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Drug Profile

The potential role of blisibimod for the treatment of systemic lupus erythematosus

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In the last 50 years, only one drug has achieved marketing approval for treatment of systemic lupus erythematosus (SLE) by global regulatory authorities. This drug, belimumab, is a monoclonal antibody that binds to and inhibits BAFF. Blisibimod is a 'peptibody' consisting of four BAFF-binding domains fused to the Fc domain of human IgG_1, and is structurally distinct from the anti-BAFF monoclonal antibodies such as belimumab and tabalumab. Compared with tabalumab and belimumab, blisibimod's binding affinity for BAFF (1 pM) is 126–250-fold higher, while its serum half-life (8–10 days) is approximately half as long. Completed Phase I and Phase II clinical trials with blisibimod provide the first evidence that subcutaneous administration of a biologic therapeutic may lead to improvements in SLE disease activity, as well as disease-associated pharmacodynamic markers, including peripheral B cells, autoantibodies and decreased complement consumption. Furthermore, the effect to significantly decrease the urinary protein:creatinine ratio suggests that blisibimod may have therapeutic potential beyond SLE in patients with mechanistically analogous autoimmune renal damage, such as lupus nephritis and IgA nephropathy.

Keywords: BAFF • B cell • blisibimod • lupus • SLE

Systemic lupus erythematosus (SLE) is an autoimmune disease associated with autoantibodies capable of provoking injury in different organs of the body [1]. Until recent years, no new treatments were developed for SLE since advent of corticosteroid pulse therapy in 1976 [2], and there was a clear need for treatment options to address the long-term effects of the disease or chronic steroid use on quality of life, tissue damage and mortality [3]. Over the last decade, new strategies for SLE treatment have emerged from preclinical research and entered clinical development. In particular, drug mechanisms that target various stages of B-cell differentiation and survival have been under intense scrutiny [4], although the effects of these drugs on positively modulating the natural history of this disease remains to be determined. These B-cell strategies have drawn considerable attention, starting with the anti-CD20 monoclonal antibody therapeutic, rituximab, and continuing with belimumab, a monoclonal antibody that inhibits BAFF (also known as BLyS). This line of research and clinical investigation ultimately led to the approval of belimumab, the first biological treatment for SLE [5].

The first approach to directly modulate B-cell function tested clinically in patients with SLE was to deplete B cells with the anti-CD20 monoclonal antibody, rituximab [6]. Rituximab is approved for treatment of multiple autoimmune and hematological diseases, including rheumatoid arthritis (RA), small-vessel vasculitides, non-Hodgkin's lymphoma and chronic lymphocytic leukemia, and its potential to benefit patients with SLE was reasonably inferred from its effects in related diseases. CD20 is expressed on the surface of B cells from the immature stage in the bone marrow through naive, activated and memory cell lineages, but not on plasma cells. Although the randomized, placebo-controlled

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clinical trials with rituximab in patients with SLE and lupus nephritis failed to show therapeutic benefit when compared with placebo [7,8], the potential benefit of this drug is supported by numerous open-label and anecdotal reports where dramatic improvements in disease activity are reported [6,9]. Analyses of the failed trials raised the question whether inadequate drug efficacy or study design might account for the apparent failure of the trials [10]. In the EXPLORER trial (rituximab in patients with SLE) and LUNAR trial (rituximab in patients with lupus nephritis) patients received high-dose corticosteroid therapy upon randomization to the study drug, which may have masked improvements due to rituximab, and definitions of treatment response were possibly too stringent to enable meaningful statistical comparisons [8,10,11].

BAFF is primarily expressed in both the membrane-bound form and soluble form by macrophages, monocytes, dendritic cells, neutrophils and B cells, and is known to mediate B-cell differentiation and survival via signaling through its three cognate receptors: BAFF receptor, BCMA and transmembrane activator and TACI [12,13]. The three BAFF receptors are expressed predominantly on B cells and plasma cells. A role of BAFF in autoimmune diseases is implied from the increased activity of B cells and plasma cells, as well as the increased expression of BAFF in autoimmune diseases in patients and/or animal models, such as SLE, IgA nephropathy, lupus nephritis, Sjögren's syndrome and RA [14–20]. In several of these diseases, for example SLE and IgA nephropathy, the elevations in BAFF were found to be significantly correlated with disease activity or severity. BAFF has also been associated with hematological malignancies such as multiple myeloma [21,22]. In nonclinical studies, transgenic mice that overexpress BAFF exhibit symptoms similar to lupus. The recent demonstration in two global Phase III clinical trials that belimumab significantly decreases SLE disease activity strengthens the concept that B cells and BAFF are involved in SLE [23,24].

Three BAFF inhibitors, belimumab, tabalumab and blisibimod, have ongoing or completed Phase III clinical trials in patients with SLE. The best known of these, belimumab, is recognized for being the first drug to be approved by the US FDA for the treatment of SLE in the last 50 years. In Phase III clinical trials, significant clinical benefit was observed with the monoclonal anti-BAFF antibody, belimumab (also known as LymphoStat-B and Benlysta®; GSK, Middlesex, UK) [23,24].

The belimumab clinical development program incorporated the critical findings from *post hoc* analyses of a failed Phase II trial in patients with SLE [25], which gave rise to a new means of measuring clinical benefit, the SLE Responder Index (SRI) [26]. The SRI consists of a four point improvement (decrease) in Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index (SELENA-SLEDAI), and no new British Isles Lupus Assessment Group A or ≥2B organ domain scores, and no worsening (<0.3 increase) in Physician's Global Assessment. In two global Phase III clinical trials, BLISS-52 and BLISS-76, significant improvement in SRI was observed over 52 weeks of intravenous belimumab therapy (10 mg/kg) compared with placebo [23,24] . Belimumab was safe and generally well tolerated. Serious and severe adverse events, including infections, laboratory abnormalities, malignancies and deaths, were comparable across placebo and belimumab groups.

