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Open-label, prospective, phase II descriptive pilot trial of belimumab therapy for refractory and/or non-criteria manifestations of Antiphospholipid Syndrome: Study Protocol

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This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

Short title: Belimumab in Antiphospholipid Syndrome

Abstract

Objective: to evaluate the safety and tolerability of belimumab given for 24 months in patients persistently positive for antiphospholipid antibodies (aPL)with clinical features attributable to aPL(refractory and/or non-criteria manifestations of the Antiphospholipid Syndrome-APS).

Methods: in this investigator-initiated, single-center, open-label, prospective, phase II descriptive pilot trial,belimumabwill be administered in 15 patients attending San Giovanni Bosco Hospital (Turin) showing refractory and/or non-criteria manifestations of APS. Subjects will receive belimumab 10 mg/kg intravenously (in addition to their ongoing APS treatment) with regimen at 0, 2, 4 weeks and every 4 weeks thereafter (up to week 104). Study endpoints determined at 4, 16, 24, 36, 52 and 104 weeks will include: primary (safety and adverse events) and secondary outcomes, such as changes in clinical outcomes (recurrent thromboses, thrombocytopenia, hemolytic anemia, cardiovascular events, skin ulcer, aPL-related nephropathy and cognitive dysfunction), laboratory outcomes(routine tests, aPL, ENA and anti-dsDNAtests, thrombin generation assay, interferon-signature analysis, lymphocytes immunophenotyiping, BLyS determination) and QoL evaluation.

Expected results: targeting B-cells is emerging as an appealing strategy for patients with APS. Preliminary observations showed aPLnegativization after starting therapy with belimumab. The clinical relevance of these findings will be investigated in this prospective study. If confirmed, the current 'anti-thrombotic' approach to APS patients could be complemented, at least in selected cases, with an'immunomodulatory' strategy.

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Keywords: Antiphospholipid syndrome; Antiphospholipid antibodies; Belimumab; Trial;

Autoimmunity.

1. Introduction

The updated Sapporo classification criteria define antiphospholipid syndrome (APS) as vascular thromboses and/or recurrent pregnancy morbidity occurring in persons persistentlypositive for antiphospholipid antibodies (aPL), including lupus anticoagulant (LA), anti-cardiolipin antibodies(aCL), and anti–β2-glycoprotein I antibodies(aβ2GPI) [1]. While APS is known for its vascular and obstetric manifestations, it is now recognized that its clinical spectrum is characterized by a wider number of aPL-related complications, such as cytopenia (mainly thrombocytopenia), cardiac valve disease (CVD), nephropathy, skin ulcers, *livedo reticularis,* andcognitive dysfunction, collectively referred to as *non-criteria*APS manifestations [1,2].

Form one hand, APS is considered the most common acquired form of thrombophilia[2]and it can potentially affect the vascular system at any levels. Thrombotic events canoccur in arteries, veins and microvasculature, leading to a vast set of clinical phenotypes. From the other hand, while thrombotic APS is the most common and investigated form of the disease, not all clinical features of APS can be explained by an underlying thrombotic mechanism. To date, only a limited number of studies has addressed the pathogenesis and treatment of *non-criteria*APS manifestations, which could require therapeutic strategies beyond anti-thrombotic approaches[2]. Although the exact pathogenesis of extra-criteria manifestations of APS is far from being fully elucidated, they are believed to be caused by mechanisms other than thrombosis, such as phlogosis, activation of the complement pathway and platelet activation[3–5]. Based on thedifferences in the pathogenesis, it is not surprising that traditional therapeutic approaches, mainly directed to counterbalance the pro-thrombotic status, are not sufficient when trying to treat patients with non-criteria manifestations, deeply affecting prognosis

and outcomes of aPL positive patients. Therefore, different therapeutic approaches are highly needed in this subgroup of patients.

Our group recently reported the aPL disappearance in three patients with APS associated with systemic lupus erythematosus (SLE) while on treatment with belimumab, potentially paving the way for the development of new targeted therapies for APS [6]. Our preliminary observation was followed by other reports, further confirming the rationale for considering belimumab as an appealing strategy in APS patients[7,8].

