PROTOCOL

STUDY TITLE:

A Phase I/II Trial to Evaluate the Safety and Tolerability of Clazakizumab® (Anti-IL-6 monoclonal) to Eliminate Donor Specific HLA Antibodies (DSAs) and Improve Transplant Rates in Highly-HLA Sensitized Patients awaiting Renal Transplant.

Study Drug

Clazakizumab (Anti-IL-6 monoclonal)

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Abbreviations

Abbreviation	Description	Abbreviation	Description
ABMR	Antibody mediated rejection	SAE	Serious adverse events
PLEX	Plasmapheresis	LFT	Liver function test
cABMR	Chronic active ABMR	4W	4 weeks
TG	Transplant glomerulopathy	eGFR	Estimated Glomerular filtration rate
DeKAF	Deterioration in Kidney Allograft Function (DeKAF)	ELISA	Enzyme linked immunosorbtion assay
C4d	Complement-4d protein	PCRs	Polymerase chain reaction
DSAs	Donor specific antibody	EBV	Epstein barr virus
HLA	Human leukocyte antigen	CMV	Cytomegalovirus
FDA	Food & Drug Administration	BKV	Polyoma BK virus
IL-6	Interleukin-6	CG3	Chronic glomerulitis level 3 (severe)
IL-6R	Interleukin-6 Receptor	HBV	Hepatitis B virus
Anti-IL-6R	Anti-interluekin-6 Receptor	HCV	Hepatitis C virus
T_{reg}	T-regulatory cells	RIBA	Recombinant immunoblot assay
T_{fh}	T-follicular cells	TB	Tuberculosis
IgG	Immunoglobulin	WBC	White blood cell
dnDSA	De novo DSA	Hgb	Hemoglobin
SLE	Systemic lupus erythematosus	SGOT	Serum glutamic oxaloacetic transaminase
IgA	Immunoglobulin A	SGPT	Serum glutamic-pyruvic transaminase
CTLA4-Ig	Cytotoxic T-lymphocyte-assocated protein 4	PTLD	Post-transplant lymphoproliferative disorder
Th17	T-helper type 17	PML	Progressive Multifocal Leukoencephalopathy
IL-21	Interleukin 21	DES	Desensitization
mMR16-1	Mousenized rat- anti-mouse IL-6 receptor monoclonal antibody	AEs	Adverse events
IgM	Immunologublin M	JC	Polyoma JC virus
BM	Bone marrow	IV	Intravenous
GVHD	Graft versus host disease	EXP	Expiry date
RA	Rhuematoid arthritis	TNF	Tumor necrosis factor
CXCR5	Chemokine receptor type 5	ULN	Upper limit of normal
NHP	Non-human primate	LDL	Low density lipoprotein
MMF	Mycophenolate mofetil	CD	Crohn's disease
ATG	Anti-thymocyte globulin	MTX	Methotrexate
SOC	Standard of care	GI	Gastrointestinal
DSA+	Donor specific antibody positive	mAbs	Monoclonal antibodies
DSA-	Donor specific antibody negative		
IVIG	Intravenous Immunoglobulin		
SQ/SC	Subcutaneous		
CDC	Complement dependent cytotoxicity		
CNI	Calcineurin inhibitors		
AR	Acute rejection		
AMR	Antibody mediated rejection		
CMR	Cell mediated rejection		
sCR	Serums creatinine		
IL-10	Interleukin -10		
IL-17a	Interleukin-17a		
IFNγ	Interferon gamma		
C1q	Complement 1q protein		
HLAi	Human leukocyte antigen incompatible		
IgG1	Humanized immunoglobulin G1 antibody		
pM	Picomolar		
sIL-6R	Soluble interleukin 6 receptor		
STAT3	Signal transducer and activator of transcription 3		
CRP	c-reactive protein		
PsA	Psoriatic arthritis		
PK	Pharmacokinetic		
PD	Pharmacodynamic		
pSTAT3	Phosphorylated Signal transducer and activator of transcription 3		
nM	Nanmolar		
ePPND	Enhanced pre- and post-natal development		

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1.0 **Background & Rationale**

Causes for the accelerated decline of renal allografts are multifactorial, however recent data indicates a reversal of the long held opinion that calcineurin inhibitor (CNI) toxicity was primarily responsible for the majority of chronic allograft failures[2]. Now, it is recognized that alloimmune responses are responsible for the majority of renal allograft failures which total 5,000 per year in the U.S[3]. The cost associated with failed allografts represents a considerable financial burden to the health care system while decreasing the length and quality of life of those affected. Patients returning to the transplant list after allograft failure now represent the fourth largest category for new patient listings in the U.S. These patients represent a major problem for transplant centers as they are highly-HLA sensitized and unlikely to receive another transplant without significant desensitization. Development of novel therapies to decrease allo-sensitization and improve transplant rates is critical. Today, this represents one of the most important and potentially achievable goals of transplant medicine. There are currently no FDA approved drugs in this category.

To increase renal transplant rates in sensitized patients, new protocols for HLA desensitization have emerged. These approaches require the application of IVIG, rituximab and plasma exchange (PLEX). Currently, there is a growing interest in development of novel immune-modulatory drugs likely to improve antibody reduction in transplantation. Therapeutic approaches that are less expensive and more convenient are desirable.

Current Desensitization Therapies

Two desensitization regimens are now widely accepted for efficacy - low-dose intravenous immunoglobulin with plasma exchange (IVIG/PLEX) and high-dose IVIG (HD-IVIG). IVIG/PLEX has been used successfully in ABO incompatible and positive crossmatch (+CMX) living donor renal transplantation[4,5], while HD-IVIG has been used to desensitize both living-donor +CMX and HS-DD recipients on the waitlist [6-10]. HD-IVIG (2gm/kg) in multiple dosing regimens is considered a reasonable approach for desensitization[11]. The B-cell depleting agent, rituximab, is often used in combination with HD-IVIG and IVIG/PLEX protocols[4,7-9]. Published experience with the IVIG/rituximab protocol has shown rituximab has a critical role in modifying allo-reactive B-cells and prevention of DSA rebound[12-14].

A major issue with desensitization regimens is how to interpret CMX and DSA results when IVIG and rituximab are present in test sera. IVIG given at the 2gm/kg (maximum 140 grams) dose will likely interfere with the luminex test for DSA, giving false positive results. This is best avoided by waiting at least 1 month after IVIG administration to perform luminex single antigen bead (LSA) testing since the ½ life of IVIG is 30-40 days. Rituximab does not interfere with the LSA testing platforms, but does give “false positive” CDC+ and flow cytometry (FCMX)+ B-cell crossmatches that may be wrongly interpreted as being due to DSAs. Pronase treatment of B-cells prior to FCMX and CDC testing usually reduces the effect of rituximab, but this is not always dependable[15].

Desensitization with IVIG and IVIG + Rituximab

Archdeacon et al.[16] summarized the proceedings of a Food and Drug Administration (FDA) symposium on desensitization and treatment of (ABMR). An important concern is the absence of FDA–approved drugs for desensitization or treatment of ABMR. Despite these concerns, outcomes of desensitization have overall been good[4], but reports of desensitization failures are noted[17,18]. We recently reported on the efficacy, side effects and outcomes of desensitization with IVIG + rituximab during renal transplantation[19,20]. We compared outcomes to a similar group of age-matched and ESRD cause-matched patients with cPRA>80% (calculated PRA) who remained on dialysis during the study period. The mean wait time on dialysis for our sensitized patients was 114±56 months before desensitization. After desensitization, the mean wait time to transplantation was 4.4±4.9 months. We were able to transplant 146 of 207 patients treated. Most patients

still remained crossmatch and DSA positive at the time of transplantation. Thus, reduction in crossmatch and DSA levels is the goal since total elimination of DSAs is rarely possible. Data by Montgomery et al.[5] and Orandi et al[21] in a larger multi-center study, demonstrated a significant reduction in risk of mortality for HS sensitized patients who underwent desensitization using PLEX + low dose IVIG and transplantation compared with patients who remained on dialysis or received dialysis or HLA-compatible transplant. Our analysis also is supportive of this conclusion[19,20].

We recently performed a study assessing the cost/benefit analysis of desensitization compared with dialysis. This study also showed that the costs associated with transplantation after desensitization including all medications, organ acquisition, treating rejection episodes, and cost of returning to dialysis for those who lost their allografts compared favorably with the costs of remaining on dialysis over the same period of time[19]. Most important was the survival benefit engendered by transplantation in this cohort. At 3 years, the desensitized and transplanted patients had a mortality rate of 3.5% compared to 22.8% for those remaining on dialysis.

Rituximab (Anti-CD20, Anti-B-cell) in Desensitization

In 2005, we performed a study to assess the efficacy of IVIG + rituximab as desensitization agents during renal transplantation. This trial showed an increased ability to transplant HS patients (80%) with excellent patient and graft survival[7]. These observations have been sustained for nearly 10 years[19,20]. We recently undertook a placebo-controlled trial (IVIG + placebo v. IVIG + rituximab) to determine the efficacy of rituximab in desensitization (NCT01178216, FDA IND# 109067). The main finding in this study was a demonstration that the risk for ABMR was significantly greater in the IVIG + placebo group due to rebound DSA responses that occurred after transplantation. No patients in the IVIG + rituximab group experienced ABMR and protocol biopsies at 1 year showed no evidence of transplant glomerulopathy. Thus, from this study, we concluded that rituximab was an important adjunct for desensitization due to its ability to prevent memory B-cell activation and DSA rebound[22].

Van Den Hoogen et al.[23] reported on a placebo controlled trial of rituximab as an induction agent for kidney transplant recipients. 280 patients were examined (138 randomized to rituximab and 142 placebo). Data showed that there was no difference in graft rejection rates. However, when data for high-risk patients (repeat transplants and HLA sensitized) were analyzed, there was a significant reduction in rejection episodes for those who received rituximab (17.9% v. 41.1%, p=0.039).

Despite these successes, there are a number of notable deficiencies of current desensitization protocols. These include: 1) Failure of current therapies to completely remove DSAs before transplantation resulting in risk for early ABMR. 2) Risk of rebound DSA formation post-transplant with attendant injury to the allograft, both acute and chronic and 3) The failure of current protocols, especially those utilizing complement inhibitors to prevent chronic antibody mediated rejection (cABMR). The current medical need requires an agent that would properly control DSA generation and rebound, span the effector functions of the B-cell -> plasma cell and regulate T-cell activation of Th17 and Tfh cells by inducing Tregs. To this end, IL-6 inhibitor therapies have demonstrated benefits in animal models of allo-sensitization that will likely have applications in human transplantation.

1.1 **IL-6/IL-6R Inhibition: An Important Therapeutic Option for Prevention & Treatment Desensitization**

Interleukin-6 is an important mediator of inflammation and the development, maturation, and activation of T-cells, B-cells and plasma cells[24,25]. Excessive IL-6 production has been linked to a number of human diseases characterized by excessive and unregulated antibody production and autoimmunity[26,27].

Tocilizumab (Actemra®, Roche/Genentech, CA, USA) is the first in class humanized monoclonal aimed at the IL-6 receptor (IL-6R). Tocilizumab binds to both soluble and membrane bound forms of the IL-6R receptor. Tocilizumab was recently approved by the FDA for treatment of rheumatoid arthritis and juvenile idiopathic arthritis. Since the introduction of the drug, other reports indicate that inhibition of the IL-6/IL-6R pathway may have significant benefits in SLE and other vasculitic disorders and reduces antibody producing cells in treated patients. Recent reports demonstrated a significant reduction in anti-ds-DNA antibodies and circulating plasma cells in SLE patients treated with Tocilizumab[28,29]. Tocilizumab treatment can also result in a reduction of peripheral pre- and post-switch memory B cells in rheumatoid arthritis patients. These patients also showed significant reductions in IgG+ and IgA+ B cells and reduction in serum levels of IgG and IgA. Thus, B-cell hyper-reactivity is significantly impacted in humans treated with tocilizumab[28].