Belimumab has gained marketing approval for treatment of SLE in multiple countries including the USA, Canada, Brazil, Canada and Germany, and is seeking marketing approval in several others. Additional clinical trials in patients with SLE are ongoing with belimumab, including efficacy studies following subcutaneous administration to patients with SLE, in pediatric patients with SLE and in patients of black race with SLE. The latter study is especially critical given the prevalence of SLE in this population, and the concerns arising from analyses in the small racial subgroups in the Phase III trials where lower responder rates to belimumab were observed in patients of black race. A registry has also been established to follow the effect of the drug on pregnancy, which is critically important given that SLE predominantly affects women. Additional ongoing trials aim to explore the efficacy of belimumab in other immune and autoimmune diseases, including active lupus nephritis, vasculitis, Waldenström's macroglobulinemia, kidney transplant rejection, idiopathic membranous nephropathy and Sjögren's syndrome.

Two global Phase III trials with the monoclonal anti-BAFF antibody, tabalumab (also known as LY2127399), are ongoing in patients with SLE. While no data to evaluate the effect of tabalumab have been reported to date, improvements in ACR20 scores in patients with RA were reported from three completed Phase II trials with this drug [27–29]. In patients with RA with inadequate response to methotrexate or anti-TNFα therapy, significant improvements in joint count were observed as early as 6 weeks after initiation of therapy with concomitant reductions in $CD20^+$ B cells and IgD^+CD27^- naive B cells, and increases in IgD^-CD27^+ memory B cells. However, surprisingly, emerging data at similar doses of tabalumab showed no improvements in ACR20 scores in patients with RA in a larger Phase III trial despite significant pharmacodynamic effects on

B cells subsets and immunoglobulins [30]. As of February 2013, the Phase III program with tabalumab in RA was formally ended but the Phase III trials in patients with SLE proceed despite this. Although no data for tabalumab are available in patients with SLE as yet, the observations in patients with RA engender a hope that the improvements in joint counts seen in this disease may be mirrored in patients with SLE where musculoskeletal manifestations are common [23].

Other drugs that target B-cell signaling pathways are in late-stage clinical development in lupus. The observations with these molecules lend further support to the hypothesis that targeting the B-cell pathways is of therapeutic benefit. Atacicept is a soluble recombinant fusion protein that binds to BAFF and APRIL (a proliferation-inducing ligand), the endogenous ligands for BAFF receptor, TACI and BCMA receptors, and thereby regulates maturation and survival of B cells [31]. Atacicept was found to reduce the numbers of peripheral B cells, and to rapidly and profoundly decrease immunoglobulins IgM, IgG and IgA in patients with RA and lupus nephritis [32–34]. More recently, atacicept was reported to reduce the risk of severe flares in patients with SLE with concomitant decreases in immunoglobulins, naive and memory B-cell subsets, and plasma cells [35,36]. Concerns around the risk of serious infections prevail with atacicept as the high atacicept dose group in this study was discontinued due to serious infections, and an earlier Phase II study with mycophenolate combination therapy was terminated due to the early appearance of rapid decline of serum immunoglobulins [34]. Epratuzumab is a humanized monoclonal antibody targeting CD22 that is being studied in clinical trials for patients with a variety of rheumatic and hematologic conditions, including SLE [37]. Significant improvements in SLE disease activity were observed following 12 weeks of treatment with epratuzumab in the Phase II EMBLEM study [38]. Furthermore, emerging data from the open-label study suggest long-term clinical benefit with epratuzumab over 2 years [39]. Multiple other drug mechanisms, including those not specifically targeting B-cell pathways are under active evaluation in nonclinical and clinical studies for lupus: orencia, a costimulation modifying agent (CTLA-4-Fc) [35,40]; rigerimod, a fragment of spliceosomal small nuclear ribonucleic particles [41]; inhibitors of IFN-α, sifalimumab, MEDI-546, rontalizumab and IFN-α kinoid [42–44]; the anti-IFN gamma antibody AMG 811; toll-like receptor inhibitors; the anti interleukin 6 antibody sirukumab [45]; the phosphodiesterase 4 inhibitor apremilast; the anti-CD74 monoclonal antibody milatuzumab; and inhibition of the B7RP-1 pathway with AMG 557.

The hope that springs from this expanding list of prospective lupus therapies is bolstered by the refinements in SLE clinical design learned from trials over the last decade of research . In particular, important partnerships between the clinical community, regulatory authorities and industry have given rise to significant improvements in trial methodology including: measurement of efficacy, identification of likely drug responders, and ethical methods for evaluating drug effects on a background of ongoing SLE care [7,23,25,26,38]. These improvements benefit the development programs for all future drugs, including blisibimod.

Blisibimod's structure & nonclinical properties

Blisibimod (also known as A-623 and AMG 623) is a 'peptibody' composed of the Fc domain of human IgG_1 fused to four BAFF-binding domains that bind with high affinity to BAFF (Figure 1). Peptibodies offer a viable alternative to existing monoclonal antibody approaches and the approval of romiplostim for the treatment of immune thrombocytopenia purpura validates the feasibility and clinical use of this unique structural class [46]. Blisibimod was discovered and developed through Phase I clinical trials by Amgen, Inc. (CA, USA) and subsequently licensed by Anthera Pharmaceuticals, Inc. (CA, USA) who conducted/initiated the Phase II and III trials. Unlike other anti-BAFF drugs in clinical trials, all of which are monoclonal antibodies, blisibimod's peptibody structure confers unique structural attributes to the drug, including the