Belimumab is a monoclonal antibody blocking the B-lymphocyte stimulator factor and avoiding B-cell activation and proliferation. It is the first biological drug approved for the treatment of autoantibody positive SLE in active phase and it has shown its capability to reduce the antibodies levels, including anti-dsDNA[9]. Intriguingly, in murine models of APS in association with SLE, belimumab proved its ability to stop disease progression and to reduce mortality rate[10]. However, its use in APS patients needs further investigation. It is currently unknown whether belimumab treatment eliminates clinically significant aPL or whether it is truly effective against aPL-related manifestations.

The primary objective of the BeLimumab Antiphospholipid Syndrome Trial (BLAST) is to evaluate the safety and tolerability of belimumab given for 24 months in patients persistently positive for aPL and clinical features attributable to aPL that are resistant to traditional anticoagulant treatmentand/or classified among the non-criteria APS manifestations.

2. Methods

2.1 Study design

The BLAST trial is an investigator-initiated, single-center, open-label, prospective, phase II descriptive pilot trial of belimumab therapy for refractory and/or non-criteria manifestations of APS. The study will be conducted at the San Giovanni Bosco Hospital (ASL Città di Torino and University of Turin, Turin, Italy). **Figure 1** shows the time line of the study, as well as the primary and secondary objectives of the trial.

Subjects will receive belimumab 10 mg/kg in addition to their ongoing APS treatment regimen. Belimumab will be administered intravenously at 0, 2, 4 weeks and every 4 weeks thereafter (up to week 104). Study endpoints will be determined at 4, 16, 24, 36, 52 and 104 weeks.

The trial was approved by the Ethical Board committee (2020-004568-25) and will be conducted according to the Declaration of Helsinki. The study was registered at ClinicalTrials.gov (identifier: NCT05020782).

2.2.1 Statistical analysis

Clinical characteristics, safety data (primary endpoint), and efficacy data (secondary endpoints) will be reported in a descriptive manner, using the mean ± SD and range. The proportion of patients who will achieve response (complete and partial response) in aPL profiles (4, 16, 36, 52 and 104 weeks) and clinical outcome measures (4, 16, 24, 36, 52 and 104 weeks) will be analyzed as a categorical variable.

Categorical variables will be presented as number (%) and continuous variables will be presented as mean (S.D.). The significance of baseline differences will be determined by the chi-squared test,

Fisher's exact test or the unpaired t-test, as appropriate. Linear and logistic regressions will be performed. A ROC curve analysis will also be performed. A two-sided P-value <0.05 was statistically significant. All statistical analyses will be performed using SPSS version 26.0 (IBM, Armonk, NY, USA).

2.2.2 Sample Size calculation

We based our sample calculation on a simple but robust approach to sample size estimationfor single-arm phase II clinical trials with heterogeneous outcome probabilities [11].Recognition of patient heterogeneity relating to expected responses to particular therapeutic regimens is becoming increasingly common in clinical practice, and this approach formalizes incorporation of this heterogeneity into the design of early phase IIclinical trials.

Sample size of 15 patients was calculated with Bayesian Phase II Single Arm Clinical Trials-Binary Outcomes based on previous experiences by Furie and colleagues[12]. The authors found that 97% of patients treated with belimumab suffered for anyside effect (55 out of 57). The majority of adverse events(AEs) were mild to moderate in severity.In detail, we based our calculation on the following assumptions:

1) It is assumed that numberof AEs follow binomial distributions with proportion parameters for treatment group andcontrol (controls for Furie et al[12]) group. Proportion parameters are assumed to be randomvariables themselves possessing beta prior probability distribution with parameters $\alpha = \beta = 1$.

2) It is also known that for control group, there are 97% rates of AEsamong 57 subjects.The Null and Alternative Hypotheses: The null hypothesis to be tested is that the rate of AEsin patients treated with belimumab with APS=control cohort, against the alternative hypothesis rate of AEs in patients with APS>AEs in patients with SLE as the controlcohort.