Reports have shown that tocilizumab also reduces antibody-producing cells, diminishes inflammatory markers, and improves clinical symptomatology in a number of other autoimmune diseases[26,27,30,31].Recent clinical observations and animal models have shown that IL-6 may be important in mediation of allograft rejection. IL-6 production increases in mouse allografts undergoing rejection and is responsible for allogeneic T-cell infiltration[24]. In addition, IL-6 deficiency, in combination with costimulatory pathway blockage by CTLA4-Ig induces graft acceptance[32]. It is accepted that IL-6 drives CD4 T-cells toward T-helper type 17 (Th_{17}) phenotype while negating regulatory T-cell differentiation[26,28]. Neutralization of IL-6 reduces allograft rejection by allowing emergence of regulatory T cells (T_{reg})[24]. Recent evidence also indicates that IL-6 triggers IL-21 production by follicular T-helper cells (T_{fh}) driving B cell maturation to plasma cells during antibody responses[1,33]. Anti- IL-6R antibodies have shown significant reduction in graft-versus-host disease and allograft rejection in animal models associated with increased T_{reg} differentiation[34,35]. We have previously reported on the utility of a mousenized rat- anti-mouse IL-6 receptor monoclonal antibody (clone mMR16-1) in a mouse model of HLA.A2 sensitization[24]. The study found that anti- IL-6R treatment attenuates de novo DSA, including both immunoglobulin (Ig)M and IgG responses. We designed experiments to investigate the ability of anti-IL-6R to modify antibody recall responses to alloantigen which mimics the most relevant clinical scenario of highly sensitized patients. We hypothesize that anti- IL-6R suppresses donor-specific IgG response by blocking IL-6 signaling in plasma cells, which is critical for terminal differentiation of memory B cells to plasmablasts and for survival of long-lived plasma cells in the bone marrow (BM)[1]. Recent data[1] also suggests that IL-6 production by antigen-activated plasmablast is responsible for T_{fh} cell development and germinal center formation. This data was obtained in humans. Indeed, when patients with rheumatoid arthritis were examined, circulating T_{fh} and plasmablast numbers were elevated in patients with active disease. Treatment with tocilizumab significantly reduced T_{fh} cell numbers, IL-21 production by T_{fh} and circulating plasmablast (see Figure 1). Other recent data also show that tocilizumab induces significant increases in T_{reg} cells in patients with rheumatoid arthritis (Figure 2). This also correlated with responses to therapy[33]. These findings have potentially important implications in prevention and treatment of allograft rejection in humans.

Currently, there are two trials of tocilizumab for GVHD in humans. In addition, we have completed a trial of tocilizumab as a desensitization agent for HS patients who failed desensitization with IVIg + rituximab. This study is a Phase I/II study (NCT01594424) that is open label. Data on this trial were recently reported[36]. In this trial, we found that Tocilizumab improved transplant rates in patients who had failed desensitization with IVIG + rituximab +/- PLEX. Donor specific antibodies (DSAs) that were resistant to other therapies were significantly reduced with therapy and none of the transplanted patients showed antibody mediated rejection post- transplant.

Figure1: Circulating Plasmablast Produce Copious Amounts of IL-6 which Activates Tfh Differentiation

The figure shows that healthy individuals have low levels of circulating T_{fh} cells, but RA patients express higher levels with disease. Treatment with tocilizumab results in a dramatic reduction in T_{fh} cells, IL-21 production by T_{fh} cells and

circulating plasmablast. The authors conclude that inhibition of IL-6/Il-6R interactions will likely reduce T_{fh} formation and reduce germinal center formation with subsequent reductions in pathogenic antibody production.

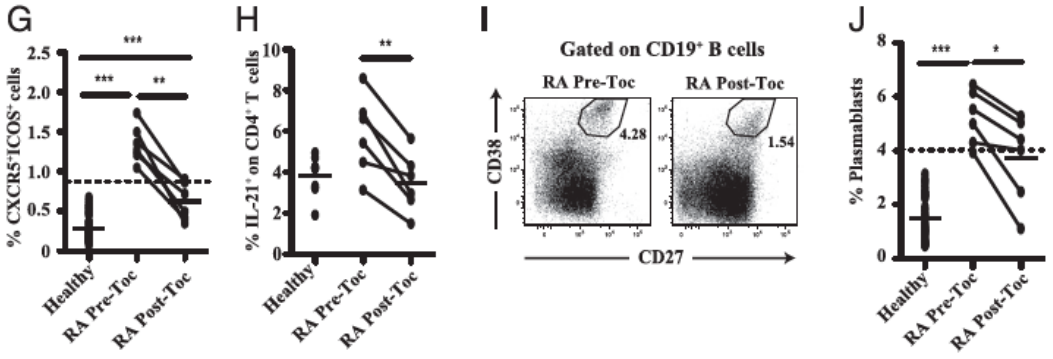
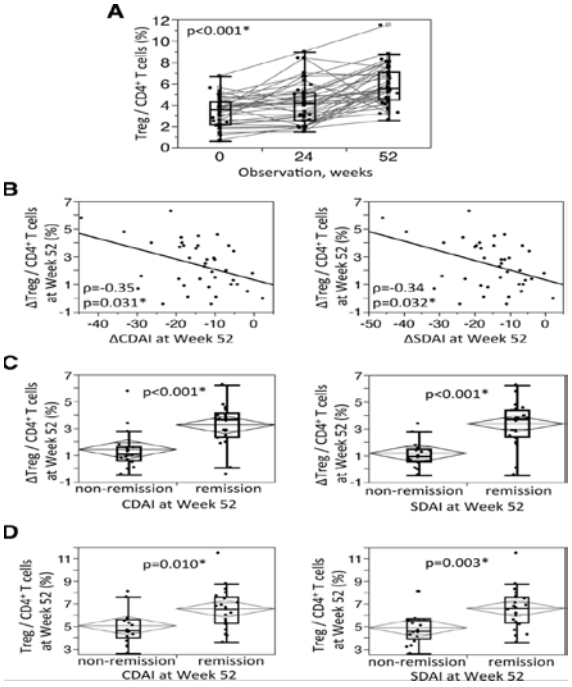


Figure 2: Tocilizumab induces T_{reg} cells in patients with RA and is associated with remission from active disease[33].

Anti-IL-6R Therapy Increases Treg Populations and is Associated With Remission in Rheumatoid Arthritis Patients



1.2 **Experience with Anti-IL-6R in a Mouse Model of Allo-Sensitization.**

Recent data from our group[24] investigated the ability of anti-IL-6R to modify immune responses to HLA-2 transgenic skin grafts. We investigated the ability to modify circulating anti-HLA-A2 antibody levels (DSA), plasma cell responses in the bone marrow and spleen of sensitized animals and the ability to modify T-cell subsets. The data are shown below:

Subsequent studies suggest that anti-IL-6R treatment is more effective than a mouse anti-mouse anti-CD20 in reducing rebound anti-HLA-A2 antibodies after re-exposure to HLA-A2 + skin grafts 90 days after 1st exposure. This simulates the

sensitization situation we seen in humans who have highly allo-reactive T & B-cells at the time they present for desensitization.

Figure 3A & 3B: This figure shows data from our group using a mousenized anti-IL-6R antibody in a mouse model of allo-sensitization[24]. Briefly, after sensitization, we can detect anti-HLA-A2 antibodies in sera of animals. Anti-IL-6R significantly reduces circulating levels of anti-HLA-A2 antibodies. In addition, as shown here, there is a significant reduction of antibody producing plasma cells isolated from the bone marrow and spleens of sensitized animals (3A). More importantly, plasma cells producing anti-HLA-A2 antibody in the bone marrow are inhibited by anti-IL-6 therapy (3B). Addition of anti-IL-6 treatment of conditioned media of bone marrow plasma cells from untreated sensitized animals also significantly reduced anti-HLA-A2 antibody production.

Figure 3A: Anti-IL6R Supresses Plasma Cells Ig Production in HLA Allosensitized Mouse Model

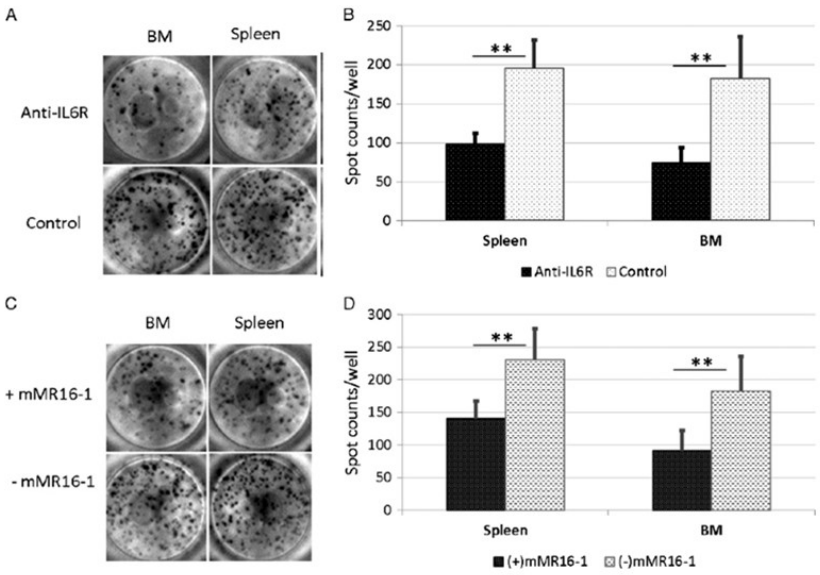


Figure 3B: M-MR16-1 (Anti-IL-6R) Significantly Reduces Anti-HLA Antibody Production by Plasma cells Isolated from Bone Marrow of Sensitized Mice

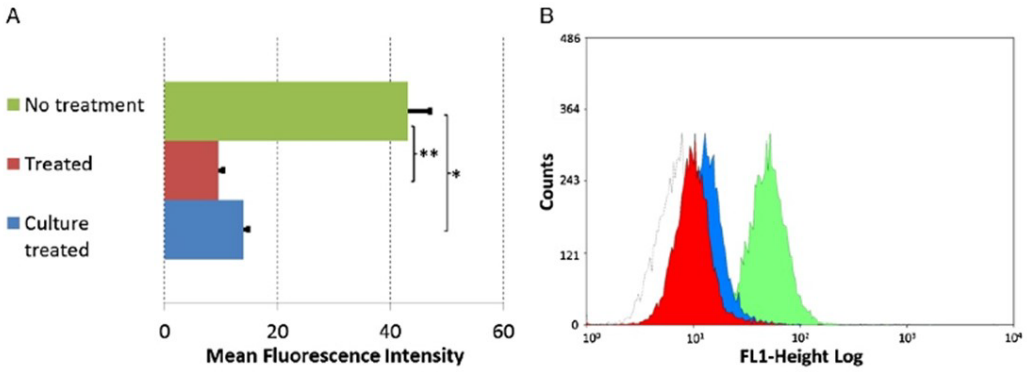
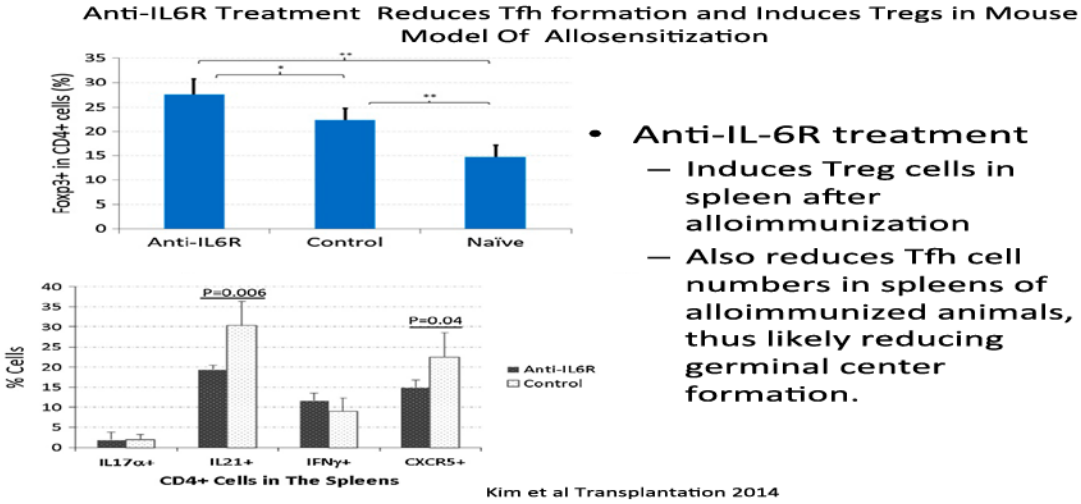


Figure 3C: This figure shows that in addition to the ability of anti-IL-6R treatment to reduce plasma cell IgG and anti-HLA-A2 production, there are significant alterations in the cellular compartments as well. First, anti-IL-6R treatment of sensitized animals is associated with a deviation of T-cell subsets to a T_{reg} profile. This is associated with a significant

reduction in the T_{fh} markers (IL-21 and CXCR5. This data suggests that anti-IL-6R therapy modifies T-cell responses to allo-antigens resulting in a diminution of inflammatory T-cell responses and likely reduction in Tfh induced germinal center formation[24].