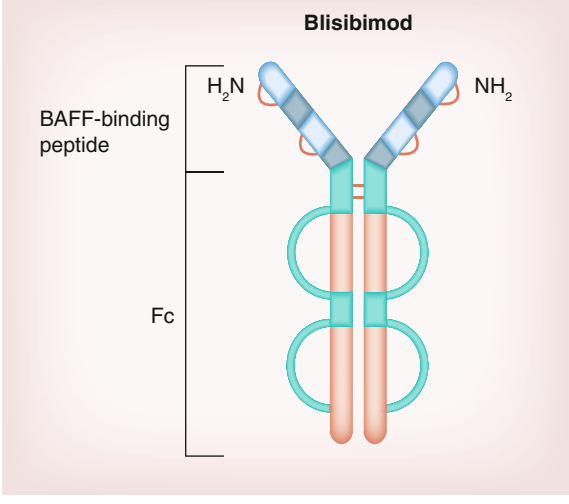


Figure 1. The structure of blisibimod. The blisibimod peptibody is composed of two identical polypeptides each with four BAFF-binding peptides (light blue), a human IgG1 Fc domain (green), and disulfide bonds (red) that form the tertiary structure, including covalent crosslinking of the dimers.

ability to be synthesized in an unglycosylated form from *Escherichia coli* cells (Table 1). Blisibimod binds to both soluble and membrane-bound BAFF with high affinity (dissociation equilibrium constant [K_D] = 1 pM for soluble BAFF), and inhibits the interaction of BAFF with all three of its cognate receptors, BAFF-R, TACI and BCMA [47]. When incubated with murine splenic B cells, blisibimod inhibited BAFF-mediated B-cell proliferation as measured by ^{3}H thymidine uptake [47]. In rodent models of autoimmune disease, including NZBxNZW lupus mice, and collagen-induced arthritis, blisibimod improved survival and disease activity as measured by proteinuria and joint activity, respectively. To date, no data with belimumab or tabalumab in nonclinical models of autoimmune disease have been reported. As such, it is not possible at present to evaluate whether blisibimod's high affinity or dual inhibition of soluble and membrane-bound BAFF has a beneficial impact on efficacy. Based on its ability to bind to and antagonize the action BAFF, blisibimod is being developed as a treatment for chronic autoimmune diseases including SLE and IgA nephropathy. To date, three randomized, placebo-controlled, double-blind, Phase I and II clinical trials with blisibimod have been completed in patients with SLE.

Pharmacokinetics of blisibimod

Key among the assessments completed in the Phase I clinical trials was the evaluation of blisibimod pharmacokinetics. Following subcutaneous administration, the peak serum concentration of blisibimod was observed approximately 2 days after subcutaneous administration of blisibimod (0.3–3 mg/kg), and the serum half-life of blisibimod was determined to be 8–10 days (Table 2), and the volume of distribution of blisibimod (approximately 3–4 l following a single dose) is approximately three-times greater than the plasma volume, demonstrating limited distribution outside plasma.

In the PEARL-SC Phase II trial in patients with SLE, administration of blisibimod was moved from weight-based dosing (i.e., in fixed mg/kg) to a fixed, weight-independent dosing (100 or 200 mg administered at weekly or 4-weekly intervals). Under the latter dosing regimens, no effect of race on trough concentrations of blisibimod was observed at any dose.

Analogous to therapeutic monoclonal antibodies, the long serum half-life observed for blisibimod compared with non-Fc-containing biologics is attributed to the 'salvage' mechanism that arises from the interaction between the fully-human IgG1 Fc domain of blisibimod and the neonatal FcR receptor [49,50]. Specifically, blisibimod has a high, antibody-like affinity for the neonatal FcR receptor (Figure 2A). Owing to its expression in *E. coli*, blisibimod is not glycosylated, and consequently has a profoundly reduced (~85-fold) binding affinity for the FcγR1 effector receptor subtype (Figure 2B). Loss of affinity for the FcγR receptors and subsequent reductions in associated effector function is established for nonglycosylated Fc domains [51,52]. As a result of aglycosylation, blisibimod, in contrast with glycosylated, wild-type, mammalian IgG_1 antibodies, is predicted to have a diminished ability to provoke antibody-dependent cell-mediated cytotoxicities.

Phase I evaluation of blisibimod safety & effects on B cells

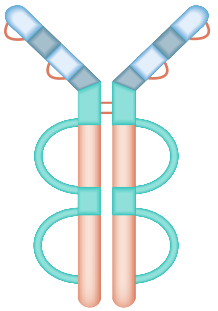
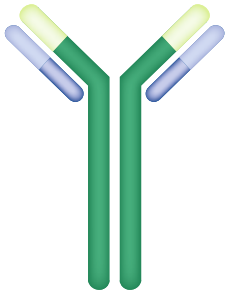
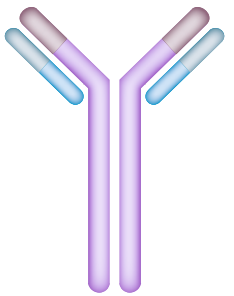
The Phase I studies explored the safety, pharmacokinetics, and pharmacodynamic effects of blisibimod on the B-cell compartment of patients with SLE following a single dose or 4 weekly doses of blinded, randomized administration of blisibimod or placebo; these methods and observations for studies were reported previously in abstract form [53]. Analogous to the effects reported with belimumab in patients with SLE and tabalumab in patients with RA, significant decreases in the numbers of total B cells ($CD19^+CD20^+$) and naive B cells (IgD^+CD27^-) were observed along with increases in $CD27^+$ memory B cells. In both of the Phase I studies, blisibimod was safe and well tolerated following subcutaneous doses of blisibimod up to 3 mg/kg, and intravenous doses up to 6 mg/kg. Among the most common adverse events reported following 4 weekly doses of study drug was nasopharyngitis, headache, injection site erythema and nausea. These events were all considered mild.

Phase IIb evaluation of blisibimod efficacy & safety

The Phase IIb PEARL-SC trial evaluated the efficacy, safety, and tolerability of subcutaneously-administered blisibimod in patients with seropositive, moderate-to-severe SLE as defined anti-double-stranded DNA (anti-dsDNA) or anti-nuclear antibodies, and SELENA-SLEDAI score ≥6. The methods and key observations for this study were reported previously in abstract form [54] Patients received placebo or blisibimod administered at one of three dose levels, 100 mg weekly (QW), 200 mg QW, or 200 mg every 4 weeks for 24–52 weeks (Figure 3) administered on top of existing, stable standard-of care medication for SLE. Common standard-of-care medications included antimalarials, corticosteroids and immunosuppressants.