2.3 Patients Characteristics, Inclusion and exclusion criteria

APS patients without a concomitant diagnosis of SLE or other concomitant autoimmune conditions (primary APS - PAPS) followed at the San Giovanni Bosco Hospital (Turin, Italy) will be screened and included in the study when meeting the two following criteria:

1)positive aPL-profile defined as:

Positive LA test as defined by the International Society on Thrombosis andHaemostasis, on two or more occasions, at least 12 weeks apart[13,14]and/or positive aCL immunoglobulin (Ig)G/M/A isotype, present in >40U,on two or more occasions, at least 12 weeks apart and/or positive aaβ2GPI IgG/M/A isotype, present in >40U, on two or moreoccasions, at least 12 weeks apart[14];

2) clinical features attributable to aPL that are resistant to warfarin and/or heparin or listed among the so-called "extra-criteria" manifestations of APS, defined by at least one of the following:

- recurrent thrombosis despite ongoing anticoagulation;
- persistent thrombocytopenia;
- persistent autoimmune hemolytic anemia;
- cardiac valve disease;
- chronic skin ulcers;
- renal thrombotic microangiopathy;
- cognitive dysfunction with/without white matter changes.

Table 1resumes the exclusion criteria for the study. Medications concomitant to the use of warfarin

and/or heparin that are not listed in Table 1 will be allowed. For instance, patients receiving anti-platelets agents, anti-malarials,anti-hypertensive drugs, statins and other medications to monitor lipid and vitamins intake will be included. Focusing on anti-malarials, the use of hydroxychloroquine will be allowed, but it won't be a necessary prerequisite for patients to be included in the study.

2.4 Laboratory testing

Selected laboratory values will be included in the analyzed parameters (including routine laboratory testing such as full blood count, creatinine, liver enzymes, complement, immunoglobulins, coagulation testing, lipidic assessment, comprehensive metabolic panel, urinalysis).

With respect to complement testing, besides the commonly used tests evaluating the total complement activity and c3 and c4 fractions, more specific testing, such as those directed to complement activation products and regulators(e.g. CH50 and C5b9), will be employed in order to consider the different proteins involved in the complement cascade[15].

A specialized immunological laboratory test will also be performed, to include aPL, antinuclear, extractable nuclear antibodies and anti-dsDNAantibodies, as previously described[16,17].

Patients will be tested also for experimental techniques such as thrombin generation assay (TGA), interferon (IFN) signature, BLySdetermination, lymphocytesimmunophenotyping, extra-criteria aPL testing, as previously described [6,18,19].

2.5 Outcome measures

2.5.1 Primary Outcome measures

The primary outcome of the study will be the number of participants experiencing serious and non

seriousAEs (Time Points for evaluation: 4, 16, 24, 36, 52 and 104 weeks).

Definitions of serious and non serious AEs are further described in the supplementary materials (**S1 appendix**).

2.5.2 Secondary Outcome Measures

The efficacy of belimumabwill be evaluated based on the baseline clinical manifestations of the patients.In detail, outcome measures will be classified as complete response (CR), partial(PR), and none (NR) at 4, 16, 24, 36, 52 and 104 weeks.

Response for the various clinical manifestations will be defined has follows:

- for recurrent thrombosis despite anticoagulation, CR will be defined as no events, PR as occurrence superficial thrombotic events, and NR as occurrence of venous;
- for persistent thrombocytopenia, CR defined as platelet countof≥150×10^6/µl,PR as 100-149x10^6/µl,and NR as <100 x10^6/µl;
- for persistent autoimmune hemolytic anemia, CR as hemoglobulinconcentrationof14-18 g/dL (males) or 12-16 g/dL (females),PRas 11-14 g/dL (males) or 10-12 g/dL (females),and NR as <11 g/dL (males) or <10 g/dL (females);
- for skin ulcer, CR is defined as disappearance, PR as 50% improvement, and NR as no change;
- for renal thrombotic microangiopathy, CR defined as a normal serum creatinine level, inactive urinarysediment, and urinary protein: creatinine 0.5;PR as a serum creatinine level 15% abovebaseline, RBCs per high-power field 50% above baseline with no casts,50%improvement in the urinary prt:cr, and estimated GFR 10%above baseline; andNR as the absence of C/PR;
- for cognitive dysfunction,Cognitive Impairment Index (CII) [20]will be used to assess the

perception of cognitive decline in memory, executive function, and language domains from both self and clinicians perspectives:CR is defined as normalization ofthe CII with 50%improvement,PR as abnormal index with50%, and NR as no change.