Figure 3C



1.3 Experience with Tocilizumab in a Non-Human Primate Model of Lung Allograft Rejection

Inflammatory responses in non-human primate (NHP) models of lung transplantation have been linked to development of acute and chronic rejection of lung allografts. Investigators at the MGH have previously shown that T-cell depletion with Thymoglobulin or treatment with the antil-IL-6R monoclonal, tocilizumab, results in upregulation of the Treg pathway. In experiments reported recently, Aoyama et al[37] demonstrated that when administered alone to NHPs, a transient upregulation of Tregs was seen that was associated with a down regulation of -IFN producing cells. When lung transplants were performed between animals, ATG did not result in long term survival of animals and was associated with an appearance of DSAs that correlated with graft loss. (Figure 4 below). However, the addition of tocilizumab resulted in long-term survival of the lung allografts without evidence of rejection and no DSAs. The investigators also demonstrated that the sequential administration of Thymoglobulin + tocilizumab resulted in a dramatic and more sustained elevation of Treg cells in the peripheral circulation that the authors' feel is responsible for the excellent outcomes observed in this model[37].

There are a number of interesting issues to discuss from this interesting abstract presented at the American Transplant Congress last year. First, the dramatic clinical results seen when T-cell depletion is combined with tocilizumab post-transplant and that no DSAs were seen. This suggests that a similar combination could offer benefits to humans. In fact, as will be described below, our group used a similar protocol for patients who were desensitized with IVIG + tocilizumab before renal transplant. At transplant, all patients received T-cell depletion with Campath-1H followed by 6 months of therapy with tocilizumab. These patients were all DSA + at transplant, but dramatic reductions were seen after transplant as shown below. Second, a potentially important mechanism of action was also revealed in this study regarding the sustained up regulation of Treg cells by the combined use of Thymoglobulin + tocilizumab induction. Tocilizumab is known to upregulate Treg cells in our model of allo-sensitization that may account for the beneficial effects seen on regulating allo-antibody. In addition, tocilizumab induces Tregs in patients with autoimmune diseases. It certainly will be important to clarify the importance Tregs in modifying allo-immunity in human kidney transplantation.

Figure 4A Figure 4B

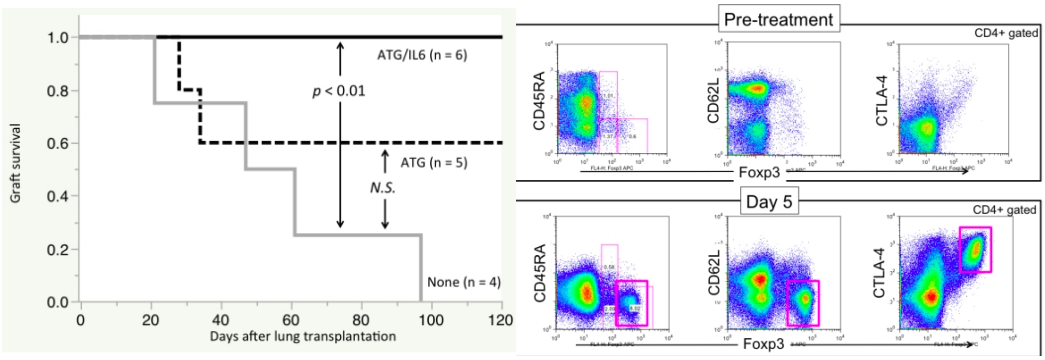


Figure 4A: Shows the beneficial effects of tocilizumab on improving allograft survival in NHP with lung transplants. Tocilizumab also prevented DSA generation, suggesting a possible inhibitor effect on T_{fh} cells and plasmablast. Figure 4B: Here investigators also showed that in the NHP model of lung allograft rejection that 5 days after treatment with Thymoglobulin + Tocilizumab that a significant increase in T_{reg} cells, a novel mechanism that could be responsible for the beneficial outcomes. The authors also conclude that this combination may have benefits in human transplantation[37].

1.4 Therapeutic Use of Tocilizumab for Desensitization in Humans Receiving HLA Incompatible Kidney Transplants

As mentioned above, alloantibodies are a major deterrent to access to and success of life-saving organ transplants. Despite advancements in desensitization, designing efficient and effective means of removal of pathogenic HLA antibodies remains a significant medical challenge. Preliminary data suggests that tocilizumab exhibits a broad range of immunomodulatory actions that could address the allo-antibody response to allografts that are so destructive.

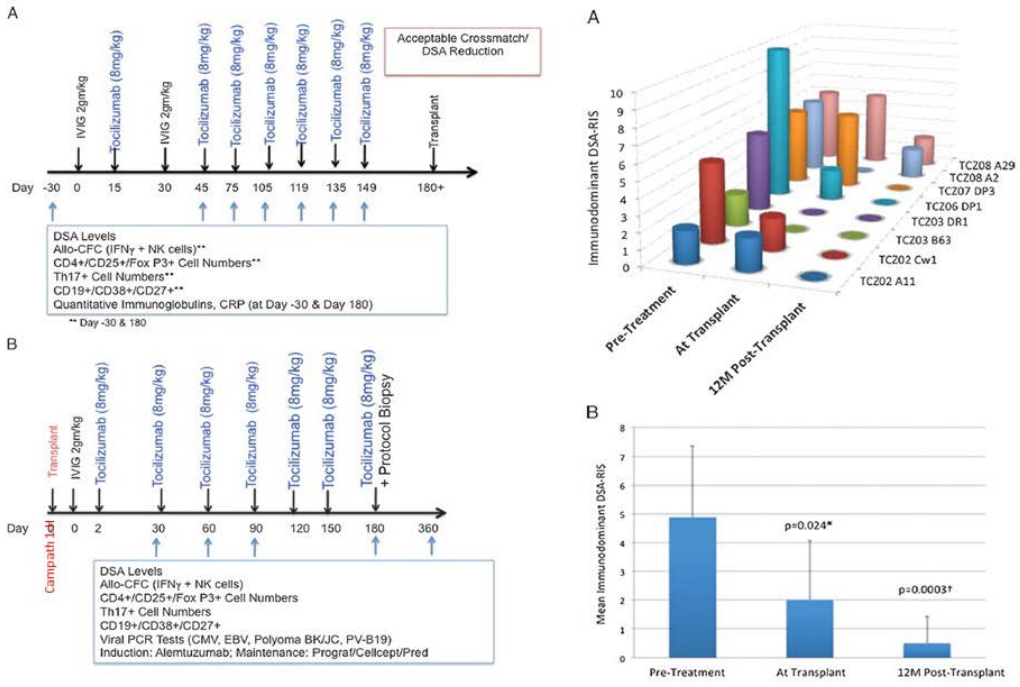
We recently completed a trial assessing the ability of tocilizumab to modify alloantibody responses and improve renal transplant rates in highly-HLA sensitized patients who received desensitization with IVIG + rituximab +/- PLEX[36]. Data from this study are shown below in Figure 5A & 5B.

This figure summarizes data from a recently completed open labeled Phase I/II clinical trial of tocilizumab in highly-HLA sensitized patients awaiting kidney transplants. All patients had previous transplants and were resistant to desensitization with IVIG + rituximab +/- PLEX. Ten patients were entered and six transplanted during the study. Two of the non-transplanted patients were withdrawn from the study due to non-compliance with the protocol. Thus, six of eight patients remaining in the study received transplants. The figures below show the course of DSAs before therapy with tocilizumab, at transplant and 12 months later. As can be seen, significant reductions in immunodominant DSAs was seen in all transplanted patients. This was most significant at 12M post-transplant. It is important to note that all patients received an additional 6 monthly doses of tocilizumab after transplant. Protocol biopsies at 6M showed no evidence of rejection in any patient. The impact of tocilizumab treatment on DSAs is shown in Figure 5A below. Briefly, from pre-treatment to 12M post-treatment, there was a significant decrease or near elimination of DSAs as shown. We also noted that none of the patients had evidence of ABMR at the 6M protocol biopsy. Renal function was stable in all patients as well. Based on this experience, we have incorporated tocilizumab into to our desensitization protocol for patients who are difficult to desensitize with IVIG + rituximab. To date, we have treated 26 patients with this protocol and transplanted 16. ABMR rejection rates remain low with excellent patient and graft survival (Abstract submitted AST 2017).

Figure 5A& 5B: This figure shows the immunodominant DSAs Pre-tocilizumab treatment, at transplant and 12M post-transplant. It is important to remember that patients received up to 6M of tocilizumab pre-transplant, Campath 1H induction at transplant and 6M tocilizumab post-transplant. At 6M no ABMR was seen on any biopsy. Thus, findings are

similar to those seen with the NHP animal model above.

Figure 5A and 5B Tocilizumab Protocol for Desensitization Pre- & Post-Transplant



2 Clazakizumab (anti-IL6): Potential as a Therapeutic Agent in Transplantation

As mentioned above, alloantibodies are a major deterrent to access to and success of life-saving organ transplants. Despite advancements in desensitization, designing efficient and effective means of removal of pathogenic HLA antibodies remains a significant medical challenge. Preliminary data suggests that Clazakizumab exhibits a broad range of immunomodulatory actions that could address the allo-antibody response to allografts that are so destructive and be useful as a desensitization agent to improve rates of renal transplantation for highly-HLA sensitized patients. This is based on data obtained from clinical trials of clazakizumab for treatment of rheumatoid arthritis.

Clazakizumab (CSL Behring LLC , King of Prussia, PA) is a humanized monoclonal antibody aimed at the cytokine IL-6 ligand. Clazakizumab has been evaluated extensively in patients with rheumatoid arthritis, but has not yet been approved by the FDA for any condition. Since the introduction of IL-6/IL-6R blocking drugs, reports indicate that inhibition of the IL-6/IL-6R pathway may have significant benefits in SLE and other vasculitic disorders and reduces antibody producing cells in treated patients. There is currently no information for Clazakizumab in HS patients awaiting incompatible (HLAi) transplants or for treatment of antibody-mediated rejection.

Clazakizumab is a genetically engineered humanized immunoglobulin G1 (IgG1) antibody that binds to human IL-6 with an affinity of 4 pM. Using multiple assays for signaling and cellular functions in response to IL-6 alone (to measure classical signaling) and a combination of IL-6 and sIL-6R (to measure trans-signaling), it was demonstrated that clazakizumab is a potent and full antagonist of IL-6-induced signaling as measured by phosphorylation of signal transducer and activator of transcription 3 (STAT3), as well as cellular functions such as cell proliferation, differentiation, activation, B-cell production of immunoglobulins, and hepatocyte production of acute phase proteins (C-reactive protein [CRP] and fibrinogen). In addition, clazakizumab is shown to be a competitive antagonist of IL-6-induced cell

proliferation. This in vitro pharmacological profile supports the potential of clazakizumab to impact multiple immune and non-immune cellular processes that are central to disease pathogenesis, and thus, to offer a new therapeutic modality in the treatment of autoimmune diseases and other IL-6 mediated diseases.