The primary end point was the percentage of subjects who achieved an SLE Responder Index-5 (SRI-5) [26] response at week 24 in the pooled blisibimod arms compared with the pooled placebo arms. An SRI-5 responder has: ≥5 point improvement in SELENA-SLEDAI, and

Table 1. Summary of the pharmacological and structural features of BAFF inhibitors in late-stage clinical development.

Name	Structure	Affinity (pM)	Isotype	Serum half-life (days)	Molecular weight (kDa)	Valency and avidity	Flexibility	Binding interactions	Expression system
Blisibimod		1	Contains IgG1 Fc domain	8–10	64	High avidity from four BAFF-binding domains	Variable linker size tolerates range of binding distances	Soluble BAFF Membrane-bound BAFF	*Escherichia coli* fermentation (aglycosylated)
Benlysta		250–350	IgG1	19.4	147	Two antigen-recognition domains (on each Fab)	Rigid antibody structure constrains binding distances	Soluble BAFF	Mammalian cell culture
Tabalumab		120	IgG4	25	~150	Two antigen-recognition domains (on each Fab)	Rigid antibody structure constrains binding distances	Soluble BAFF Membrane-bound BAFF	Mammalian cell culture

Data taken from [28,47,48].

Table 2. Mean pharmacokinetic parameters after single subcutaneous doses of blisibimod to subjects with systemic lupus erythematosus.

Dose (mg/kg)	AUC_{0-t} (μg•h/ml)	$t_{1/2z}$ (days)
0.1 (n = 6)	50.0	4.0
0.3 (n = 6)	252	6.5
1.0 (n = 9)	1140	9.8
3.0 (n = 6)	2770	8.4

AUC_{0-t}: Area under the concentration–time curve from time 0 to time of the last quantifiable concentration; $t_{1/2z}$: Terminal half-life.

no new British Isles Lupus Assessment Group A or ≥2B organ domain scores, and no worsening (<0.3 increase) in Physician's Global Assessment. Efficacy analyses were conducted in the modified intent-to-treat (mITT) population comprising of all subjects receiving at least one dose of study drug.

A total of 547 subjects meeting these criteria were enrolled from Latin America, Asia/Pacific territories and North America. The most common organ manifestations at enrollment were mucocutaneous (91%), immunological (77% with high anti-dsDNA, or low C3 or C4) and musculoskeletal (75%). A total of 14% of subjects had renal involvement. A mean SELENA-SLEDAI score of 10.1 was observed at randomization.

Although the primary end point was not met in this study, greater numbers of responders were observed in the blisibimod group compared with placebo. Furthermore, the improvements in SRI-5 responder rates compared with placebo generally best among subjects receiving the highest dose of blisibimod, 200 mg QW. Treatment benefit was greater still when compared with the regimen-matched (QW) placebo.

Significantly higher responder rates were observed with 200 mg QW blisibimod compared with matched placebo in prespecified secondary analyses using modified SRI analyses in which responders attained SELENA-SLEDAI improvements of ≥8. Furthermore, in a subgroup (n = 278) of 'severe' SLE subjects defined by baseline SELENA-SLEDAI ≥10 and receiving corticosteroids at any dose, the SRI responder rates in the 200 mg QW blisibimod group were significantly higher compared with regimen-match placebo when evaluated using the SRI-8 end point [54]. These effects of blisibimod on the SRI-5 and SRI-8 outcomes were essentially recapitulated in the subgroup of subjects enrolled from Latin America (71% of all patients enrolled). Specifically, modest improvements in SRI-5 were observed in the mITT population, while greater

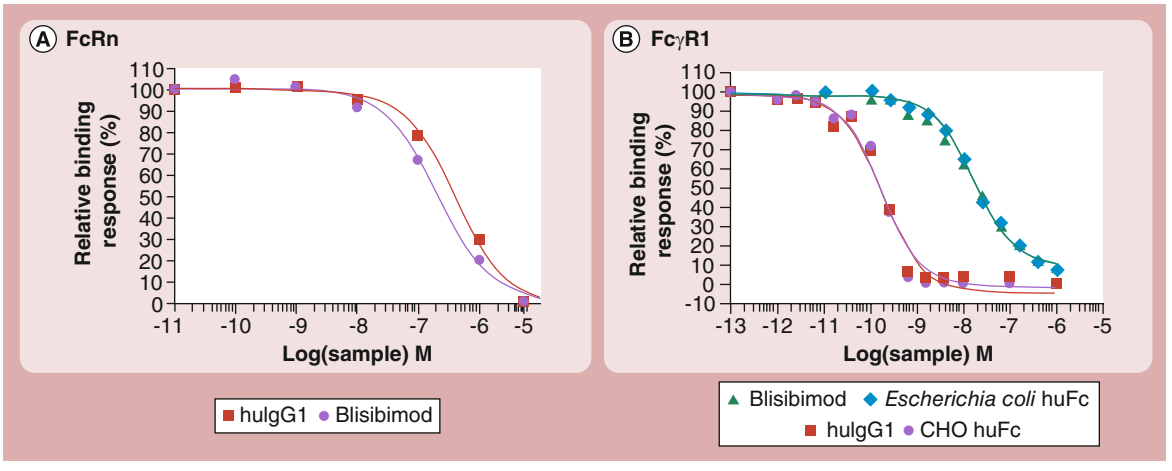


Figure 2. Assessment of binding of blisibimod, human IgG1 antibody, or human Fc domain expressed from *Escherichia coli* or mammalian (chinese hamster ovary) cells for the neonatal FcR and FcγR1 receptor subtypes determined by surface plasmon resonance. (A) FcRn and **(B)** FcγR1 receptor subtypes. Various amounts of blisibimod were incubated with 10 nM human FcRn or FcγR1 in sample buffer (50mM sodium phosphate, 150 mM NaCl, 0.1 mg/ml bovine serum albumin, 0.005% polysorbate 20, pH 6.0) for 1 h prior to injection over Biacore™ (GE Healthcare Bio-Sciences, PA, USA) sensor chips with surface-immobilized human Fc. Relative binding responses of FcRn or FcγR1 in the presence of blisibimod are shown (n = 3 for each data point). Binding comparators evaluated in this study : human Fc expressed in *E. coli* (E Coli huFc), human IgG1 expressed in CHO cells (huIgG1) and human Fc expressed in CHO cells (CHO huFc).
CHO: Chinese hamster ovary; FcRn: Neonatal FcR; huFc: Human Fc domain; huIgG1: Human IgG1 antibody; M: Molar.