Other measures that will be included in the study will be the following:

• rate of documented thrombotic events;

• reduction in aPL levels, both *criteria* and *non-criteria,* assed at 4, 16, 24, 36, 52 and 104 weeks;

• change from baseline in Physician Global Assessment (PGA) at 4, 16, 24, 36, 52 and 104 weeks (PGA is a physician-reported visual analogue scale that provides an overall measure ofthe subject's current disease activity);

• change from baseline in Patient Global Assessment (PtGA) at 4, 16, 24, 36, 52 and 104 weeks [in PtGA subjects will be asked to rate the severity of their SLE between 0 (very well) and 10 (very poor) that best represents their current level of disease activity];

• change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score and Proportion of subjects with improvement in FACIT-Fatigue score exceeding the Minimal Clinically Important Difference (MCID, >=4) at 4, 16, 24, 36, 52 and 104weeks(FACIT-Fatigue scaleincludes 13-fatigue related questions for subject rates fatigueduring the previous 7 days, yielding an overall score 0 to 52, with lowest scorerepresenting worst fatigue);

• normalization of TGA profile, assessed at 4, 16, 24, 36, 52 and104weeks;

• reduction of the IFNsignature, assed at 4, 16, 24, 36, 52 and104weeks;

• reduction of circulating Blys determination, assed at 4, 16, 24, 36, 52 and104weeks;

• normalization of lymphocytes' immunophenotyping, assed at 4, 16, 24, 36, 52 and 104weeks.

3.Benefit-Risk Assessment

3.1 Expected beneficial effects

There are currently no available tools to assess disease activity and therefore the efficacy of treatment in APS patients. However, based on the complexity of the disease, it is agreed that a single tool might not be sufficient in the assessment of disease activity in individual patients.

The following considerations will be based on benefit-risk balance in SLE, a different clinical condition when compared to APS. However, APS and SLE shared several immunological features and they often overlap, creating a solid ground for some shared considerations.

Both conditions are sustained by a pathogenic role of autoantibodies, and belimumab hasbeen found to be an effective agent in reducing autoantibodies titers in both APS and SLE[6,21].When extrapolating some considerations from SLE trials, both belimumab Phase III trials(C1056 and C1057)[22,23]achieved a significantly higher responder rate for the treatment doseapplied for 10 mg/kg compared with placebo. Belimumab treatment demonstratedbeneficial effects with higher rates of reductions in disease activity in a population with involvement of vascular, musculoskeletal, immunology, and mucocutaneous organs. In C1056 study, belimumab 10mg/kg, in addition to standard therapy, yielded 9.41% (p=0.0207,OR=1.52, 95% CI= 1.07, 2.15) more responders at week

52 as compared to standard therapyonly. In study C1057, 14% (p=0.0006, OR=1.83, 95% CI= 1.30, 2.59) more responders were the results of additional analyses and it has been showed a clinically relevant treatment effect in patientswith high disease activity as expressed by higher level of anti-dsDNA antibodies.In fact, a more robust benefit is seen in this subset of patients while limited, or even nullbenefit might be expected in the anti-dsDNA negative population.

3. 2 Uncertainty in the knowledge about the beneficial effects

The feasibility of describing the appropriate target population in an indication wording has been extensively discussed during the last years. There is a good level of agreement on the fact that APS patients refractory to standard anticoagulation need further option beyond vitamin K antagonist and heparins.

