<TITLE>**Effect of Treatment with Tabalumab, a B Cell–Activating Factor Inhibitor, on Highly Sensitized Patients with End-Stage Renal Disease Awaiting Transplantation**

<LRH>**Mujtaba et al**

<RRH>**B Cell–Activating Factor Inhibition in ESRD**

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<ABS>

<P>**B cell–activation factor (BAFF) is critical for B cell maturation. Inhibition of BAFF represents an appealing target for desensitization of sensitized end-stage renal disease (ESRD) patients. We conducted a Phase 2a, single-arm, open-label exploratory study**

investigating the effect of tabalumab (BAFF inhibitor) in patients with ESRD and calculated panel reactive antibodies (cPRAs) >50%. The treatment period duration was 24 weeks. Eighteen patients received tabalumab, at doses of 240-mg subcutaneous (SC) at Week 0 followed by 120-mg SC monthly for 5 additional months. Patients were followed for an additional 52 weeks. Immunopharmacologic effects were characterized through analysis of blood for HLA antibodies, BAFF concentrations, immunoglobulins, T and B cell subsets, as well as pre- and posttreatment tonsil and bone marrow biopsies. Significant reductions in cPRAs were observed at Weeks 16 (p = 0.043) and 36 (p = 0.004); however, absolute reductions were small (<5%). Expected pharmacologic changes in B cell subsets and immunoglobulin reductions were observed. Two tabalumab-related serious adverse events occurred (pneumonia, worsening of peripheral neuropathy), while the most common other adverse events were injection-site pain and hypotension. Three patients received matched deceased donor transplants during follow-up. Treatment with a BAFF inhibitor resulted in statistically significant, but not clinically meaningful reduction in the cPRA from baseline. (NCT01200290, Clinicaltrials.gov)

<ABB>**Abbreviations: AE, adverse event; BAFF, B cell–activation factor; cPRA, calculated PRA; ESRD, end-stage renal disease; IVIG, intravenous immunoglobulin; LLN, lower limit of normal; MFI, mean fluorescence intensity; MHCI, MHC Class I; MHCII, MHC Class II; PRA, panel reactive antibody; UNOS, United Network for Organ Sharing.**

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<H1>**Introduction**

<P>Kidney transplantation is the treatment of choice for patients with end-stage renal disease (ESRD) because it prolongs survival, decreases morbidity, improves quality of life, and is cost effective (1–4). As of August 2014, more than 100,000 patients were waiting for kidney transplantation (5), and it is clear that waiting time for a kidney transplant will continue to rise. Furthermore, the number of sensitized patients on the transplant waiting list is also increasing; these are patients who have developed antibodies against HLAs and usually have long wait times (5).

<P>Patients are sensitized to HLA through blood transfusions, pregnancy, and previous organ transplants. Because of pregnancies, women with ESRD tend to be disproportionately sensitized compared with men. Approximately 80% of highly sensitized patients are women (6). The degree of immunization is much stronger (as determined by antibody titer) and prolonged when different causes of sensitization act together within the same patient. The calculated panel reactive antibody (cPRA) values reflect the patient's degree of sensitization. Currently, 16% of patients on the waiting list have cPRA values between 20% and 79%, with another 16% of sensitized patients having cPRA values >80% (5). Less than 10% of highly sensitized patients (those with a cPRA value >80%) receive a transplant each year (5). Thus, the highly sensitized patient is likely to have an extended period of time on dialysis, which increases morbidity and mortality (7). Additionally, transplant outcomes in highly sensitized patients are inferior to those in nonsensitized patients (8). Many therapeutic protocols have been designed to reduce sensitization and improve access to transplantation for these patients (9).

<P>Current desensitization regimens are based on the removal of antibodies (i.e. plasmapheresis), immunomodulation (i.e. intravenous immunoglobulin [IVIG]), depletion of recipient B cells (i.e. anti-CD20 antibodies) and plasma cells (i.e. bortezomib); or attenuation of antibody-induced injury, (i.e. eculizumab) (2,10–14). These approaches have shown promise but are limited in the clinical situations in which they can be used. However, the short period of antibody reduction and high frequency of antibody rebound poses a real challenge (14,15), suggesting that exploration of additional approaches is warranted.

