations Contact:

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

12.0 EVALUATION OF RESPONSE

Evaluation of response to TCZ therapy will be primarily based on histologic assessments as described below.

Semiquantative assessment of inflammation on kidney transplant biopsies for each subject at baseline and 6 months follow up will be performed using the Banff “t” and “i” scores. Computer assisted image analysis will be used to calculate the quantity of interstitial LCA positive cells, CD68 positive cells and FoxP3 positive cells on biopsies at 6 months and 12 months and the results will be expressed as a percentage (%) of the total cortex (for LCA positive cells and collagen expression) or as a percentage (%) of the total number of cells (for CD68 positive and FoxP3 positive cells). The % value for any variable (inflammation or fibrosis) at 6 months will be taken as the baseline, and the increase or decrease in the

variable at 12 months calculated = (% value at 12 months minus % value at 6 months)/ (% value at 6 months)

In addition, we will perform quantitative in situ hybridization for IL-6 mRNA and protein expression on paraffin sections. Frozen or paraffin sections of the kidney biopsy will be stained (by immunofluorescence/ immunohistochemistry) for downstream IL-6 mediated inflammatory response genes (SAA2 and CRP), Janus kinase (JAK) and signal transducer and activator of transcription 3 (STAT3).

For the measurement of urinary cytokines, urine samples will be collected from enrolled patients on day 0, monthly till the end of the treatment at 12 months post-transplant, and on the day of the biopsy. The sample will be divided into supernatant and cell pellets prior to banking so that soluble mediators and gene expression by cellular sediments can be analyzed separately. The urine cell pellets will be analyzed using qRT-PCR for the presence of inflammatory mediators. We will use a combination of multiplex Luminex and ELISA to measure urinary protein in the supernatant, with focus on inflammatory mediators that are likely made by infiltrating leukocytes or induced by local inflammation and proteins that are reflective of kidney function, using a customized multiplex Luminex assay to profile inflammatory mediators reported to be altered in rejection or subclinical inflammation. Molecules to be profiled include CXCL-9 and CXCL-10, both of which have been reported to be elevated in the urine of patients with graft inflammation. PCR primers for these genes are available from Qiagen and a Sybrgreen-based real-time PCR assay will be used to quantify the transcripts.

The primary endpoints are

(a) A 40% decrease in the quantity of inflammation between kidney biopsies at baseline and 6 months follow up as measured by Banff “ti” scores and by computer-assisted quantitative image analysis of interstitial LCA (leukocyte common antigen)-positive cells.

(b) The change in the quantity and fraction of macrophages (CD68 positive cells) and regulatory T cells (FoxP3 positive cells) in the inflammatory infiltrate, as measured by computer-assisted quantitative image analysis, at baseline and 6 months follow up.

13.0 STATISTICAL CONSIDERATIONS

13.1 Determination of Sample Size

The main question is a comparison of proportion of subjects with persistent inflammation in group 1 (standard of care) vs. group 2 (TCZ group).

The null hypothesis is:

Ho: The proportion of participants with persistent inflammation at 6 months follow up in group 1 is the same as the proportion of participants with persistent inflammation at 6 months follow up in group 2.

The alternative hypothesis is:

Ha: The proportion of participants with persistent inflammation at 6 months follow up in group 1 is different from the proportion of participants with persistent inflammation at 6 months follow up in group 2.

Although we believe that it is extremely unlikely that the addition of TCZ to standard post-transplant immunosuppression will increase the probability of fibrosis, we nevertheless used a two-tailed alternative hypothesis and set alpha at 0.05. Based on a review of the relevant literature and our previous experience noted above, we anticipate that 50% of study participants randomized to group 1 (standard of care group) will manifest persistent inflammation at 6 months follow up compared with 10% of study participants randomized to group 2 (TCZ group). We will have 83% power to detect an effect of this magnitude, i.e., a 40% absolute difference between groups with a sample size of 24 per group, or a total N=48. Once consent is obtained, patients will be randomized (1:1) by block randomization to group 1 or group 2.

13.2 Analysis of Study Endpoints

Continuous data will be expressed as mean +/- standard deviations and dichotomous data as percentages. The chi-square test will be used to examine differences in categorical data (e.g., incident acute rejections) and the Mann-Whitney U-test to examine differences in continuous variables (e.g. mean Banff scores) between groups as these variables are not normally distributed. To determine differences between % of inflammation and change in % inflammation and fibrosis, comparison between groups will be made with a t-test or Mann-Whitney U test, depending on the distribution of the data). We will consider P values of 0.05 to be statistically significant.