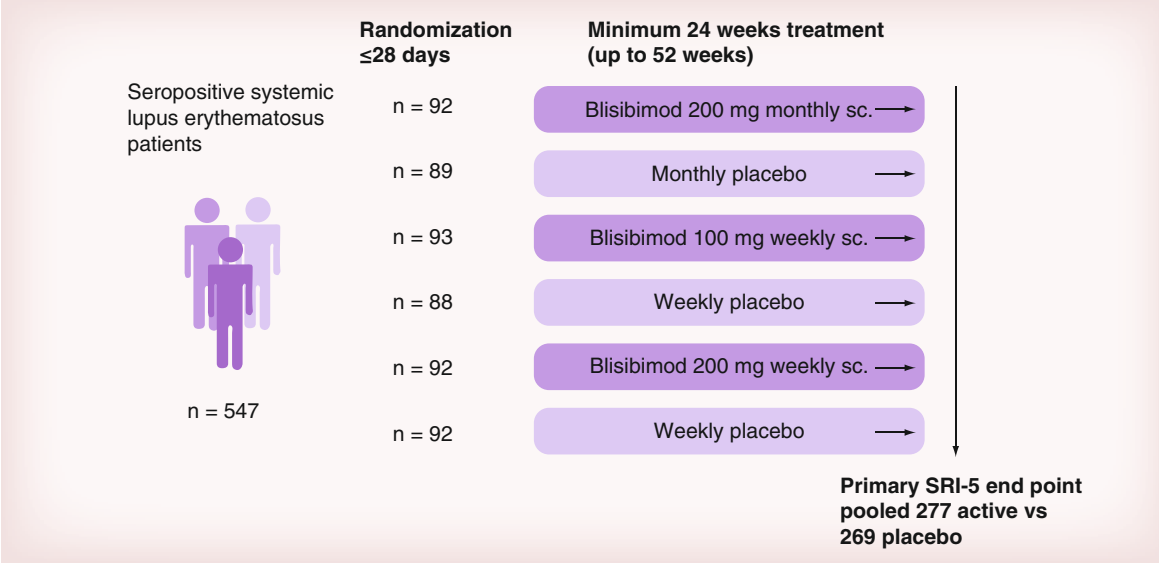


Figure 3. Study design for the Phase IIb clinical trial of blisibimod on patients with systemic lupus erythematosus. In total, 547 subjects with systemic lupus erythematosus were enrolled in the PEARL-SC study. These patients were positive for anti-double-stranded DNA or anti-nuclear antibodies and had a Safety of Estrogens in Lupus Erythematosus National Assessment version of the SRI score of ≥6 at enrollment. Subjects received the blinded study drug (blisibimod or placebo) for 24–52 weeks. The primary end point was the percentage of subjects who achieved an SRI-5 response at week 24 in the pooled blisibimod arms compared with the pooled placebo arms. An SRI-5 responder has: ≥5 point improvement in Safety of Estrogens in Lupus Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index, and no new British Isles Lupus Assessment Group A or ≥2B organ domain scores, and no worsening (<0.3 increase) in Physician's Global Assessment.
sc.: Subcutaneous; SRI: Systemic Lupus Erythematosus Responder Index.

increases in SRI-8 were observed in the mITT population, which were greater still when the SRI-8 was evaluated in the severe subgroup of the Latin American subjects: comparing 200 mg QW blisibimod to placebo, ΔSRI-5: 3.7%, ΔSRI-8: 23.9% and ΔSRI-8 in severe subjects: 39.3% (Figure 4).

In order to explore the drivers of SRI-8 response, the proportion of subjects who achieved the 'clinical SRI-8' was determined. For this analysis responders were defined as meeting all of the SRI-8 criteria excluding contributions of complement, anti-dsDNA, thrombocytopenia and leukopenia to the SELENA-SLEDAI score. A significant improvement in clinical SRI-8 was observed with 200-mg QW blisibimod in subjects in the severe SLE subgroup (p = 0.004, Figure 5). The proportions of subjects achieving the clinical SRI-8 response criteria was only 2–6% lower than the proportions of subjects achieving the SRI-8 response at the corresponding time points. These data suggest that the SRI-8 is largely driven by clinical improvements and not by changes in laboratory parameters in the subgroup.

Significant decreases in peripheral B cells, anti-dsDNA autoantibody, and immunoglobulins IgG and IgM [56], as well as significant increases in complement C3 and C4, were observed with blisibimod compared with placebo. These effects demonstrate that the blisibimod doses administered in this study were pharmacologically active.