<P>B cell–activating factor (BAFF) is a cytokine in the tumor necrosis factor family that plays a major role in B cell homeostasis by enhancing survival of immature/transitional B cells leaving the bone marrow and entering the periphery, thereby making BAFF critical in B cell maturation (16,17). High levels of BAFF *in vivo* potentiate autoimmunity in part by preventing the normal

deletion of self-reactive B cells at the transition checkpoint from immature to mature B cells (18). This effect translates into a correlation between BAFF concentrations and autoantibody titers as reported in systemic lupus erythematosus (19) and Sjögren's syndrome (20). In the pretransplant setting, patients with high serum BAFF levels had both a greater risk of developing donor-specific antibodies (21) as well as increased HLA antibody titers and a greater number of different HLA antibodies (22) compared to patients with lower BAFF levels. Taken together, this suggests that inhibition of BAFF represents an appealing target for pretransplantation conditioning of HLA-sensitized patients with ESRD.

<P>We present here results of an open label trial using LY2127399 (tabalumab; a therapeutic antibody that neutralizes both soluble and membrane-bound forms of BAFF) to reduce alloantibody levels. This pilot study evaluated the impact of tabalumab (six doses administered over 20 weeks) on B and plasma cell dynamics, Ig levels, and cPRA values in HLA-sensitized patients with ESRD.

<P>Importantly, this study also evaluated cell subpopulation changes in peripheral blood, tonsil, and bone marrow to better understand the mechanism(s) of action of tabalumab, characterize pharmacodynamic changes, and advance our knowledge of BAFF neutralization in ESRD.

<H1>**Materials and Methods**

<H2>***Study design/dose rationale***

<P>This study was a Phase 2a, single-arm, outpatient, open-label exploratory study investigating the effect of tabalumab in patients with ESRD and cPRAs >50% who were awaiting kidney transplantation (NCT01200290, Clinical Trials.gov). The study was divided into three periods: Screening, Treatment, and Follow-Up (Figure 1A). The treatment period lasted 24 weeks and patients received tabalumab administered as a loading dose of 240-mg subcutaneous (SC) injection at Week 0, followed by maintenance doses of 120-mg SC injections on five occasions at 4-week intervals. Patients were followed for an additional 52 weeks to assess persistence of pharmacodynamic response and monitor patient safety.

<P>Prior experience with tabalumab treatment for up to 20 weeks suggested it was well tolerated and produced reductions in naïve B cells, serum Ig levels, and rheumatoid factor in subjects with

rheumatoid arthritis. To maximize the chance of observing reductions in alloantibodies, subjects were treated with 120 mg Q4W, which achieved maximum trough levels for a period approximating the maximum duration of exposure achieved in a previous trial (23). This dose maintained a total systemic exposure throughout the dosing interval that was less than the maximum exposure previously demonstrated to be well tolerated in a multiple-dose IV study (24).

<P>This study was conducted in accordance with local institutional review board ethical standards, good clinical practices, and the Declaration of Helsinki. The study protocol and amendment were approved by the Indiana University Institutional review board prior to implementation. All patients provided written informed consent before study participation.

<H2>***Patient population***

<P>The patient population included male and nonpregnant female patients with a diagnosis of ESRD who were on dialysis and awaiting renal transplantation. Patients could receive transplants during the study should a suitable organ become available, but transplant outcomes were not assessed in the protocol. Table 1 provides key inclusion and exclusion study criteria. To ensure at least 15 study completers, 18 patients were enrolled.

<H2>***Study objectives***

<P>The primary objective evaluated the potential for tabalumab to reduce HLA alloreactivity (measured by cPRA and single-antigen reactivity) in patients with ESRD, and characterized this effect over time. The secondary objectives explored the following pharmacodynamic parameters: (1) B cell population dynamics in blood; (2) B cell populations in secondary lymphoid tissue (tonsil) and bone marrow; and (3) serum IgG, IgA, IgM, and IgG subclass concentrations.

<H2>***Tonsil and bone marrow biopsies***

<P>Two snip biopsies were collected pretreatment, week 1, and 24 during the treatment period. One tissue section was processed for histologic examination and the other was submitted fresh for immunophenotyping when sufficient material permitted.