14.0 RETENTION OF RECORDS

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

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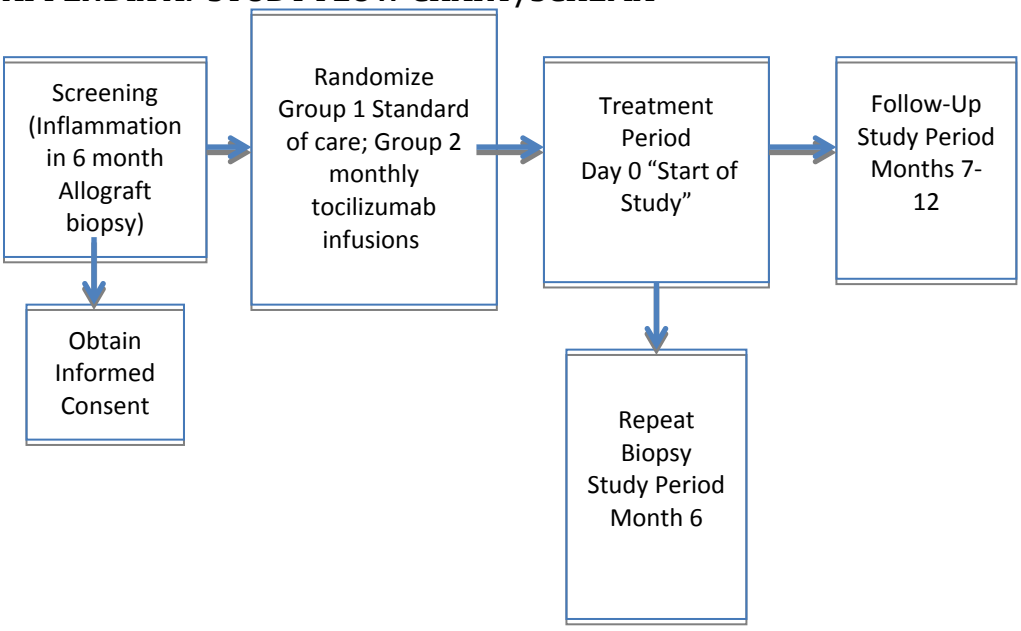
16.0 APPENDIX

APPENDIX A: STUDY FLOW CHART/SCHEMA



APPENDIX B: BANFF 1997 QUANTITATIVE CRITERIA FOR RENAL ALLOGRAFT BIOPSIES

Tubulitis "t" score

t0: No mononuclear cells in tubules

t1, t2, and t3: Foci with 1-4 cells, 4-10 and >10 cells/ tubular cross-section

Mononuclear cell interstitial inflammation “i” score in unscarred parenchyma

i0: <10% of unscarred parenchyma

i1, i2, and i3: 10-25%, 26-50% and >50% of parenchyma inflamed

Mononuclear cell inflammation “ti” score in total parenchyma (scarred and unscarred)- Banff 07 update