Importantly, a significant decrease in the protein:creatinine ratio (measured from random urine) was observed in the subset of patients with proteinuria at enrollment (n = 54). Given the reported relationship between anti-dsDNA and renal manifestations in SLE [57], the protein:creatinine observation is arguably bolstered by the concomitant decreases in anti-dsDNA autoantibodies observed with blisibimod. This reduction in protein:creatinine ratio is consistent with the significant reductions in proteinuria reported in *post hoc* observations from the BLISS-52 and BLISS-76 studies with belimumab [58]. BAFF plays a role in normal survival and proliferation of B cells (Figure 6A). Under pathological conditions, high levels of BAFF are observed, for example in serum from patients with SLE or lupus nephritis [19,59], which may lead to excessive survival signals to autoreactive B cells and plasma cells, thereby increasing the secretion of autoantibodies (Figure 6B). Inhibition of BAFF is expected to block stages of B-cell maturation and plasma cell genesis, and subsequent expression and secretion of autoantibodies (Figure 6C). This therapeutic hypothesis is supported by the observed effect of blisibimod to significantly decrease circulating B cells, anti-dsDNA, and immunoglobulins IgG and IgM [56], and further

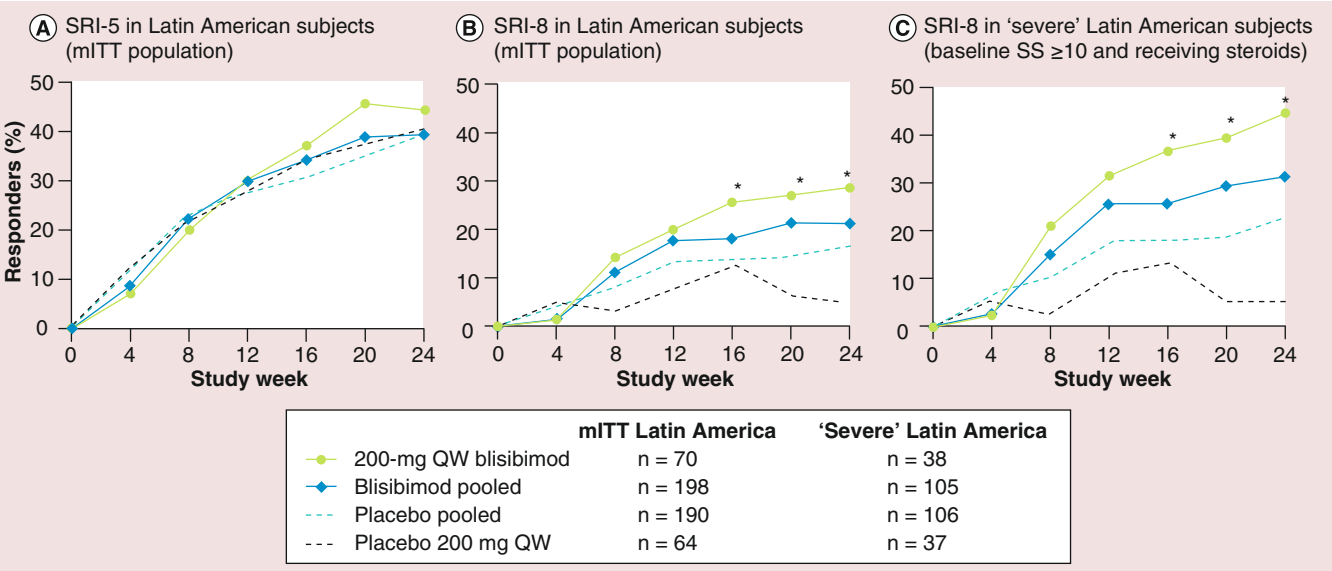


Figure 4. Effects of blisibimod on Systemic Lupus Erythematosus Responder Index-5 and -8 in subjects with systemic lupus erythematosus enrolled from Latin America into the PEARL-SC Phase II trial. The main findings of the study were recapitulated in the subgroup of subjects enrolled from Latin America (71% of all patients enrolled). **(A)** Specifically, modest improvements in SRI-5 were observed in the mITT population, **(B)** while greater increases in SRI-8 were observed in the mITT population, **(C)** which were greater still when the SRI-8 was evaluated in the 'severe' subgroup of the Latin American subjects. SRI-5 and SRI-8 responders achieve a ≥5 or ≥8 point improvement in SELENA-SLEDAI (respectively), and no new British Isles Lupus Assessment Group A or ≥2B organ domain scores, and no worsening (<0.3 increase) in Physician's Global Assessment.
*$p \leq 0.05$ vs pooled placebo.
mITT: Modified intent-to-treat; QW: Weekly; SRI: Systemic Lupus Erythematosus SLE Responder Index.
Reproduced from [55].

corroborated by observations with belimumab in patients with SLE in the BLISS-52 and BLISS-76 studies where rapid and significant decreases in peripheral plasma cells were observed, along with significant decreases in immunoglobulins, including IgA, IgG and anti-dsDNA antibodies [60,61]. Therefore, further evaluation of the effect of blisibimod in larger cohorts of patients with renal manifestations of SLE is warranted. If corroborated, the finding has the potential to provide a new alternative to the existing therapeutics where toxicities are known and limiting. Arguably, the data additionally support evaluations of blisibimod efficacy in patients with similar autoimmune renal diseases, such as lupus nephritis and IgA nephropathy, which are associated with similar infiltration to the glomerular and tubular basement membranes of immune complexes, which stain positive for autoantibodies and complement [62,63].

Throughout the 24–52 weeks of dosing, blisibimod was safe and well tolerated at all dose levels with no meaningful imbalances in serious adverse events or infections between blisibimod and placebo. Among the commonly reported adverse events, imbalance was observed only with injection site reactions, but these were never serious or severe.

In addition to the safety and efficacy findings from the prospective analyses of the PEARL-SC study, a rapid improvement in cryoglobulins was reported in a case study of one of the subjects. The patient had intermittent cutaneous vasculitis associated with elevated levels of polyclonal cryoglobulins of mixed type IgG-IgM, and had previously discontinued rituximab treatment due to anaphylactoid reaction. She was randomized to the placebo group during the PEARL-SC study, and initiated treatment with blisibimod during the ensuing open-label extension study. Within 6 months of initiating blisibimod therapy her serum cryoglobulins were reduced to below detectable levels and remained low throughout the continuing blisibimod treatment [64].