<P>Additionally bone marrow aspirates were collected pretreatment and week 24. Bone marrow smears were prepared for cytologic evaluation, and antibody-secreting cells (isolated CD138+ plasma cells) to MHC Class I/MHC Class II (MHCI/MHCII) antigens were quantitated by enzyme-linked immunospot. Purified HLA antigens (One Lambda, Inc., Canoga Park, CA) were selected for each patient based on pretreatment anti-HLA antibody profile.

<H2>***Lymphocyte subsets, HLA antibody quantitation/cPRA***

<P>Blood samples for lymphocyte subsets and HLA antibody quantitation were collected at multiple time points during treatment and follow-up periods. Samples were stained with antibodies to lymphocyte surface antigens (supplemental material Table S1). RBCs were lysed using ammonium chloride and samples were analyzed using a FC500 cytometer with CXP software (Beckman Coulter, Miami, FL). Cells of interest were identified by measuring relative percentages of fluorochrome-positive cells in the gated region, and relative percentages were used to calculate absolute counts of the various lymphocyte subsets in blood.

<P>HLA antibodies were quantitated using multiplex bead technology (LABScreen® Single Antigen Class I and II, One Lambda Inc.) where microbeads were coated with recombinant single antigen HLA molecules and patient serum reactivity was measured by flow cytometry. Once antibody reactivity was determined, unacceptable (positive) antigens were entered into the United Network for Organ Sharing calculator (optn.transplant.hrsa.gov) to calculate the cPRA for each patient at each time point.

<H2>***Statistical analyses***

<P>All analyses were conducted on patients that received at least one dose of tabalumab. No adjustments for multiplicity were performed. All demographic, baseline characteristics, efficacy, lymphocyte subset and antibody outcomes were summarized using descriptive statistics for continuous variables and frequencies were tabulated for categorical variables. cPRA values were

analyzed using a parametric mixed-model repeated measures analysis of postbaseline cPRA values with baseline cPRA value and time included as fixed effects, and patient included as a random effect. Models were generated using an arcsine transformed version of cPRA data as well as raw cPRA data; however, statistical significance was determined on arcsine transformed data. An unstructured covariance matrix was used to model within-patient error correlation. Contrasts between baseline cPRA and each post-baseline cPRA were tested using a paired t-test. A similar model was also used to analyze serum immunoglobulins and flow cytometry parameters. Changes in biomarkers from baseline to postbaseline were considered significant when $p \leq 0.05$.

<H1>**Results**

<P>Eighteen patients were enrolled and received at least one dose of tabalumab (intent to treat population); 15 patients completed both the treatment and follow-up periods (Figure 1B). The mean patient age was 44.2 years; 55.6% were female and 44.4% were male. No patients were of Hispanic or Latino ethnicity; 61.1% were black or African American, 33.3% were white, and 5.6% were Asian. The majority of patients (94.4%) had received previous immunosuppressants (i.e. cyclosporine, mycophenolate mofetil, prednisone, azathioprine, tacrolimus) and followed protocol-specified washout periods. The patients' mean baseline cPRA was 94.4%. The mean number of days on the transplant waiting list was 1830.8 days (range, 36 to 4703 days) and the mean number of previous transplants was 1.2 (range, 1–2). A detailed summary of baseline patient characteristics is presented in Table 2 and de-identified individual patient demographic data are provided in supporting information, Data Files S1 and S2.

<H2>***Efficacy analysis: primary objective***

<P>Statistically significant reductions in cPRA were observed at Week 16 (least-square means [LSM] change from baseline, -0.054%; p = 0.043) and 16 weeks after the last administration of tabalumab, at Week 36 (LSM change from baseline, -0.076%; p = 0.004). Treatment with tabalumab resulted in statistically significant, but not clinically meaningful, small (<5%) reductions in cPRA from baseline. Two of the three patients who received transplants during the

study had larger cPRA decreases of -27% and -11% at Week 76. The overall factor effect for cPRA through Week 76 compared to baseline was significant ($p = 0.04$).

<P>Individual patients had variable changes in cPRA (Figure 2); for example, patient 112 had an increase in cPRA at Weeks 52, 64, and 76. Patient 117 had variable reductions at Weeks 16 and 36, and increases at Weeks 52, 64, and 76. Patient 118 had reductions in cPRA from Weeks 8 to 36, but returned to baseline values from Weeks 52 to 76. Three patients who received a transplant during the study period and were treated with additional immunosuppressive therapy had reductions in cPRA during the study: patient 113 at Weeks 64 and 76; patient 102 from Weeks 16 to 64; and patient 111 had variable cPRA reductions at Weeks 16, 24, 52, 64, and 76. Individual patient cPRA data are provided in supporting information, Data File S3.