The clazakizumab development program includes a comprehensive nonclinical development program and clinical studies conducted in healthy subjects and in subjects with RA, psoriatic arthritis (PsA), Crohn's disease, graft-versus-host disease (GVHD), and oncology. To date, no studies with clazakizumab have been conducted in subjects with highly sensitized patients undergoing renal transplant, although supporting safety data are available from the previous clinical studies.

Nonclinical Studies

A comprehensive nonclinical development program has been completed. Clazakizumab was shown to be a potent inhibitor of IL-6-induced acute phase proteins. In pharmacokinetic (PK)/pharmacodynamic (PD) studies, a single dose of clazakizumab resulted in full inhibition of IL-6 activity as measured by the inhibition of IL-6-induced phosphorylated STAT3 (pSTAT3) activity in whole blood treated ex vivo with IL-6. The results of this functional PD assay correlated with drug exposures where full inhibition of pSTAT3 activity was observed when drug levels exceeded 50 ng/mL (approximately 0.3 nM). In a tissue cross-reactivity study, tissue binding of clazakizumab was observed in multiple tissues in both human and cynomolgus monkey, was generally cytoplasmic in nature, and was consistent with the known expression of IL-6 by cells and tissues. Results from both single- and repeat-dose nonclinical toxicology studies of up to 6 months in cynomolgus monkeys demonstrated an acceptable safety profile for clazakizumab. In a preliminary enhanced pre- and post-natal development (ePPND) study conducted in cynomolgus monkeys, an increase in the number of monkeys with retention of the placenta at parturition was observed at clazakizumab doses of 3 mg/kg (n=2) and 30 mg/kg (n=3), corresponding to doses 11 and 110 times the planned human dose of 50 mg. There were no other safety findings of clinical concern.

Clinical studies

Clinical studies have been conducted in healthy subjects and in the following patient populations: RA, PsA, CD, graft-versus-host disease (GVHD), and oncology. These clinical studies include a total of 1,223 subjects, of which 888 subjects were exposed to clazakizumab with doses ranging from 1 mg to 640 mg given by either intravenous (IV) or subcutaneous (SC) injection for up to 48 weeks.

<u>Clinical Pharmacology</u>

Following the administration of clazakizumab as a 1-hour IV infusion, the PK of clazakizumab were linear over the dose ranges of 30 mg to 640 mg in healthy subjects and 80 mg to 320 mg in subjects with RA as indicated by consistent clearance at these dose levels. The T-half of clazakizumab at all doses was very similar in healthy male subjects and in subjects with RA and was consistent with that expected for a humanized IgG1 antibody. Across the doses studied, the mean T-half of clazakizumab ranged from 19.5 to 31.0 days in healthy male subjects and from 26.4 to 30.9 days in subjects with RA. The T-half of clazakizumab after SC administration in healthy male subjects was similar to the IV administration. In a Phase 1 study comparing IV and SC dosing in healthy male subjects, the mean T-half of clazakizumab was 30.7 days after a single IV dose and 31.1 to 33.6 days after SC administration. The bioavailability of clazakizumab after SC administration was 60% of the IV formulation. As expected, Cmax was lower and Tmax was longer for the SC administration relative to IV administration.

Population PK analysis of the data from clinical studies in RA, PsA and healthy subjects have indicated that body weight affects the PK of clazakizumab such that both clearance and central volume of distribution increase with increasing body weight. Therefore, heavier subjects will have lower drug exposure compared with less heavy subjects.

Clinical Efficacy and Safety Studies

Efficacy and safety data for clazakizumab is available from clinical studies conducted in RA, PsA, and oncology. Studies conducted in GVRD and Crohn's disease were prematurely terminated due to safety concerns and therefore no efficacy conclusions are available for these studies.

In Phase 2 studies in RA and PsA, doses from 5 mg SC once every 4 weeks (Q4W) up to 320 mg IV once every 8 weeks were significantly effective with clinical response evident as early as 12 weeks post treatment. One study in RA also demonstrated that the efficacy of clazakizumab is comparable or may be better than the standard of care treatment (adalimumab + methrotrexate (MTX)) in RA.

Efficacy with clazakizumab was not shown in the 2 Phase 2 studies in oncology (head and neck cancer and non-small cell lung cancer).

Two studies were terminated prematurely due to safety concerns. A Phase 2 study in Crohn's was terminated early because of GI perforation in 3 subjects who had received clazakizumab and this indication is no longer being studied. Although these subjects had multiple confounding medical issues, and the disease itself has an inherent risk of mucosal perforation, gastrointestinal perforations were also observed during the clinical studies with tocilizumab in patients with RA. Gastrointestinal perforation is a recognized risk of anti-IL-6 mAbs. After only 3 subjects were enrolled, a study in subjects with GVHD was also prematurely terminated due to 2 subjects experiencing similar serious adverse events (SAEs) (i.e., acute renal failure) which led to death. Both subjects had severe GVHD disease at the time of death.

Overall, the safety findings from the clinical studies conducted with clazakizumab to date are consistent with the known effects of blocking the IL-6 pathway (see Actemra® prescribing information]). Identified risks associated with clazakizumab administration include the following: infections, liver function test (LFT) abnormalities, changes in hematology parameters (i.e., neutropenia and thrombocytopenia), dyslipidemia (i.e., hypercholesterolemia and hypertriglyceridemia), and gastrointestinal perforations

For further details regarding clinical studies with clazakizumab, please consult the Investigator's Brochure.

2.1 **Study Hypothesis**

Since alloantibodies are the major exclusionary factor for transplantation of highly-HLA sensitized patients and that current approaches for desensitization are not always sufficient to completely overcome these barriers, an unmet medical need exist to improve our ability to reduce pre-existing HLA antibodies to a level that would allow patients to receive life-saving organ transplants. To this end, we hypothesize that the use of clazakizumab in patients who are highly-HLA sensitized and are awaiting incompatible kidney transplantation will represent a more robust and complete technique to reduce or eliminate DSAs from the sera of HS patients and rapidly reduce complement dependent cytotoxicity (CDC) and antibody dependent cytotoxicity (ADCC) will allow for significant improvements in our ability to transplant these patients. Here we propose initiation of desensitization in UNOS eligible candidates who are highly-HLA sensitized and awaiting incompatible deceased donor (DD) or living donor (LD) renal transplants. Patients will receive antibody reduction therapy with plasma exchange (PLEX) X 5-7 sessions followed by IVIg 2gm/kg (maximum 140 grams) X 1. One week post-IVIg, the patients will initiate clazakizumab 25mg SC Q4W X 6 doses with monitoring of the

alloantibody levels and other immune parameters on select visit dates. Patients will be given up to day 270 (9M) to be transplanted. The primary end point of this open label study will be reduction of HLA antibodies from baseline based on luminex assessment with appropriate dilutional studies.

The protocols for pre and post-transplant clazakizumab desensitization are shown below:

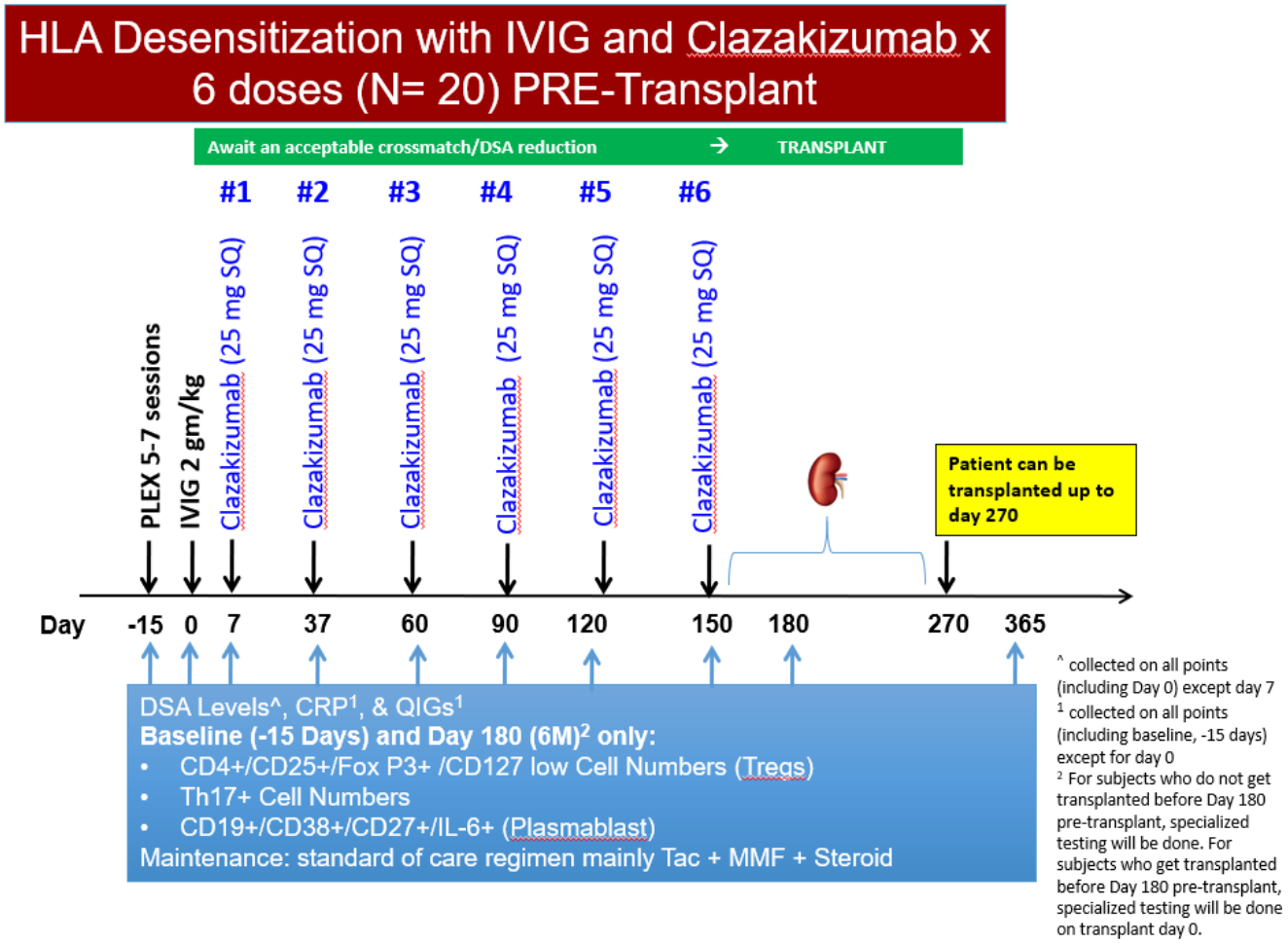


Figure 6A: Figure 6A shows the planned approach to desensitization using IVIG + Clazakizumab pre-transplant. Patients will receive up to 6 doses of Clazakizumab with monitoring of HLA antibodies, T_{reg} cell and plasmablasts at select time points during the study. This information will help us understand if the proposed mechanisms of action of Clazakizumab are correct.