ti0: <10% of total parenchyma

ti1, ti2, and ti3: 10-25%, 26-50% and >50% of parenchyma inflamed

Interstitial fibrosis “ci” score

ci0: Interstitial fibrosis in up to 5% of cortical area

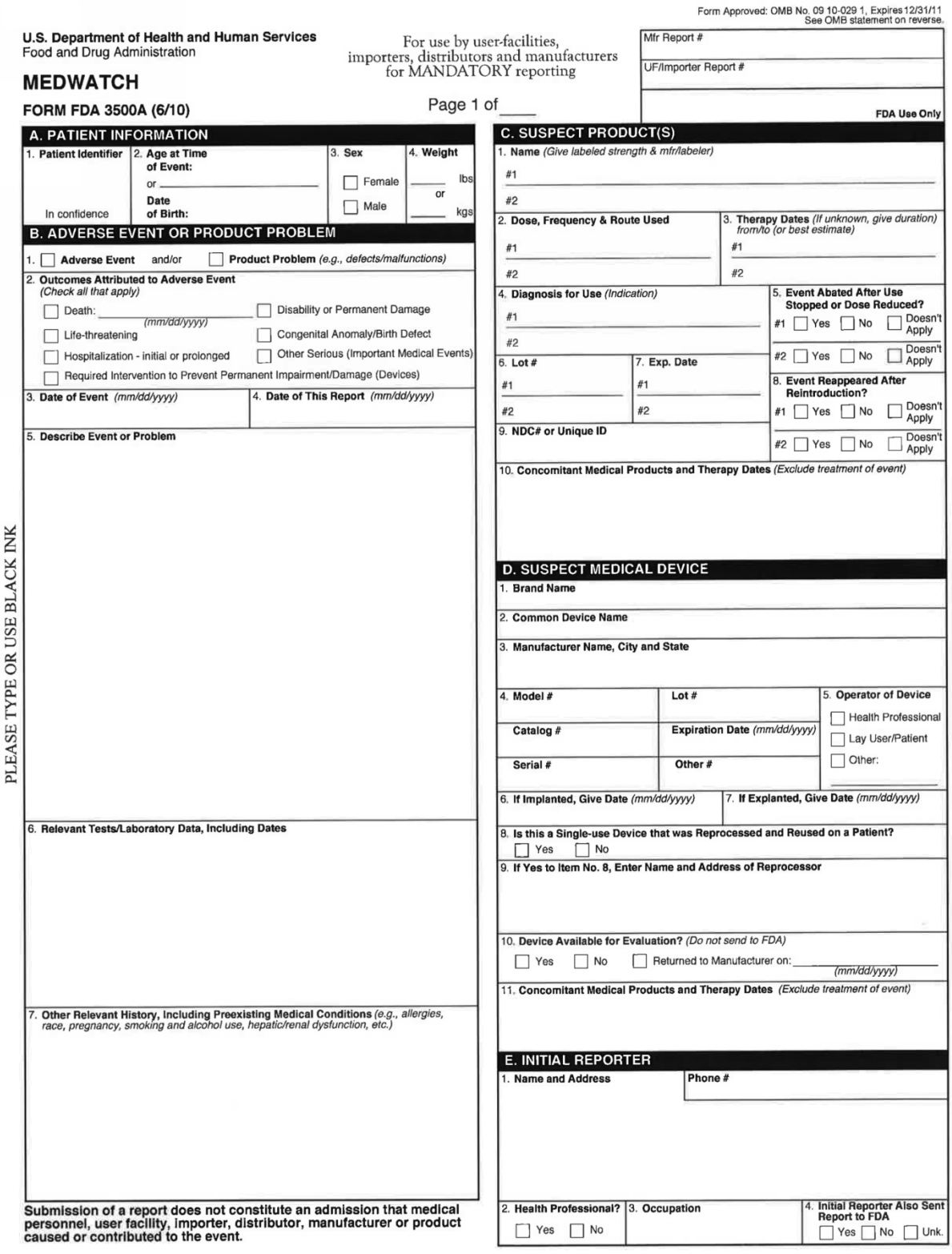
ci1, ci2, and ci3: Interstitial fibrosis in 6-25%, 26-50% and >50% of cortical area

Tubular atrophy “ct” score

ct0 No tubular atrophy

ct1, ct2, and ct 3: Tubular atrophy <25%, 26-50%, and >50% of the area of cortical tubules

APPENDIX C: FDA MEDWATCH 3500A FORM



Form Approved: OMB No. 09 10-029 1, Expires 12/31/11
See OMB statement on reverse.

U.S. Department of Health and Human Services
Food and Drug Administration

MEDWATCH

FORM FDA 3500A (6/10)

For use by user-facilities, importers, distributors and manufacturers for MANDATORY reporting

Page 1 of ____

Mfr Report #

UF/Importer Report #

FDA Use Only

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier — In confidence
2. Age at Time of Event: or Date of Birth:
3. Sex — ☐ Female ☐ Male
4. Weight — ____ lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☐ Adverse Event and/or ☐ Product Problem *(e.g., defects/malfunctions)*

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)*
☐ Disability or Permanent Damage
☐ Life-threatening
☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged
☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*

4. Date of This Report *(mm/dd/yyyy)*

5. Describe Event or Problem

6. Relevant Tests/Laboratory Data, Including Dates

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)*

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

C. SUSPECT PRODUCT(S)

1. Name *(Give labeled strength & mfr/labeler)*
#1
#2

2. Dose, Frequency & Route Used
#1
#2

3. Therapy Dates *(If unknown, give duration)* from/to *(or best estimate)*
#1
#2

4. Diagnosis for Use *(Indication)*
#1
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #
#1
#2

7. Exp. Date
#1
#2

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC# or Unique ID

10. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

D. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

3. Manufacturer Name, City and State

4. Model # / Lot # / Catalog # / Expiration Date *(mm/dd/yyyy)* / Serial # / Other #

5. Operator of Device
☐ Health Professional
☐ Lay User/Patient
☐ Other: ____

6. If Implanted, Give Date *(mm/dd/yyyy)*

7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

10. Device Available for Evaluation? *(Do not send to FDA)*
☐ Yes ☐ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

11. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

E. INITIAL REPORTER

1. Name and Address

Phone #

2. Health Professional? ☐ Yes ☐ No

3. Occupation

4. Initial Reporter Also Sent Report to FDA ☐ Yes ☐ No ☐ Unk.

APPENDIX D: 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) 225-5288

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 ___