<P>In an attempt to determine whether specific Class I or Class II antibodies decreased significantly, the top 10 highest antibody levels by HLA class were evaluated for each individual patient. Line plots for individual patients are provided in supporting information Figures S1 and S2 and median change from baseline in MHCI and MHCII mean fluorescence intensities (MFIs) in Figure 3. None of the top 10 Class I or Class II MFI values of single anti-HLA antibodies changed enough to be considered a shift from positive to negative during the treatment or follow-up periods. Individual patient single antigen data are provided (supporting information, Data File S4.)

<H2>***BAFF concentrations***

<P>Expected increases in serum BAFF concentrations of 50- to 80-fold were observed in the treatment period, reflecting the binding of tabalumab to BAFF in circulation. The mean BAFF concentration at baseline was 1165 ± 712 pg/mL and individual patient BAFF concentrations over time are presented in Figure 4. The largest increase in mean BAFF concentrations occurred at Week 8 (92 158 ± 35 551 pg/mL; mean change from baseline [MCFB], 91 017 ± 35 381 pg/mL); mean BAFF concentrations declined after week 24 (86 560 ± 23 893 pg/mL), but remained above baseline average through Week 76 (1570 ± 767 pg/mL) (MCFB, 500 pg/mL). Individual patient BAFF data are provided (supporting information, Data File S5.)

<H2>***Serum immunoglobulins and preexisting immunity to tetanus, mumps, and rubella***

<P>Figure 5 summarizes MCFB in total IgG, IgA, and IgM, IgG subclasses and tetanus, mumps, and rubella IgG. Significant decreases from baseline were observed at all postbaseline visits through Week 36 for IgA ($p \leq 0.034$, all), IgG ($p < 0.001$, all), IgG1 ($p \leq 0.002$, all), and IgG3 ($p \leq 0.033$, all). Decreases in IgM from baseline were significant at all postbaseline visits ($p \leq 0.023$, all).

<P>Significant decreases from baseline were observed in IgG4 at Week 36 ($p = 0.021$), and in IgG2 at Weeks 16–36 ($p \leq 0.036$, all). In two patients, IgM levels fell below the lower limit of normal (LLN). Four patients had IgG2 levels below the LLN; however, in all patients the total IgG level remained above the LLN.

<P>Only antitetanus IgG demonstrated a significant mean decrease from baseline at any time, while mean increases were observed at Weeks 24 and 52. The reduction noted at Week 8 is not considered clinically meaningful since all patients with preexisting tetanus antibodies pretreatment remained above baseline levels, which all were above the LLN at >0.15 IU/mL. No consistent or statistically significant changes in mumps virus and rubella antibody IgG levels were observed.

<H2>***Peripheral blood immunophenotyping***

<H3>***B cells/B cell subsets/plasma cells:*** Figure 6 summarizes mean percent change from baseline in select B cell subsets and total T cells. Total CD19+ B cells increased 35% at Week 1 ($p < 0.001$) followed by significant decreases in both CD19+ and mature naïve B cells ($p \leq 0.002$, all) from Weeks 4 to 52 with maximum reductions from baseline of 64% and 54%, respectively, at Week 36 ($p < 0.001$). Both CD19+ and mature naïve B cells returned to baseline levels at Weeks 64 and 76. Both switched and nonswitched memory B cells were increased at Weeks 1–52 with a decreasing tendency toward baseline levels at weeks 64 and 76. Transitional B cells (CD19+CD38+CD24+CD10+) decreased at Weeks 4–24 and returned to baseline levels beginning at week 36. An additional transitional B cell subset (CD19+CD27-IgD+CD10+) also showed decreases at Weeks 4–76. No changes were noted in plasma cells.