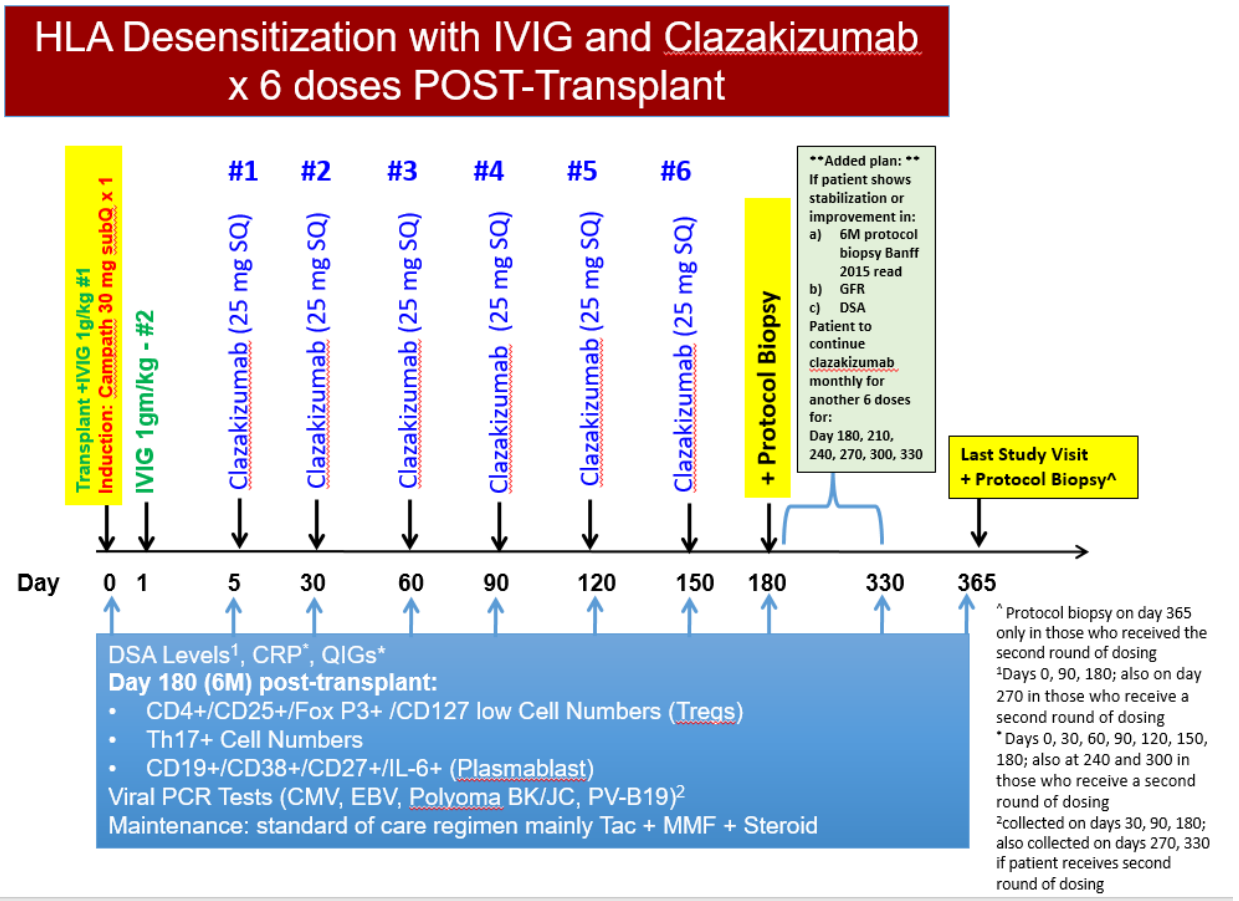


Figure 6B shows the protocol for patients who receive a transplant after Clazakizumab desensitization.

If patients are transplanted during the study, they will receive 6 doses of clazakizumab 25mg SC every four weeks starting 5-7days post-transplant, then a 6 month protocol biopsy will be performed. Based on protocol biopsy result, stabilization of GFR, and low intensity DSA, the patient is to continue clazakizumab monthly for another 6 doses up to day 330 post transplant. Patients who receive 12 doses post-transplant will then receive a 12 month protocol biopsy. If a biopsy was collected via standard of care; allowable to file the SOC biopsy in place of the protocol biopsy per PI discretion.

In the event a patient does not show improvement after receiving 6 doses of clazakizumab, no further treatment will be given and the patient will return at Day 365 for a final study visit.

Long term dosing option at conclusion of 12 months (after Study Day 365 visit) For those patients who complete the 12-month protocol, patients may continue to receive clazakizumab 25 mg SC every 8 weeks long term extension phase (LTE), per PI discretion. Please see Appendix E for the LTE visit schedule. Biopsies during the LTE will be conducted at 12 months per PI discretion or for cause (suspected rejection). The long term extension of the study is planned as an ongoing protocol, with patients to continue in the LTE if approved on an annual basis by PI and CSL Behring. Participants in the LTE component of the study will be removed if it is determined that there is no longer a clinical benefit of therapy or if there is an observed issue with safety. The LTE will be allowed until clazakizumab is FDA approved in the US or if the study is terminated. The objectives for the LTE are included in Sections 3 and 3.1.

2.2 **Rationale for Study**

Antibodies to HLA antigens have a strong impact on mediation of allograft injury and loss and remain a persistent and often impenetrable barrier to successful transplantation for thousands of patients on renal transplant lists world wide. As depicted in Figure 7 below, pre-formed or de novo DSAs activate complement, induce endothelial cell proliferation and mediate ADCC resulting in a progression of allograft dysfunction and loss. More than 5,000 renal allografts are lost each year in the U.S., approximately 75-80% to antibody mediated injury[38]. Thus, understanding the pathophysiology of ABMR and B-cell activation are critical to improving the longevity of existing allografts and development of successful strategies for desensitization to prevent ABMR. A clearer understanding will also lead to improved therapeutics for prevention and treatment of ABMR. It is also imperative that we develop novel therapies for desensitization since there are currently no FDA approved drugs for this condition or for treatment of ABMR. Clazakizumab has the potential to address both of these issues.

The study outlined above will determine if clazakizumab can modify DSAs and other immune parameters that have been identified to initiate and perpetuate injury to allografts and subsquently prevent re-transplantation. This could represent a very important way forward for treating these difficult conditions.

Figure 7

Course of Acute and Chronic Antibody-Mediated Allograft Injury

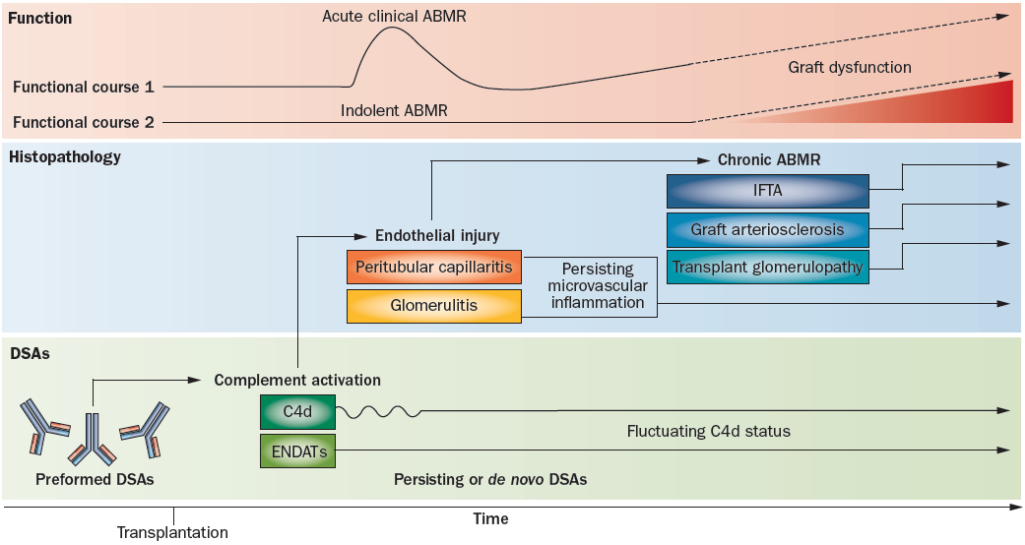


Figure 7 shows the time course of DSAs , their impact on allograft histology and the eventual progression to allograft failure, leaving the recipient highly HLA sensitized. It is important to point out the multi-faceted ability of DSAs to mediate allograft injury. Many of the pathologic features were once thought to be consequencs of CNI toxicity leading to reduced dosing of these critical medications which further accelerated allograft loss. Emerging knowledge in this area is critical for development of newer techniques for suppression of DSA responses. What is important here is the persistence of the immune attack on the allograft. This eventually results in interstitial fibrosis and tubular atrophy (IF/TA), TG and allograft loss. Patients returning to dialysis have little hope of receiving a subsequent transplant and often face a higher risk of death on dialysis. DSAs are also known to accellerate atherosclerosis in the allograft thus hastening the vascular demise of the kidney[38]. Thus strategies to eliminate or reduce DSAs prior to transplant are benefical in extending the longevity of allografts.

3. Primary Objectives

This study will be an open label design to assess the safety and efficacy of clazakizumab in eliminating DSAs and inducing Treg subsets in HS patients awaiting HLA incompatible (HLAi) renal transplantation. The protocol is outlined in Figure 6A &6B above. Safety determinations will be aimed at assessments of any side effects associated with clazakizumab administration and risk for infectious complications associated with clazakizumab therapy for desensitization of HS patients awaiting renal HLAi transplantation. Limited efficacy determinations will include assessment of the reduction of DSA levels that allow rates of transplantation to increase and subsequent prevention of ABMR (eGFR, SCr) after clazakizumab treatment. Patients will be followed and assessed for safety after treatment as well (see more information in the adverse event section).

Long term primary objectives include:

1. to assess the safety and efficacy of clazakizumab 25 mg SC given every 8 weeks in eliminating DSAs and subsequent prevention of ABMR (eGFR, SCr) after clazakizumab treatment
2. assessment of composite surrogate end points including patient and graft survival, and safety throughout study duration.

3.1 **Major Secondary Objectives**

To determine if clazakizumab treatment, can significantly reduce or eliminate ABMR episodes and C4d deposition in incompatible allografts transplanted to highly-HLA sensitized patients post-clazakizumab desensitization. Assess allograft function up to 6-12 M post-transplant, determine renal function using SCr, MDRD GFR calculations (Schwartz equation will be used to estimate CrCl for patients under 18 years of age) and DSA levels. A protocol biopsy will be performed at 6M post-Clazakizumab therapy (unless a biopsy was collected via standard of care; allowable to file the SOC biopsy per PI discretion). We will also record any late ABMR episodes after Clazakizumab therapy. In addition, several immunologic determinations of blood samples will be assessed at time points before and after initiation of clazakizumab therapy. These include the following:

- Assessment of T_{reg} cells (CD4+,CD25+,FoxP3+CD127^{dim})
- Assessment of T_{fh} cells (CD4+,ICOS+, CXCR5+, IL-21+)
- Assessment of circulating plasmablast (CD19+, CD38+, CD27+, IL-6+)
- Assessment of CRP and IL-6levels

This study protocol is shown in Figure 6A&6B. These secondary end points will help us understand the biology of alloimmune responses to allografts and to determine the ability and mechanisms of clazakizumab's beneficial effects. We will also monitor viral PCRs as per standard-of-care. Long term secondary objectives include:

1. determine renal function using SCr, eGFR
2. DSA levels
3. A protocol biopsy will be performed at 12M, 24M post-clazakizumab LTE (per PI discretion)
4. record any late cABMR episodes after clazakizumab therapy.
5. Assessment of CRP and IgG
6. Viral PCR monitoring by center protocol for EBV, CMV and Polyoma BK

3.2 **Inclusion Criteria**

- ✓ Age 15-75 years at the time of screening.
- ✓ HS patients (cPRA≥50%) awaiting DD or LD kidney transplant on the UNOS list.
- ✓ Previous history of pregnancies, blood transfusion and/or renal transplant.
- ✓ Subject/Parent/Guardian must be willing to participate fully with study requirements.
- ✓ Subject/Parent/Guardian must be able to understand and provide informed consent.
- ✓ Pneumococcal vaccinated

- ✓ Negative Tuberculin (ppd) placement result or negative Quantiferon TB gold results

3.3 **Exclusion Criteria**

- ✓ Multi-organ transplant (e.g. kidney and pancreas)
- ✓ Intolerability to clazakizumab or other IL-6 inhibitor therapies
- ✓ Lactating or pregnant females.
- ✓ Women of child-bearing age and male partners of women of child-bearing age who are not willing or able to practice FDA-approved forms of contraception during study and for 5 months after last dose.
- ✓ HIV-positive subjects.
- ✓ Subjects who test positive for HBV by HBVeAg/DNA or HCV infection [positive Anti-HCV (EIA) and confirmatory HCV RIBA].
- ✓ Subjects with latent or active TB. Subjects must have negative Quantiferon TB gold test result.
- ✓ Recent recipients of any licensed or investigational live attenuated vaccine(s) within two months of the screening visit (including but not limited to any of the following:
    - Adenovirus [Adenovirus vaccine live oral type 7]
    - Varicella [Varivax]
    - Rotavirus [Rotashield]
    - Yellow fever [Y-F-Vax]
    - Measles and mumps [Measles and mumps virus vaccine live]
    - Measles, mumps, and rubella vaccine [M-M-R-II]
    - Sabin oral polio vaccine
    - Rabies vaccines [IMOVAX Rabies I.D., RabAvert])
- ✓ A significantly abnormal general serum screening lab result defined as a ANC <2000, platelet count < 100 X 10^3/ml, an SGOT or SGPT > 1.5X upper limit normal.
- ✓ Individuals deemed unable to comply with the protocol.
- ✓ Subjects with active CMV or EBV infection as defined by CMV-specific serology (IgG or IgM) and confirmed by quantitative PCR with or without a compatible illness (Quantitative PCR cut off defined as having > 50 copies of CMV or EBV DNA/PCR)
- ✓ Use of investigational agents within 4 weeks of participation.
- ✓ History or active Inflammatory Bowel Disease or Diverticular Disease or gastrointestinal perforation
- ✓ Recent infection (within past 6 weeks of screening) requiring any antibiotic use (oral, parenteral or topical).
- ✓ Present or previous (within 5 years) malignancy except for basal cell carcinoma, fully excised squamous cell carcinoma of the skin or non-recurrent (within 5 years) cervical carcinoma-in-situ.