Further clinical development of blisibimod

Whether the effects of blisibimod observed in PEARL-SC translates to meaningful clinical benefit for patients with SLE remains to be determined in larger trials. The safety observations from the completed Phase I and II trials suggest that blisibimod may safely be administered in long-term clinical trials. The observations from the secondary efficacy and subgroup analyses of the PEARL-SC study essentially dictate the design of the Phase III clinical program with blisibimod, CHABLIS-SC, with respect to dose, trial end point and study population. Specifically, they suggest that the probability of successful therapeutic

intervention may be optimized by evaluation of the effect of 200 mg QW blisibimod on SRI-8 responder rates in patients with severe SLE (defined as having baseline SELENA-SLEDAI ≥10 and receiving corticosteroid at enrollment). The design of the CHABLIS-SC Phase III program additionally incorporates several learnings from clinical trials with other drugs in patients with SLE. For example, the confounding effects of some background medications and initiation of corticosteroid medication at the same time as study drug, which may have compromised the evaluation of rituximab efficacy in the LUNAR and EXPLORER studies, are mitigated by the requirement that subjects enrolled in the CHABLIS-SC trials be on stable background medication at the time of enrollment. Furthermore, in keeping with the methodology used in the belimumab Phase III trials, elevations in background medications after enrollment are allowed if medically necessary, and are imputed as protocol-defined treatment failures for the SRI end point if they exceed predefined medication limits. In *post hoc* analyses of the belimumab trials, various baseline disease characteristics were associated with greater benefit from belimumab therapy: SELENA-SLEDAI ≥10, anti-dsDNA ≥30 IU, low C3, low C4 and receiving steroid medication [65]. These observations corroborate the findings in the severe SLE population in the PEARL-SC trial with blisibimod, and lend confidence to the plan to focus on this patient population in Phase III trials. In addition, the decision to focus on the severe patients who have the greatest unmet need responds to a medical and commercial imperative to ameliorate disease in the patients who have inadequate disease control under existing therapeutic options.

Enrollment into CHABLIS-SC Phase III clinical development program has commenced. Assuming similar SRI-8 responder rates for 200-mg QW blisibimod (42%) and placebo (26%) to those observed in the PEARL-SC study in this severe population, and assuming use of a two-sided analysis at the $\alpha = 0.05$ level of significance, the power to detect an SRI-8 treatment effect is 92% for an evaluable study size of 400 subjects. Efficacy will be evaluated after 52 weeks of treatment. An earlier futility analysis of clinical data is to be conducted by an independent unblinded statistician after a minimum of 100 subjects have completed 24 weeks of treatment to confirm the clinical and commercial assumptions of the design of this study. This futility analysis will not provide any rules for stopping for overwhelming efficacy, change in study sample size or alteration of the study design.

The significant reductions in protein:creatinine ratio observed in the PEARL-SC study support further exploration of blisibimod effect in patients with autoimmune renal diseases, such as lupus nephritis and IgA nephropathy where safe therapeutic options are urgently needed. A Phase II/III trial in patients with IgA nephropathy is currently enrolling.

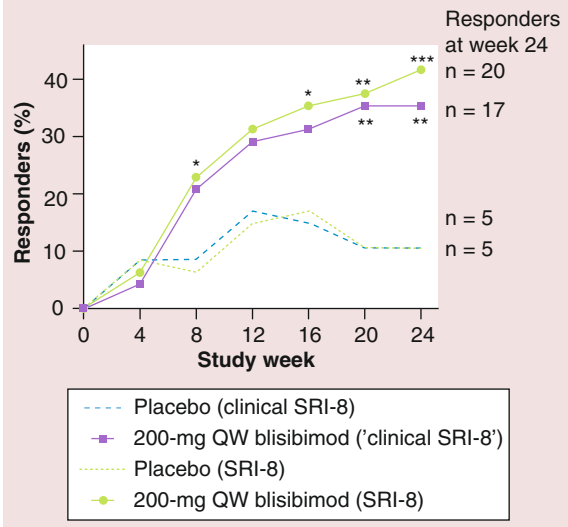


Figure 5. Effects of blisibimod on subjects in the 'severe' systemic lupus erythematosus subgroup (Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index ≥10 and receiving steroid at baseline) that met the criteria for the Systemic Lupus Erythematosus Responder Index-8 and the 'clinical Systemic Lupus Erythematosus Responder Index-8'. The 'clinical SRI-8' end point includes all of the parameters of the SRI-8 except that it does not count the contributions of complement, DNA binding, thrombocytopenia or leukopenia to the Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index score. At all time points through week 24, SRI responder rates with blisibimod were compared with pooled placebo ($p < 0.05$) and regimen-matched placebo.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.
SRI: Systemic Lupus Erythematosus Responder Index.
Reproduced from [54].

Conclusion

Taken together, the nonclinical and clinical data with blisibimod support continued development of blisibimod in SLE. The structure of blisibimod is designed to optimize its pharmacological, pharmacokinetic and toxicologic properties. Specifically, the four BAFF-binding domains confer a potential for higher avidity that can be achieved from the obligate bivalent monoclonal antibodies. This feature may account for the 126–250-fold higher affinity observed with blisibimod compared with tabalumab and belimumab. The human IgG1 Fc domain, expressed in an aglycosylated form from *E. coli*, enables the observed 8–10-day serum half-life while minimizing risk of cell-mediated cytotoxicities.