<H3>***T cells/T cell subsets.*** No change was noted in absolute counts of total T cells; however, relative percentages of T cells increased at Weeks 4–52 ($p < 0.05$, Weeks 24–52) and returned to baseline levels at Weeks 64 and 76. No changes were noted in total T helper, central memory T helper, effector memory T helper, naïve T helper, or T follicular helper (TFH) cells. Similarly, no changes were noted in total T suppressor, central memory T suppressor, or effector memory T suppressor cells. Median values of the relative percent of CD8+ naïve T cells (CD3+CD8+CCR7+CD45RA+) increased from baseline from Weeks 8 to 76 (data not shown).

<H3>***Tonsillar biopsy flow cytometry and histology.*** While no changes were noted in histologic assessment of tonsillar tissue at Weeks 1 and 24, relative percentages of the following subsets were reduced (reported as percent change from baseline) at Week 24: total B cells (-25%) mature naïve B cells (-22%, $p = 0.005$), Bm2' germinal center B cells (-61%, $p < 0.001$), and TFH cells (-53%, $p = 0.001$). Total T cells and both switched and unswitched memory B cells were increased at Week 24 (173%, $p = 0.079$; 93%, $p < 0.001$; and 224%, $p = 0.038$; respectively).

<H3>***Bone marrow assessments (cytology and antibody secreting cells):*** Most patients had no change in bone marrow cellularity at Week 24; however, reduced myelopoiesis with no change in plasma cells was observed in one patient. Two other patients showed changes in erythropoiesis, consistent with preexisting anemia or treatment for anemia. The majority of the patients showed no decrease in antibody-secreting cells, or the changes were consistent with changes observed to individual patient autoantigens, which suggests the changes were not meaningful. Two patients showed reductions in antibody-secreting cells to MHCII antigens (data not shown).

<H2>***Pharmacokinetic/Pharmacodynamic (PK/PD) Analyses***

<P>We investigated the PK/PD relationship for serum tabalumab concentrations and cPRA level, BAFF concentration, and B cell subsets. These response endpoints did not change with increasing exposure; therefore, no PK/PD relationship was observed. C_{trough} concentrations were approximately 5–20 µg/mL in this study. Previous analyses have shown that near maximum effects are achieved on biomarkers (i.e. BAFF and B cell subsets) at serum concentrations of 5 µg/mL. Therefore, these results were expected based on the observed C_{trough} results, suggesting complete BAFF saturation over the concentration range observed in this study.

<H2>***Adverse events***

<P>Two deaths occurred during the follow-up period; neither was determined by the investigator to be treatment or procedure related. One death, due to cardiorespiratory arrest, occurred approximately 1 month after the patient received the last dose of study drug; the other death, due to an arrhythmia, occurred approximately 1 year after last dose of study drug.

<P>Five patients (27.8%) reported one serious adverse event (AE) each during the treatment period. One patient reported a right lower lobe pneumonia, which was determined by the investigator to be of moderate severity and possibly related to study drug. This event resolved in 2 days and did not result in discontinuation. Another patient reported worsening of preexisting peripheral neuropathy that did not resolve and resulted in discontinuation. This event was determined to be treatment related by the investigator. Three other patients reported serious AEs of peritonitis, hyperparathyroidism, and anemia, but these events were determined by the investigator to be unrelated to study drug.

<P>The most common AEs reported were injection-site pain (94%) and hypotension (28%). Further details of observed AEs are provided (Tables S2 and S3 in supporting information)**.**

<H2>***Transplant***

<P>Three patients received deceased donor kidney transplants while in the study due to the availability of matched donors, not due to significant tabalumab-associated reduction in cPRA. All three patients had completed the treatment period, and were in the posttreatment follow-up period.

<H1>**Discussion**

<P>Kidney transplantation is the most effective treatment option for patients suffering with ESRD (25,26). Many barriers remain, however, in the journey to transplant waitlisted patients, not the least of which is sensitization to HLA antigens. As has been noted earlier in this article, patients who have HLA antibodies are transplanted at a much slower rate than those who are unsensitized (5). With the advent of solid-phase antibody identification and the ability to quantitate the degree of antibody development, the transplant community has attempted to find a way to durably remove HLA antibodies with the goal of making the patient safer to transplant. That endeavor has thus far resulted in limited success (14,15). As noted, interventions to minimize sensitization have ranged from plasmapheresis and IVIG to pharmacological interventions including terminal complement and proteasome inhibition with multiple combinations thereof. Less pharmaceutically intensive attempts have included the use of paired donation to avoid or minimize antibody incompatibility (27). Despite the use of all of these interventions, sensitized patients, as a population, remain disadvantaged in their ability to receive a kidney transplant.