4 Study Design & Methods

Background: This is a single center, Phase I/II, open label single-arm exploratory study. The trial will primarily examine the safety and tolerability of clazakizumab given after consented and eligible patients begin desensitization therapy to achieve HLAi renal transplantation at Cedars-Sinai Medical Center. 20 subjects (ages 15 to 75) who are highly-HLA sensitized (HS) as determined by the cPRA ≥50% and are eligible for desensitization will be evaluated. All patients will be accrued from the renal transplant program at Cedars-Sinai Medical Center. Once desensitization begins, anti-HLA antibodies will be assessed which are associated with ABMR and/or graft loss. HLA antibodies will be detected using solid phase assay systems currently utilized at the Cedars-Sinai Medical Center HLA Laboratory (Dr. Xaiohai Zhang, Director, Phone: 310-423-4979)[15]. These anti-HLA antibodies may result naturally or from previous pregnancy, transfusions, or prior transplants. Patients treated with clazakizumab x 6 doses for desensitization will have blood sampling for HLA antibodies, and other monitoring blood samples as well as immunologic studies as outlined (See Study Protocol in Appendix A). If patients receive an HLAi transplant during the study, they will receive the standard post-

transplant immunosuppressive protocol, and clazakizumab 25 mg SC Q4W X 6 doses with immune monitoring as indicated.

Immune monitoring in blood samples for T_{reg}, T_{fh}, Th_{17} and B-cell subsets as well as IL-6 and CRP monitoring will be carried out at the Cedars-Sinai Transplant Immunology Laboratory (Mieko Toyoda, PhD, Director, Phone: 310-423-8282)

Patients identified as study participants will be HS and listed for HLAi renal transplantation at Cedars-Sinai Medical Center. Our center is a major U.S. desensitization center and performs ~80 HLAi renal transplants per-year. ~ 100 new HS patients are referred to our center each year as potential candidates for desensitization. Eligible patients entering the study will initially receive PLEX (5-7 sessions) + IVIG and receive clazakizumab 25 mg SC one week post-IVIG. If no safety/tolerability/efficacy issues are observed after the initial dose, patients will receive 5 additional injections Q4W (see Appendix A). If patients receive an HLAi transplant, clazakizumab will be continued for 6M post- transplant at 25mg SC Q4W for 6 doses (starting at Day 5 post-transplant). A protocol biopsy will be performed at 6M post-transplant to assess the allograft for evidence of ABMR, including C4d staining and TG using Banff 2015 criteria[39]. Patients will continue another 6 doses over 6 months if improvements are seen after the 6th dose of clazakizumab. Patients who develop evidence of persistent allograft dysfunction may have non-protocol biopsies for cause. Patients who receive 12 doses of clazakizumab post-transplant will receive a 12M protocol biopsy. In the event a patient does not show improvement after receiving 6 doses of clazakizumab, no further treatment will be given and the patient will return at Day 365 for a final study visit. For the patients continuing in the long-term extension (LTE) phase, after Study Day 365, LTE study visits will be conducted every 8 weeks. The protocol is summarized in Fig. 6A and Fig. 6B. All subjects will be evaluated on an intent-to-treat basis. The subject accrual rate will be limited to no more than 2-4 patient screenings per month once the first 2 patients receive the dose to assure safety to all subjects. Repeat laboratories will be performed at the completion of clazakizumab therapy to determine effect on levels and correlation with any potential events. A detailed analysis of the study is discussed below.

The subjects will be followed to determine if the use of clazakizumab for desensitization in this high risk transplant population is safe and without infectious risks. In addition, we will determine the effects of clazakizumab treatment on HLA antibodies in efforts to improve access to HLAi transplants for these individuals. We have previously reported our acceptance criteria for HLAi kidney transplants[40]. Renal biopsy assessments will be performed at 6M (per protocol) and 12M (for those who received 12 doses of therapy) . For the patients continuing to the LTE phase, Study Day 365 visit will be conducted in separate or in conjunction with the first Visit of the LTE phase (Study Day 0, Appendix E). Patients in LTE will receive clazakizumab 25 mg SC every 8 weeks and biopsies will be performed yearly per PI discretion. We will assess the transplanted patients to determine the number who sustain a viable and functioning kidney allograft as well. All subjects will be evaluated on an intent-to-treat basis. The subject accrual rate will be limited to no more than 1-2 subjects per month in the initial three months to assure safety to all subjects.

Study Analysis This single-center, Phase I/II, trial is designed to examine the safety, tolerability and limited efficacy of human clazakizumab (25mg, subcutaneous) given as per protocol (Appendix A & B) in 20 subjects ages 15 to 75 who are highly-HLA sensitized and are undergoing desensitization at Cedars-Sinai Medical Center for HLAi renal transplantation. Patients considered for this study would have traditionally been treated with high-dose IVIG + rituximab and/or plasmapheresis.[6,7,19]

5.1 **Defining the Sensitized Patient & Criteria for HLAi Transplantation**

For the purposes of this study, we define HLA sensitization as a patient awaiting kidney transplantation on the UNOS waitlist who has a cPRA of $\geq$50% who also has demonstrable DSA using luminex bead technology and a history of sensitizing events (previous transplants, blood transfusions and/or pregnancies). These individuals must also have sufficient wait time on the UNOS list to allow for frequent offers with a history of positive crossmatches (DD) or an incompatible (LD) with a positive flow cytometry (FCMX) and negative complement-dependent cytotoxicity (CDC+)

crossmatch[7,19,40]. Patients proceeding to HLAi transplant after desensitization will have a CDC CMX negative at 1:2 dilution, FCMX <225 channel shifts and DSAs that are at an acceptable MFI as was previously defined[41].

5.2 **Defining ABMR**

For purposes of this investigation, antibody-mediated rejection (ABMR) is defined as follows:

- ✓ Deterioration of allograft function in a high-risk transplant recipient (i.e. sensitized patient with history of DSAs) measured by serum Cr and eGFR (defined as a decline >30% from baseline).
- ✓ Association with the presence of DSA (usually increasing in strength) measured by luminex techniques.
- ✓ Biopsy evidence based on BANFF 2015 grading which includes: capillaritis, inflammation and C4d deposition.

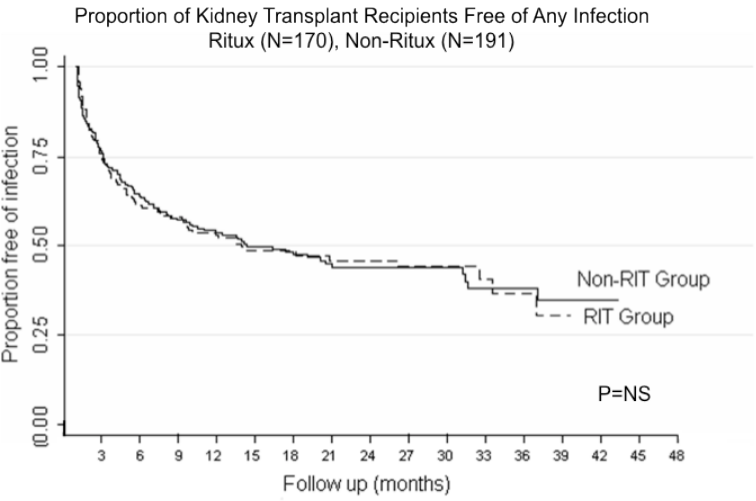
5.3 **Treatment of Allograft Rejection Episodes**

Biopsy-proven rejection episodes that occur during the study are treated with "pulse" methylprednisolone (10mg/kg/day, max 1000mg for >100kg for 3 days) and anti-thymocyte globulin (1.5mg/kg daily X 4) for cell-mediated rejection episodes that are unresponsive to pulse steroids. Patients experiencing recurrent ABMR episodes after study drug treatment will initially receive pulse methylprednisolone (10mg/kg/day, max 1000mg for >100kg) IV daily x 3 doses then, depending on severity, IVIG 10% solution 2gm/kg (max 140g for >70kg) IV X1 dose followed by rituximab (375mg/m2) IV X1 dose. In cases where rapid deterioration of allograft function is seen and/or thrombotic microangiopathy diagnosed, the patient will receive plasma exchange X3-5 sessions followed by anti-C5 (Eculizumab®) IV weekly X4 weeks (1200mg week #1 followed by 900mg/ weekly for 3 additional weeks). Efficacy of therapy will be assessed by determining renal functional improvement, monitoring DSA responses and repeat allograft biopsies, if needed.

5.4 **Monitoring for AE/SAEs Post-Transplant in HS Patients**

Adverse events (AEs) and serious adverse events will be monitored post treatment with clazakizumab. These include careful attention to infectious complications potentially associated with clazakizumab therapy.

Infectious complications associated with IVIG + rituximab desensitization and alemtuzumab induction therapy followed by maintenance therapy with tacrolimus, MMF and prednisone have been assessed by our group. Briefly, we evaluated 170 patients who were desensitized with IVIG + rituximab followed by alemtuzumab induction and maintenance therapy with tacrolimus, MMF and steroids. This was compared to a concomitant group of non-sensitized, low-risk transplants (N=191) who did not receive IVIG, rituximab or alemtuzumab (induction with IL-2R blockers). A careful analysis of all infections and serious infections that occurred over the next 4 years was compiled and is shown in Figure 8A &8B. Briefly, these data show that the use of this desensitization
protocol followed with alemtuzumab induction does not increase the risk for common or serious infections post-transplant compared to a low risk group of patients. Serious infections were defined as any viral infection and fungal or bacterial infections requiring i.v. antibiotics or hospitalizations[15]. Thus risk for infections in the study group (clazakizumab) after ABMR treatment will likely be similar and comparable to non-sensitized patients. All patients entered into this study are required to be vaccinated for Streptococcus pneumoniae.