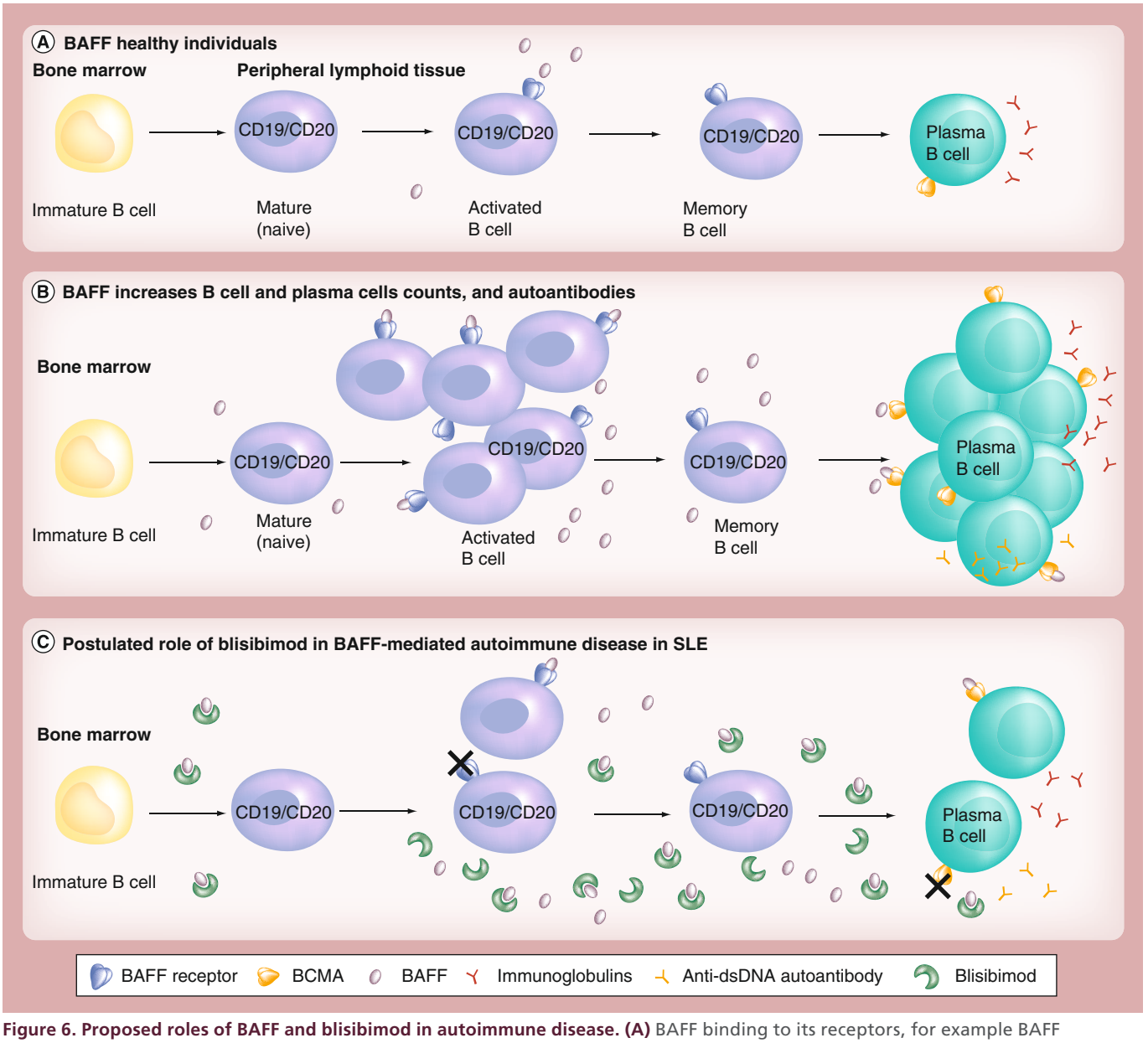


Figure 6. Proposed roles of BAFF and blisibimod in autoimmune disease. (A) BAFF binding to its receptors, for example BAFF receptor and BCMA, promotes the differentiation and survival of B cells and plasma cells, and increases secretion of antibodies. **(B)** In autoimmune disease, upregulation of BAFF leads to increased numbers of B cells, plasma cells and autoantibodies (e.g., anti-double-stranded DNA). **(C)** Inhibition of BAFF by blisibimod is postulated to decrease B cell and plasma cell counts, thereby attenuating the autoimmune insult and associated damage.

When evaluated in humans, blisibimod was safe and well tolerated in the completed Phase I and II studies, and observed clinical improvements as adjudged using the SRI were supported by pharmacological effects of B cells, autoantibodies and serum complement. Importantly, the PEARL-SC study provides the first evidence that SLE may be improved following subcutaneous therapy with a biological therapeutic agent. Moreover, the efficacy and subgroup analyses inform the Phase III trial design, including the selection of optimal blisibimod dose (200 mg QW), and identification of a suitable end point (SRI-8) for use in a patient population likely to benefit from blisibimod (severe patients with baseline SELENA-SLEDAI ≥10 and receiving corticosteroid). As further demonstration that the SRI-8 response is clinically relevant, *post hoc* evaluation of the SRI-8 response determined it to be largely driven by 'clinical' improvements and relatively independent of improvements in complement, dsDNA binding, thrombocytopenia or leukopenia.

Continued research and development of B-cell-targeted therapeutics such as blisibimod, as well as drugs with

other therapeutic modalities will hopefully provide alternatives to existing drugs with known toxicities such as high dose corticosteroids and cyclophosphamide. The emerging data with blisibimod fuel this hope.

Financial & competing interests disclosure

MA Scheinberg was a clinical investigator on Anthera's Phase 2 PEARL-SC study. Both RS Martin and D Srinivasan are current employees and share holders of Anthera Pharmaceuticals Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

- Blisibimod, a novel 'peptibody' therapeutic agent, has pharmacological, pharmacokinetic and pharmacodynamic properties that support the following:
- ○High affinity for BAFF (1 pM);
- ○8–10 day serum half-life;
- ○Significant effects on peripheral B cells, autoantibodies (anti-double-stranded DNA) and complement (C3 and C4).
- The observations from the Phase II trial identify optimal conditions for CHABLIS-SC Phase III trials with blisibimod in patients with systemic lupus erythematosus (currently enrolling):
- ○200 mg blisibimod, administered once a week via subcutaneous injection;
- ○Focus on a population of severe systemic lupus erythematosus patients (baseline Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index ≥10 and receiving steroid);
- ○Evaluate the blisibimod effect using the SRI-8 where subjects must have ≥8 point improvement in Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index (respectively), and no new British Isles Lupus Assessment Group A or ≥2B organ domain scores, and no worsening (<0.3 increase) in Physician's Global Assessment.
- The observations from the Phase II trial further identify a potential role for treatment of patients with autoimmune renal disease, for example, lupus nephritis and IgA nephropathy (currently enrolling).

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