The effect of belimumab has been demonstrated in a SLE patient population with mainly musculoskeletal, vascular, mucocutaneous and hematological involvement, which shared some clinical features with APS (namely vascular involvement and cytopenia)[6,24,25]. Whether the effect will remain in patients with involvement of vital organ/systems(cardiovascular/respiratory, central nervous system and renal) is unknown. Similarly to SLE, there are some uncertainties concerning optimal treatment duration, maintenance doses, treatment holidays and rebound phenomenon.

3.3.1 Risk unfavorable effects

In the placebo-controlled IV SLE controlled repeat dose studies (i.e. primary safetypopulation), the incidence and distribution of AEs was generally fairly similar between theplacebo group and the 1 mg/kg and 10 mg/kg belimumab groups[22,23]. Common events that werereported slightly more

frequently in both belimumab groups compared with placeboincluded: nausea, diarrhea, nasopharyngitis, bronchitis, pain in extremity, and depression.Other events that were more commonly reported in the 10 mg/kg belimumab group compared with placebo included leukopenia, pyrexia, cystitis, viral gastroenteritis, migraineand insomnia. However, the differences in incidence between the treatment groups for thesecommon events were small. Similarly, the incidence of SAEs in the controlled SLE studies wassimilarly distributed across the treatment groups.In the long-term open-label continuation studies, the overall incidence of events did notappear to increase over time, and some events declined. Relatively few subjects discontinuedbecause of an AE. The AEs data in the RA studies (secondary safety population) were consistent withthe IV SLE controlled repeat dose studies (CRD)[26].

Taken the above together, we expect a very similar safety profile of belimumab inAPS when compared to SLE, also taking into account the similarity between these diseases.Since belimumab is a biologic agent inhibiting the survival and differentiation of B cells,additional important events were considered the risk of infection and malignancy. In the IV SLE CRD studies, the incidence of infections was generally comparable between the1mg/kg and 10mg/kg belimumab treatment groups compared with placebo, with theexception of bronchitis and nasopharyngitis, which were slightly more common in thebelimumab groups. The incidence of serious bronchitis was also higher for belimumab (0.4%in the 10 mg/kg group compared with 0.1% for placebo).The incidence of sepsis was low but also somewhat higher for belimumab compared withplacebo (0.7% for the 10 mg/kg group compared with 0.4% for placebo). There were five SAEsof sepsis (0.7% of subjects) in the belimumab 10mg/kg group compared with one subject(0.1%) in the placebo group.Overall, there were no significant differences regarding Grade 3 or Grade 4 lymphopenia,neutropenia and

IgG levels between the placebo and the belimumab 1mg/kg or 10mg/kggroups in the controlled SLE studies. However, subjects in the belimumab groups whoexperienced Grade 3 or Grade 4 lymphopenia, neutropenia, or low IgM or IgG exhibitedslightly higher rates of infections versus placebo and versus subjects without theseabnormalities.

Again, we expect a similar safety profile of belimumab in APS when compared to SLE interms of risk of infection.Ideally, due to the fact that patients with APS are not routinely treated withimmunosuppressive agents, the risk of infection could be expected to be even lower whencompared to SLE.

3.3.2 Uncertainty in the knowledge about the unfavorable effects

Belimumab is a human monoclonal antibody that specifically binds and inhibits the activity ofsoluble human BLyS, a member of the tumor necrosis factor (TNF)-ligand superfamily. BLyS promotes B-celldifferentiation, proliferation, and Ig class switching and survival. Risks that may be associatedwith the use of immunomodulators in general are the risk of (opportunistic) infections andthe potential risk for malignancy[27–29]. It is not known to what degree these potential concernsmay also apply to belimumab.

In general, in the placebo-controlled IV SLE CRD studies, the incidence and distribution of AEswas fairly similar between the placebo group and the 1mg/kg and 10mg/kgbelimumab groups, which would be indicative of a generally favorable safety profile. Aspreviously stated, due to the fact that patients with APS are not routinely treated withimmunosuppressive agents, the risk of infection could be expected to be even lower whencompared to SLE.