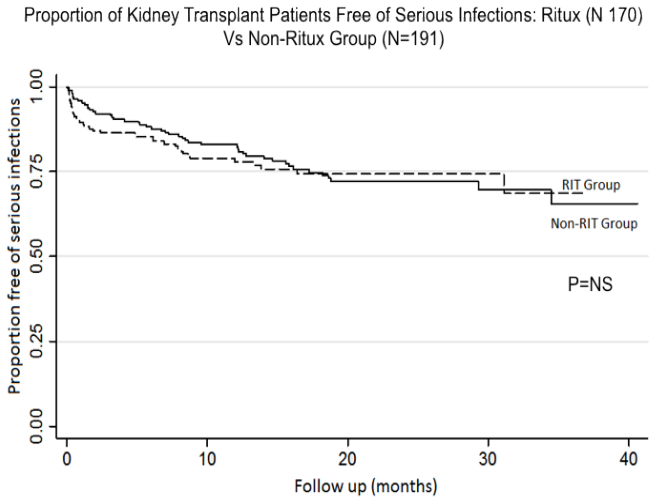


Figure 8A & 8B: This figure shows the proportion of kidney transplant recipients who developed infections (all infections 16A, or serious infections 16B) post-transplant. Patients were in the low-risk group (non-Ritux #191) who did not receive IVIG/ritux or alemtuzumab or (Ritux #171) who received desensitization with rituximab, IVIG followed by transplantation. Follow up for up to 45 months shows that infection rates are similar. The commonest infection was urinary tract infection in both groups. The incidence of CMV was greater in the non-Ritux group while there were more BK infections in the Ritux group. No patients in the Ritux group developed PTLD or PML while 2 patients in the non-Ritux group developed PTLD[42].

5.5 Safety Reporting of Adverse Events

Safety Reporting of Adverse Events

Assessment of Safety

Specification of Safety Variables

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

Adverse Events

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

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with clazakizumab infusion that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., renal protocol biopsy).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Serious Adverse Events

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

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

Methods and Timing for Assessing AND Recording Safety variables

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to the FDA, appropriate IRB(s), and CSL Behring LLC in accordance with CFR 312.32 (IND Safety Reports).

Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 150 days after the last dose of study drug.

5.5.1 Reporting of Serious Adverse Events Associated with Clazakizumab®

Any Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)/Special Situation that occurs during the course of the STUDY and is associated with the use of a CSLB study drug must be forwarded within **one (1) working day** from Date of First Receipt to CSLB by e-mail or fax (see Table) irrespective of whether it is assessed to be related to this product.

The exchange of all SAE/SAR/AR case report information shall be in English language by using a Case Report Form agreed on by CSLB.

CSLB shall acknowledge receipt within **two (2) working days**. Should the INSTITUTION not receive a confirmation of the case receipt within the **two (2) working days**, the INSTITUTION shall request confirmation that the report has reached CSLB.

The INSTITUTION should cooperate with CSLB and provide missing information in a timely manner as well as responses to queries until the event has resolved, or, in case of permanent impairment, until stabilized. Follow-up information obtained by the INSTITUTION should be handled accordingly, and forwarded as per the timelines stated above.

Contact for Exchange of SAE/SAR/AR *resp*. SUSAR/Pregnancy/Special Situation Information:

Name	Helen Sborlini (Case Reports) Samantha Gan (AE-Reconciliation)
Title	Case Management Team Lead, CSLB-GCSP King of Prussia US ICSR Compliance and Reconciliation Lead, CSLB-GCSP Parkville AU

e-mail	AE reporting: adverse.events.global@CSL Behring.com Global AE reconciliation email: Global.Reconciliation@csl.com.au
Fax	+1 610-878-4487

Contact for other Safety Issues regarding the PRODUCT:

Name	David Gao
Title	Director, Clinical Safety Physician, Immunology Global Clinical Safety and Pharmacovigilance
e-mail	Zhiyong.Gao@cslbehring.com
Phone	+1 610-290-7659 (for AE reporting only)

Contact for Study Report distribution (refer to section 1.3):
email subject 'Report from Clazakizumab IIT, please distribute to responsible CSP/CSS and CM'

Name	Global Periodic Reports Office
e-mail	PeriodicReports.GCSP@cslbehring.com

SAE Reporting	Contact Information
Study Coordination Center/Principal Investigator: Stanley C. Jordan, M.D.	Tel: 310-423-2641 Fax: 310-423-6369
IRB Contact information and fax # Keren Dunn Cedars-Sinai Medical Center Director, Research Compliance	Tel: 310-423-3783 Fax: 310-423-4195

AND:

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 CSL Behring 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 CSL Behring Drug Safety representative noted above.

With completion of the STUDY, the INSTITUTION shall provide to CSLB via email or fax (see APPENDIX 01) the final/clinical study report within three months after completion of Study conduct or termination of this agreement.. Any interim report is to be provided by the INSTITUTION has to be forwarded on a bi-annual basis.

In addition, the INSTITUTION shall provide a line listing/table including the causality assessment for each SAE/SAR/AR/AE/Special Situation within **five (5) working days** after closure of the database. The PARTIES will agree on the event-level detail prior to forwarding to CSLB.

Study Drug Relationship:

The investigator will determine which events are associated with the use of the study drugs. The causality assessment is the determination of whether there exists a reasonable possibility that the Study treatment caused or contributed to an adverse event:

Not related: Temporal relationship to Study treatment administration is missing or implausible, or there is evidence of another cause.

Possibly related: Reasonable time sequence to administration of Study treatment, but the event could also be explained by concurrent disease of other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Definitely related**:** Plausible time relationship to Study treatment administration; event cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.

5.5.2 **Pregnancy Reporting**

Should a patient or female partner of a male under treatment with a CSLB product become pregnant during the course of the STUDY, this information must be forwarded to CSLB within **ten (10) calendar days**. The INSTITUTION shall follow-

up until outcome of pregnancy is known and potential safety concerns have been clarified. As soon as outcome of pregnancy is available to the INSTITUTION this information has to be provided to CSLB within **one (1) working day.**

In case of a pregnancy in the female partner of a male subject, the Investigator should obtain informed consent of the pregnant partner prior to monitoring of the pregnancy.

5.6 **Infection Prophylaxis Protocols and Viral Monitoring Post-Transplant**

All study patients, regardless of their cytomegalovirus (CMV) status, will receive IV ganciclovir while inpatients and valganciclovir as outpatients for 6 months post kidney transplant, with dose adjustments for renal function. Fungal prophylaxis was accomplished with fluconazole 100 mg daily for 1 month post transplant. Pneumocystis jirovecii pneumonia and bacterial prophylaxis is accomplished with trimethoprim 80 mg and sulfamethoxazole 400 mg daily for 12 months post transplant.

Viral polymerase chain reaction assays for CMV, Epstein Barr virus, Parvovirus B-19, Polyoma virus BK and JC will be performed on study patients monthly for 6 months post-transplantation. Methodologies used for monitoring viral replication have been described previously [25].

6 **Clazakizumab**

Dosing

Clazakizumab will be administered at a dose of 25mg SC Q4W starting at Day 7 post initial desensitization with PLEX + IVIG, and repeated at Q4W intervals for a maximum of 6 doses. If patient get transplanted they will receive clazakizumab monthly starting post transplant day 5 (after IVIG doses) for a maximum of 12 doses. If the patient proceeds to the LTE, they will receive clazakizumab 25 mg SC Q8W for a duration of 2 years.

Product Description, Storage and Administration Instructions

Clazakizumab will be provided by CSL Behring LLC

Generic name:	Clazakizumab
Active ingredient:	Genetically engineered humanized anti-IL-6 mAb
Strength:	25 mg/mL (or 12.5 mg/mL)
Excipients:	L-histidine, L-histidine monohydrochloride, sorbitol, polysorbate-80, and water for injection
Appearance:	Clear to slightly opaque, colorless to dark yellow-colored solution
Dosage form:	Single-dose vials (25 mg/mL or 12.5 mg/mL) for injection.
Manufacturer:	Ajinomoto Althea, San Diego CA
	Patheon Manufacturing Services LLC, Greenville, NC

Clazakizumab vials should be stored at ≤-20°C (-4°F) with protection from light.

The drug product will be administered undiluted at a concentration of 25 mg/mL or 12.5 mg/mL.

Prepared syringes may be stored for up to 24 hours in a refrigerator, 2°-8°C (36°-46°F) ≤-20°C (-4°F), and up to 4 hours of the 24 hours may be at room temperature, 15°-25°C (59°-77°F). The prepared syringes should be protected from light.

Prior to administration, clazakizumab should reach room temperature by storing unrefrigerated for 30 to 60 minutes before use.

IP requests should be sent to: CentralGroup.CTS@cslbehring.com

6.1 Storage and Handling

Clazakizumab will not be used after the expiry date (EXP) shown on the kit or vial.

6.2 Clazakizumab Overdose

There are no specific antidotes or measures to take in the event of an overdose of clazakizumab injection. Subjects should be treated with the appropriate supportive care.

Dose Modification/Toxicity Management

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

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

6.3 Adverse Drug Reactions

Opportunistic Infections and Serious Infections

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

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

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

Gastrointestinal Perforations

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

Demyelinating Disorders

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

Hematologic Abnormalities and Bleeding Events

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

For patients with concomitant medications associated with hematologic toxicity, the reduction or interruption of the suspected medication is recommended prior to modifying clazakizumab.

Table 1: Neutropenia Risk Mitigation

ANC (cells/mm^3)	Action
> 1000	Maintain dose.
500 – 1000	Interrupt clazakizumab dosing. When ANC increases to > 1000, resume clazakizumab 25mg SQ monthly
< 500	Discontinue clazakizumab.
ANC = absolute neutrophil count	

Table 2: Thrombocytopenia Risk Mitigation

Platelet count (cells/mm^3)	Action
> 100,000	Maintain dose.
50,000 – 100,000	Interrupt clazakizumab dosing. When platelet count increases to > 100,000, resume Clazakizumab at 25mg SQ monthly
< 50,000	Discontinue clazakizumab.

Elevated Liver Enzymes and Hepatic Events

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

Table 3:

Lab Value	Action
> 1 to 3x ULN	Dose modify concomitant transplant immunosuppressive drugs if appropriate For persistent increases in this range, interrupt clazakizumab until ALT/AST have normalized Restart with 25mg SQ monthly as clinically appropriate
> 3 to 5x ULN (confirmed by repeat testing)	Interrupt clazakizumab dosing until < 3x ULN and follow recommendations above for >1 to 3x ULN For persistent increases > 3x ULN, discontinue clazakizumab Discontinue clazakizumab if total bilirubin >2 x ULN
> 5x ULN	Discontinue clazakizumab

Cardiovascular Events and Elevated Lipids

Patients with RA have an increased risk for cardiovascular disorders, therefore, risk factors for cardiovascular disease (eg, hypertension, hyperlipidemia) should be managed as part of their standard of care. See section on Drug Interactions.

For patients with LDL cholesterol ≥160 mg/dL, it is strongly recommended that investigators advise therapeutic lifestyle changes that may include initiation lipid-lowering agents. Lipid-lowering agents should also be considered for patients with lower LDL cholesterol levels as part of their therapeutic lifestyle changes depending on their overall risk as defined in NCEP ATP III or other national guidelines.

Malignancies

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

Hypersensitivity or Anaphylaxis

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

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

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

Healthcare professionals administering clazakizumab should be trained in the appropriate administrative procedures, be able to recognize the symptoms associated with potential anaphylactic or hypersensitivity reactions, and have the

appropriate medication available for immediate use in case of anaphylaxis or hypersensitivity reaction during or after administration of clazakizumab. Healthcare professionals should also instruct patients to seek medical attention if they experience symptoms of a hypersensitivity reaction outside of the clinic.

If a patient has symptoms of anaphylaxis or serious hypersensitivity, or requires an interruption of the study drug because of symptoms of anaphylaxis or hypersensitivity, administration of clazakizumab must be discontinued permanently. The patient should be treated according to the standard of care for management of the hypersensitivity reaction. A blood sample for the presence of anti-clazakizumab antibodies should be obtained.

Clazakizumab should not be administered to subjects who have had any previous allergic reactions to monoclonal antibodies. To date, no infusion reactions have been associated with clazakizumab administered by IV infusion. Injection site reactions have been reported with SC administration. Reactions have been mild or moderate and have resolved without treatment. Both allergic reactions and injection site reactions should be treated with standard of care. Subjects who have developed significant allergic reaction to study drugs should not be re-challenged.