<P>This study was undertaken with the hope of developing a mechanism to decrease the degree of antibody production in the sensitized patient population. In theory, as BAFF is necessary to promote survival of B cells as they leave the bone marrow to enter the periphery, lowering of BAFF levels would appear to be an attractive target to affect ongoing antibody production. Indeed, in the murine model, BAFF-deficient recipients have extended cardiac allograft survival (28). The use of tabalumab appears to be effective in binding BAFF as evidenced by a rise in the BAFF/tabalumab complex in the periphery posttreatment; a similar increase in BAFF complex has been reported in a nonhuman primate model with atacicept, which blocks both BAFF and APRIL (29). Unfortunately, in looking at the desired outcomes of measured alloantibody parameters, the effectiveness of tabalumab was limited. While total immunoglobulin decreased, this did not lead to a durable decrease in cPRA. As noted, there was a statistically significant cPRA drop as a group, but this was both transient and did not appear to be clinically relevant. Indeed, in view of the new deceased donor kidney allocation algorithm, without a reasonable

drop in cPRA and the resultant clinically relevant removal of unacceptable antigens in determining an acceptable crossmatch, a small lowering of the cPRA might actually disadvantage the patient if the cPRA is lowered outside the range allowing national sharing of allografts (below cPRA 97%) (30). In those patients transplanted after receiving this medication, the lowering of antibody levels presumably facilitated by this medication was not sufficient to make transplant possible. Reviewing the solid-phase testing data, no patient had any of their top 10 Class I or Class II antibodies removed after treatment. However, in some instances, as evidenced by the statistically significant lowering of cPRA, antibody levels at the lower levels of significance did tend to fall. This change was durable in only those patients who were treated with immunosuppression after transplantation. While no changes were noted in mature plasma cells, the decreases in naïve and transitional B cells and increases in memory B cells returned to baseline numbers by Week 76.

<P>Of note, this study provided new immunopharmacologic characterization of BAFF inhibition in tissue, showing reductions in tonsillar B cells, Bm2' germinal center B cells, and TFH cells and increases in switched memory B cells at Week 24. Bone marrow cellularity and antibody-forming cells were not affected by tabalumab treatment. Importantly, pre-existing immunity to tetanus, mumps, and rubella were maintained.

<P>The complex immune response required for T cell–dependent anti-HLA antibodies is not likely to be susceptible to a single therapeutic intervention. In fact, while our study was in progress, a study using belimumab was terminated for not demonstrating efficacy (31). Current literature clearly indicates a multiprong approach targeting different B cell stages, bone marrow–derived plasma cells, antibody production, and complement dependent and independent effector mechanisms is more effective. CD20 transgenic mouse data demonstrate that a combination of B cell memory depletion (e.g. anti-CD20) and blockade of microenvironment survival signals (e.g. TACI and/or BAFF) is more effective at achieving depletion of B cell depletion–resistant compartments such as the germinal centers (32,33). Since the germinal center reaction is central to the development of antibody-producing cells, class switching, somatic hypermutation, and affinity maturation of antibodies, it is not surprising that any combined approach targeting such reaction would result in a more effective reduction of antibody production. It is therefore likely that the combination of antagonists of BAFF or its receptor (i.e. TACI antibodies) with new-

generation anti-CD20 or anti-CD154 antibodies would be more efficacious in suppressing anti-HLA antibody production than monotherapy. While our study did not produce the desired results, as only small cPRA reductions were seen, BAFF inhibition should not be completely discounted.

<H1>**Summary**

<P>BAFF inhibition in the setting of the highly sensitized patient provided only a small and likely clinically irrelevant reduction in the cPRA. Further studies are needed to determine a role for BAFF inhibition, especially in evaluating the potential combination with other immunologic interventions to lower antibody levels.

<H1>**Acknowledgments**

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<H1>**Disclosure**

<P>The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. WK, EN, and JH are employees of and own stock in Eli Lilly and Company. The other authors have no conflicts of interest to disclose.

<SUPPL>**Supporting Information**

<P>Additional Supporting Information may be found in the online version of this article.