A major increase in infection incidence was not observed in the belimumab studies. Thenumber of deaths related to sepsis in the controlled studies was slightly higher in thebelimumab groups, compared with placebo. However, a possible relationship to belimumabwas not always clear since it was used as an add-on treatment to standard ofcare SLE therapy, which typically includes other immunosuppressant drugs; this is not thecase of APS.

While cases of progressive multifocal leukoencephalopathy (PML) have been reported forother immunosuppressive drugs, to date no cases have been reported for belimumab.There were slightly more reports of psychiatric disorders in the belimumab groups comparedwith placebo. The differences were small but the reasons are unclear, considering thatbelimumab primarily acts on B-cells. Long-term follow-up data will be of value to determinewhether there is a signal.

No particular trends regarding malignancy were observed in the relatively short observationperiod of 52 weeks of controlled data. In general, it is known that the risk of malignancy isgreater in patients with SLE compared with a non-SLE population but no solid data areavailable for APS[30–32]. Across the Phase IIandIIIIV SLE studies (LBSL02, C1056, C1057, and theopen-label study LBSL99), the rate of malignant neoplasms (excluding NMSC) per 100-subjectyears with belimumab was similar to the rate observed in a large international SLE cohortstudy[22,23,33,34]. Overall, no conclusions can be drawn with some certainty until more and longerduration follow-up data are available.No particular trends regarding malignancy were observed in the relatively short observation period of 52 weeks of controlled data.

3.4 Benefit-risk balance

There is an unmet medical need for novel options in APS treatment, especially in casesrefractory to vitamin k antagonist and heparins or in the presence of the extra-criteria manifestations. In fact, no immunomodulatory drug have been approvedfor theindicationof APS.

While a limited number of treatment options are available for APS, many patients suffer for recurrences despite ongoing treatment, resulting in irreversible damage to internal organ system. Standard therapy includes anticoagulation and anti-platelets agents, aiming to counterbalance the pro-thrombotic status, but with no proven effect on the pathogenies of the disease. Consequently, a new drug providing additional disease control or presenting amore favorable safety profile when compared to life-long anticoagulation would be considered of clinical value.

Alternative analyses performed for the two pivotal Phase IIIstudies support a clinicallyrelevant treatment effect of belimumab in reducing autoantibodies titres and thisobservation creates a promising background for its use in APS. In SLE a substantiallyincreased likelihood of a treatment response has been shown for the subpopulation ofanti-dsDNA antibodies positive patients[9,35–38].

The addition of 10mg/kg belimumab to standard SLE therapy was generally well tolerated,although a small increase in infections incidence was observed. Some patientsdeveloped infusion related reactions, some of which were reminiscent of hypersensitivityreactions. The mechanism of these reactions has not been clarified. In any case, this is notconsidered a major obstacle against belimumab use if appropriate preventive measuresare taken. Besides, due to the lack of concomitant immunosuppressive therapy, whencompared to SLE, APS patients are supposed to have a lower *a priori* risk for infections.

Potential concerns relating to the long-term use of immunomodulators in general are the riskfor (opportunistic) infections and the potential risk for malignancy. It is not known to whatdegree these

potential concerns also apply to a compound such as belimumab. Given that SLEis a life-long illness that requires chronic treatment, identification of such risks is of greatimportance.

4. Conclusions

When putting all these considerations together, the combined favorable effects ofbelimumab treatment might be considered to outweigh the unfavorable effects.Results from alternative analyses in SLE support a larger effect in patients with high levels ofautoantibodies, indicating that belimumab could be valuable for APSpatients. The safetyprofile for this patientssubgroup does not appear to be significantly different to the safetyprofile for the overall study population and consequently the benefit-risk is consideredpositive.

Belimumab represents a novel concept to treat APS patients aiming to target thepathogenic antibodies at the base of the disease. Thus, uncertainty exists regarding thepotential for development of malignancies, as well as other potential long-term risks such asincreased risk of developing opportunistic infections, or PML. This emphasizes the need for aproper long-term follow up.