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

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 clazakizumab, the formation of CYP450 enzymes could be normalized. When starting or stopping therapy with clazakizumab, patients taking medications which are individually dose-adjusted and metabolized via CYP450, 3A4, 1A2, or 2C9 (e.g. atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, cyclosporine, or benzodiazepines) should be monitored as doses may need to be adjusted to maintain their therapeutic effect. Given its long elimination half-life (t1/2), the effect of clazakizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

Pregnancies and Women of Child Bearing Potential

There are no adequate well-controlled studies in pregnant or lactating women. In nonclinical studies, an increase in the number of monkeys with retention of the placenta at parturition was observed at clazakizumab doses corresponding to 11 and 110 times the planned human dose of 50 mg. In 3 of the 5 monkeys with retained placentas, the resulting excessive uterine hemorrhage led to moribund status in the mothers.

Three pregnancies have been reported to date in subjects taking clazakizumab. The outcomes included one spontaneous abortion (outcome unknown for the other 2 pregnancies).

All subjects of child bearing potential being treated with clazakizumab (and their partners) must be informed of this risk, and use highly effective birth control. Administration of clazakizumab may decrease the efficacy of hormonal oral contraceptives.

Under no circumstances shall clazakizumab injection be administered to women known to be pregnant or lactating. All pregnancies must be reported to CSL Behring LLC within 24 hours and in accordance with SAE reporting procedures.

7 **Therapy Stopping Points**

As indicated previously, the study will be halted and re-evaluated by the Data and Safety Monitoring Board (DSMB) if any patient in the study group develops SAEs or evidence of severe infusion related or infectious complications. In addition, we will note if patients develop severe ABMR after desensitization with clazakizumab and fail to respond to this treatment and require reinstitution of standard of care treatments (IVIG + rituximab +/- PLEX). If more than 2 patients fail to show improvements in ABMR, the study will be halted and reassessment of the study goals and complications will be done and discussed with CSL Behring LLC (collaborator), the DSMB and FDA prior to reinitiating the study. (see appendix C).

8 **Statistical Analysis**

Due to the exploratory nature of this study that involves safety endpoints only and the small sample size that is not powered for efficacy end points, our primary objective will be to assess safety end points and limited efficacy. Most important will be tolerability in the ESRD population and determination of the effects of clazakizumab treatment on circulating DSAs as well as the ability to improve rates of successful transplantation for HS patients. We will however plan to assess biopsies 6M post-transplantation in patients desensitized with clazakizumab treatment to determine if there are durable effects in prevention of ABMR both acute and chronic.

9 References

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Appendix A: Pre Transplant Visit Schedule

Study/Protocol Title: "A Phase I/II Trial to Evaluate the Safety and Tolerability of Clazakizumab® (Anti-IL-6 monoclonal) to Eliminate Donor Specific HLA Antibodies (DSAs) and Improve Transplant Rates in Highly-HLA Sensitized Patients.

Study visit	**Day -21 Screening**	**Day 0 IVIG**	**Day 7 ± 3d CLAZ#1**	**Day 37 ± 14d CLAZ#2[5]**	**Day 60 ± 14d CLAZ#3[5]**	**Day 90 ± 14d CLAZ#4[5]**	**Day 120 ± 14d CLAZ#5[5]**	**Day 150 ± 14d CLAZ#6[5]**	**Day 180 ± 30d**	**Day 365/ Early Termination Visit +/- 30 d**
Medical History/ Complete Physical Exam	X	X						X		X
Vital signs/weight	X	X								X
12-lead ECG (SOC)[4]	X									
Chest X-Ray (SOC) [4]	X									
Review Historical Serologies for HIV, HBV, HCV, CMV and EBV*	X									
TB test [Quantiferon TB Gold][4]	X									X
Luminex HLA specificities[2,4]	X					X			X	X
PLEX x 5-7 sessions	X									
IVIG 2g/kg or 1g/kg x 2 days (>70kg max 140g)		X								
Medical History/ Complete Physical Exam			X							
Vital signs/weight			X	X	X	X	X	X		
Informed Consent	X									
Inclusion/Exclusion criteria review	X									
Safety laboratory tests[4] (CBC with differential, CMP)[4]	X			X	X	X	X	X		
Pregnancy test (for WOCP)[3]	X			X	X	X	X	X	X	X
Clazakizumab SC injection			X #1	X #2	X #3	X #4	X #5	X #6		
CRP[4]	X		X	X	X	X	X	X	**X**	X
IgG[4]	X					X			X	X
Treg cells (CD4+, CD25+, FoxP3+, CD127+) Tfh cells (CD4+, ICOS+, CXCR5+, IL-21+) Plasmablast (CD19+, CD38+, CD27+, IL-6+) Exosomes Microparticles	X								X[1]	
Concomitant Medication										
Adverse Event Monitoring			X	X	X	X	X	X	X	X

1: For subjects who do not get transplanted before Day 180 pre-transplant, specialized testing will be done. For subjects who get transplanted before Day 180 pre-transplant, specialized testing will be done on transplant day 0. **2. DSA to be collected prior to clazakizumab infusion. 3. Women of child bearing age is between 12-55 years old. 4. At or within 1 month prior to appt date**

*** At screening or within 2 months prior to screening date**. . 5. Allow 28 days between clazakizumab doses

Appendix B: Post Transplant Visit Schedule: Study/Protocol Title: "A Phase I/II Trial to Evaluate the Safety and Tolerability of Clazakizumab® (Anti-IL-6 monoclonal) to Eliminate Donor Specific HLA Antibodies (DSAs) and Improve Transplant Rates in Highly-HLA Sensitized Patients.

**** Based on patient's protocol biopsy results and/or PI confirmation, patient will continue a second six month course of clazakizumab. If no improvement is observed after 6 months of initial Clazakizumab treatment, the patient will come back for a final last study visit (Day 365) after the Day 180 protocol biopsy. Patients that continue the second course will receive a 12 month protocol biopsy.**

Study visit	**Day 0 Tx and IVIG#1**	**Day 1 IVIG#2**	**Day 5 -2/+14d CLAZ#1[4]**	**Day 30 ± 14d CLAZ#2[4]**	**Day 60 ± 14d CLAZ#3[4]**	**Day 90 ± 14d CLAZ#4[4]**	**Day 120 ± 14d CLAZ#5[4]**	**Day 150 ± 14d CLAZ#6[4]**	**Day 180 ± 30d+**	**Day 210** ±14d[4]**	**Day 240** ±14d[4]**	**Day 270** ±14d[4]**	**Day 300** ±14d[4]**	**Day 330** ±14d[4]**	**Day 365 ± 30d**
Medical History/ Complete Physical Exam	X	X	X	X	X	X	X	X	X			X**			X
Vital signs/weight	X	X	X	X	X	X	X	X	X	**X	**X	**X	**X	**X	X
Safety laboratory tests (CBC with differential, CMP, UA)^&	X	X	X	X	X	X	X	X	X	**X	**X	**X	**X	**X	X
Review Historical Serologies HIV, HBV, HCV, CMV; EBV	X														
EBV, CMV, PBK, DNA PCR				X		X			X			**X		**X	X
Estimated GFR (using MDRD equation or Schwartz equation will be used to estimate CrCl for patients under 18 years of age)	X	X	X	X	X	X	X	X	X	**X	**X	**X	**X	**X	X
Donor –specific antibodies (DSA)[2]	X					X			X			**X			X
Alemtuzumab Induction	X														
IVIG 1g/kg x 2 days (>70kg max 140g over 2 days)	X	X													
CNI Levels&			X	X	X	X	X	X	X	X**	X**	X**	X**	X**	X
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X**	X**	X**	X**	X**	X
Clazakizumab SC injection			**X #1**	**X #2**	**X #3**	**X #4**	**X #5**	**X #6**	**X**#7**	**X**#8**	**X**#9**	**X**#10**	**X**#11**	**X**#12**	
TB test [Quantiferon TB Gold]															**X**
CRP	X			X	X	X	X	X	X	X**	X**	X**	X**	X**	X
IgG	X					X			X						X
Pregnancy test (for WOCP)[3]	X				X	X	X	X	X	X**	X**	X**	X**	X**	X
Treg cells (CD4+, CD25+, FoxP3+, CD127+) Tfh cells (CD4+, ICOS+, CXCR5+, IL-21+) Plasmablast (CD19+, CD38+, CD27+, IL-6+) Exosomes; Microparticles	X[1]								X						
Allograft biopsy									X						**X
Review of allograft loss									X						X
Review of non-protocol biopsy results									X						X
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	**X	**X	**X	**X	**X	X

1: For subjects who do not get transplanted before Day 180 pre-transplant, specialized testing will be done. For subjects who get transplanted before Day 180 pre-transplant, specialized testing will be done on transplant day 0. **2. DSA to be collected prior to clazakizumab infusion. 3. Women of child bearing age is between 12-55 years old. ^ UA in patients who are producing urine. & Within 1 month prior to appointment; if applicable (pt receiving CNI agent).** + The biopsy can occur -30 days from day 180 but a minimum of 28 days must elapse between Claz dose #6 and dose #7. **4.** Allow 28 days between clazakizumab doses

Appendix C:

Lab	Address
Anti-CLAZ Antibody, PK	ICON Bioanalytical Lab 8282 Halsey Road Whitesboro, NY 13492
Donor specific antibody	Cedars-Sinai HLA Laboratory Comprehensive Transplant Center 8723 Alden Drive, SSB 197 Los Angeles, CA 90048
Transplant Immunology Lab	Cedars-Sinai Transplant Immunology Lab 8723 Alden Drive, Steven Spielberg Building, Room 336 Los Angeles, CA 90048
Reference Lab	Cedars-Sinai Medical Center Dept of Pathology and Lab Medicine 8700 Beverly Blvd, Room 3719 Los Angeles, CA 90048

Appendix D: DSMB Charter & FDA Guidance for Clinical Trial Sponsors



Clazakizumab
DSMB Charter 03.06



FDA Guidance for
Clinical Trial Sponso

Appendix D: Safety Reporting Forms



FDA Med watch
mandatory reporting.

Appendix E. A Phase I/II Trial to Evaluate the Safety and Tolerability of Clazakizumab® (Anti-IL-6 monoclonal) to Eliminate Donor Specific HLA Antibodies (DSAs) and Improve Transplant Rates in Highly-HLA Sensitized Patients awaiting Renal Transplant.
The Schedule Below to repeat annually per PI discretion.

Study visit	Visit 1 Follow up year Day 0 CLAZ#1 %**	Visit 2 Week 8 -7d/+ 10days	Visit 3 Week 16 -7d/+ 10days	Visit 4 Week 24 -7d/+ 10days	Visit 5 Week 32-7d/+ 10days	Visit 6 Week 40-7d/+ 10days	Day 365 ± 30 days [3]
Medical History							X
Complete Physical Exam							X
Vital signs/weight	X	X	X	X	X	X	
Safety laboratory tests (CBC with differential, CMP, UA)^	X	X	X	X	X	X	
EBV, CMV, PBK DNA PCR^				X			X
IgG^				X			X
CRP^				X			X
Donor –specific antibodies (DSA)^				X[1]			X
CNI Levels^	X	X	X	X	X	X	
TB testing [Quantiferon TB Gold]							X&
Clazakizumab injection	X #1%	X #2	X #3	X #4	X #5	X #6	
Estimated GFR (using MDRD equation or Schwartz equation will be used to estimate CrCl for patients under 18 years of age)	X	X	X	X	X	X	
Pregnancy test (for WOCP)[2^]	X	X	X	X	X	X	
Concomitant Med Review	X	X	X	X	X	X	
Kidney Biopsy							X*
Review of allograft loss							X
Review of non-protocol biopsy results							X
Adverse Event Monitoring	X	X	X	X	X	X	

& TB testing to be completed once a year. TB test will be collected if not done in the last 2 months.

^ At or within 1 month prior to appointment; if applicable (pt receiving CNI agent)

1. DSA to be collected prior to clazakizumab infusion.

2. Women of child bearing age is between 12-55 years old.

* At 12 Months Per PI discretion (any other biopsies will be conducted for cause)

% Timed minimum 4 weeks from last clazakizumab dose3. Visit should be combined with either visit 1, 2, 3, 5, or 6. Depending on which visit is closest to day 365

** Study Day 0 of LTE may be combined with Study Day 365 (Appendix B)