<SFIGURE>**Figure S1: Individual patient class I alloreactivity over 76 weeks following 24 weeks of tabalumab treatment and up to 52 additional weeks of follow-up.**

<SFIGURE>**Figure S2: Individual patient Class II alloreactivity over 76 weeks following 24 weeks of tabalumab treatment and up to 52 additional weeks of follow-up.**

<STABLE>**Table S1:** Lymphocyte subsets enumerated over 76 weeks following 24 weeks of tabalumab treatment and up to 52 additional weeks of follow-up

<STABLE>**Table S2:** Serious adverse event summary

<STABLE>**Table S3:** Adverse event summary: other (not including serious) adverse events, frequency threshold of 5%

<P>**Data File S1:** Individual de-identified subject demographic data

<P>**Data File S2:** Transplant-related subject demographic data

<P>**Data File S3:** cPRA data by subject over entire study period

<P>**Data File S4:** BAFF (total, bound+unbound) concentration data by subject over entire study period

<P>**Data File S5:** HLA single antigen data by subject over entire study period

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<FIGURE>**Figure 1: Study diagram (A) and patient disposition (B).**

<FIGURE>**Figure 2: Individual patient cPRA values following 24 weeks of tabalumab treatment and up to 52 additional weeks of follow-up.** cPRA, calculated panel reactive antibody level.

<FIGURE>**Figure 3: Mean change from baseline in MHC class I (A) and MHC class II (B) antibodies following 24 weeks of tabalumab treatment and up to 52 additional weeks of follow-up.** MFI, mean fluorescence intensity.

<FIGURE>**Figure 4: Individual patient total BAFF (bound and unbound) concentrations following 24 weeks of tabalumab treatment and up to 52 additional weeks of follow-up.** BAFF, B cell activation factor.

<FIGURE>**Figure 5: Mean change from baseline in total IgG, IgA, IgM (A), IgG subclasses (B), and preexisting tetanus, mumps, and rubella IgG (C) following 24 weeks of tabalumab treatment (120 Q4W) and up to 52 additional weeks of follow-up.**

<FIGURE>**Figure 6: Mean percent change from baseline in select B cell subsets and total T cells in blood following 24 weeks of tabalumab treatment (120 Q4W) and up to 52 additional weeks of follow-up; relative percent of total lymphocytes.**

<TABLE>**Table 1:** Key study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
≥18 years of age	Had a tonsillectomy

Stable and elevated cPRA, defined as: 1. All cPRA values were >50% in the year preceding study enrollment (including screening cPRA) 2. Must have at least two cPRAs meeting criteria 1 above with a minimum 2-month interval between at least one historical cPRA and the screening cPRA 3. Not more than a 20 percentage point difference between the maximum and minimum cPRA in the year before the study (including screening cPRA)	Had received any immunosuppressive or immunomodulatory therapy within 3 months of baseline (or five elimination half-lives, whichever was longer)
	Treated with IVIG or plasmapheresis within 6 months of baseline
	Received rituximab or any other B cell therapy at any time
	Presence of clinically significant cardiac disease or uncontrolled arterial hypertension
	Known hypogammaglobulinemia or screening serum IgG, IgM, or IgA concentration less than the LLN
	Abnormal PT or APTT; or significant hematologic abnormalities
	Evidence of HBV/HCV/HIV or TB infection
	Had a serious infection with recovery <3 months before screening or had an active or recent infection within 30 days of screening

<TLEGEND>APTT, activated partial thromboplastin time; cPRA, calculated panel reactive antibody; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IVIG, intravenous immunoglobulin; LLN, lower limit of normal; PT, prothrombin time; TB, tuberculosis.

<TABLE>**Table 2:** Patient demographics and other characteristics

Category	Mean ± SD[1]
Age (years)	44.2 ±12.09
Sex (n) (male/female)	8/10
Race (n) AA/white/Asian	11/6/1
BMI	26.9 ± 4.4
Systolic BP	140.6 ± 20.77
Diastolic BP	82.4 ± 11.11
Baseline cPRA	94.4 ± 9.15
Number of days on transplant wait list	1830 ± 1579
Previous transplant (n)	17
Previous pregnancy (n)	10
Previous transfusion (n)	18

<TLEGEND>AA, African American; BP, blood pressure; cPRA, calculated panel reactive antibody level; SD, standard deviation.

<TLEGEND>[1]Unless otherwise specified.