All in all, being APS a disease orphan of a tailored therapy, targeting B-cells is emerging as an appealing strategy, especially when thrombosis recurs despite well-conducted anticoagulation or when extra-criteria manifestations occur. Preliminary observations showed aPL-negativization after starting belimumabtherapy. This study has the potential to explore the clinical relevance of these findings in a prospective fashion. If confirmed, the current ‘anti-thrombotic’ approach to APS patients could be complemented, at least in selected cases, with an ‘immunomodulatory’ strategy.

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Legend of Figures and Table

Figure 1.

Timeline of the study, including primary and secondary outcomes. In blue are represented the main time points corresponding to the infusion of belimumab, with particular emphasis on weeks 4, 16, 36, 52 and 104 during which will be evaluated the study endpoints. In the background (yellow rectangle) are illustrated the primary outcomes: safety and adverse events. In the foreground are represented the main secondary outcomes: clinical outcomes [cognitive dysfunction, hemolitic anemia, cardiac valve disease, skin ulcer, aPL-nephropaty, recurrent thrombosis and thrombocytopenia (orange)], laboratory outcomes [aPL titers reduction, thrombin generation assay, cytofluorimetry, interferon-signature and circulating BlyS levels (green)] and quality of life evaluation [FACIT, PGA and PtGA

(purple)]. The complete data analysis will be realized at the end of the study (red). [The figure has been realized using BioRender (https://biorender.com)]

Figure 1.

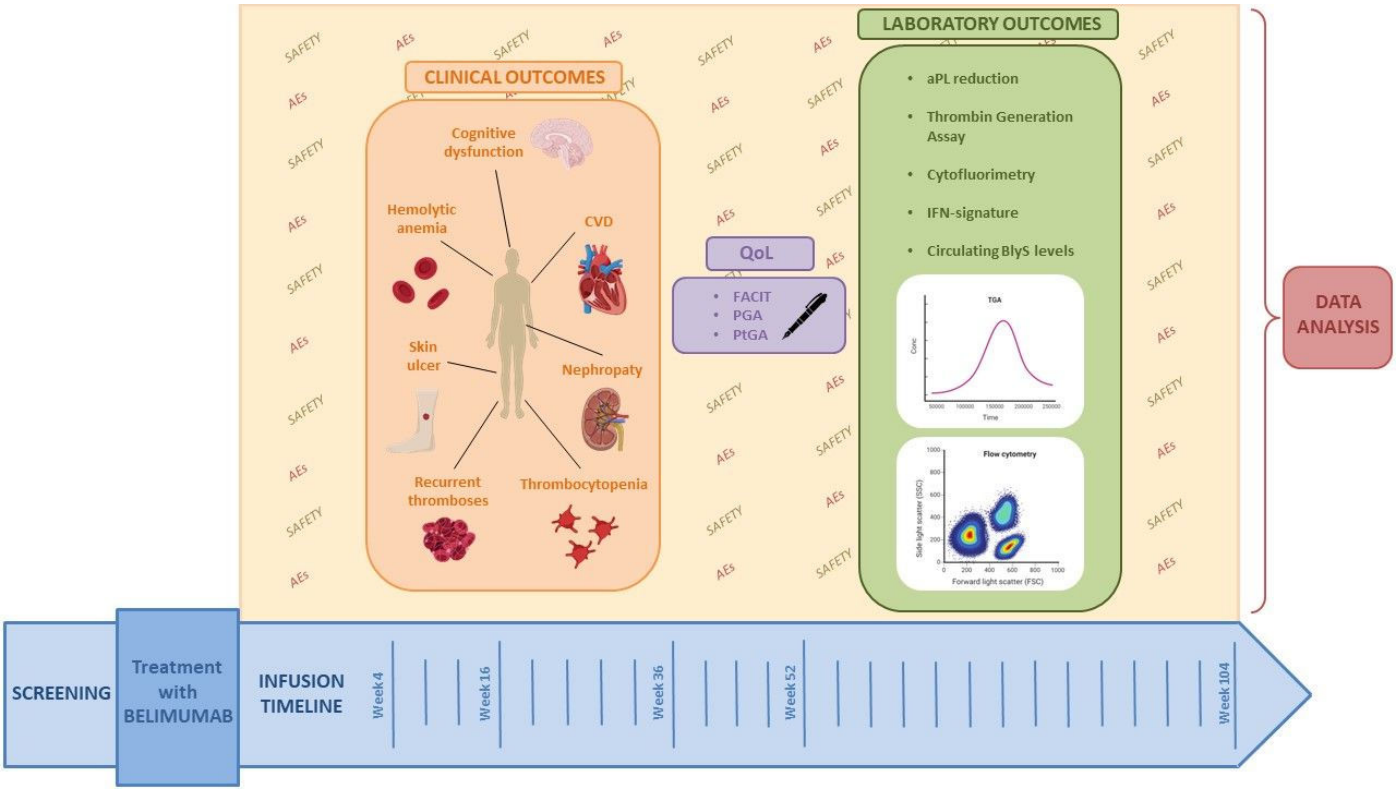

Table 1. Exclusion criteria applied to this study.

Table 1.

EXCLUSION CRITERIA
1. ≥4/11 American College of Rheumatology Classification Criteria for SLE
2. Acute thrombosis *(arterial or venous acute thrombosis diagnosis less than 30 days before study screening)*
3. History of stroke *(only for patients with cognitive dysfunction)*
4. Acute or chronic pancreatitis
5. Ongoing pregnancy
6. Significant cardiac or pulmonary disease (NYHA classification III-IV)
7. History of malignant neoplasm within the last 5 years *(except basal cell or squamous cell carcinoma of the skin treated with local resection only or carcinoma in situ of the uterine cervix treated locally and with no evidence of metastatic disease for 3 years)*
8. Evidence of serious suicide risk including any history of suicidal behaviour in the last 6 months and/or any suicidal ideation in the last 2 months or who in the investigator's judgment, poses a significant suicide risk
9. History of a primary immunodeficiency
10. Significant IgG deficiency *(IgG level < 400 mg/dL)*
11. IgA deficiency *(IgA level < 10 mg/dL)*
12. Known active bacterial, viral fungal mycobacterial, or other infection
13. Infectionhistory: • *currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria)* • *hospitalization for treatment of infection within 60 days of Day 0* • *use of parenteral (IV or IM) antibiotics (anti-bacterial, antiviral, anti-fungal, or anti-parasitic agents) within 60 days of Day 0*
14. Have current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within 365 days prior to day 0
15. Historically positive HIV test or test positive at screening for HIV
16. Hepatitis status: • *Serologic evidence of current or past hepatitis B (HB) infection based on the results of testing for HBsAg and HBcAb as follows:* - *patients positive for HBsAg or HBcAb are excluded* - *positive test for hepatitis C antibody*
17. History of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies
18. Any other clinically significant abnormal laboratory value in the opinion of the investigator
19. If Women of Child-Bearing Potential (WCBP) are included, please see special instructions: • *urine or serum pregnancy testing acceptable* • *timing of pregnancy test must be < 7 days prior to first dose* • *pregnancy testing for IV belimumab - prior to each IP administration, but not more than once a month* • *at least 4 months (5 half-lives) post last dose*

20.	Have any intercurrent significant medical or psychiatric illness that the investigator considers would make the candidate unsuitable for the study
EXCLUDED CONCOMITANT MEDICATIONS	
1.	Anti-B celltherapy: • *wash-out of 5 therapeutic half-lives after prior B-cell therapy, or until pharmacodynamic effect would be minimal (e.g. 1 year following rituximab)*
2.	365 daysprior to belimumab: • *any biologic investigational agent (e.g.abetimus sodium, anti-CD40L antibody, BG9588/IDEC 131)* *(investigational agent applies to any drug not approved for sale in the country in which is being used)*
3.	90 daysprior to belimumab: • *intravenous cyclophosphamide* • *subjects receiving CYC whose leukocyte count is <2000/m3*
4.	30 days prior to belimumab (or 5 half-lives, whichever is greater): • *any non-biologic investigational agent* *(investigational agent applies to any drug not approved for sale in the country in which is being used)*
5.	Live vaccines within 30 days prior to baseline or concurrently with belimumab