Multicenter randomized double-blind study comparing the efficacy and safety of belimumab in the treatment of non-infectious active cryoglobulinemia vasculitis compared to placebo
TRIBECA STUDY (**T**reatment after **RI**tuximab with **BE**limumab in **C**ryoglobulinemia **A**ssociated vasculitis)

INTERVENTIONAL RESEARCH PROTOCOL INVOLVING HUMAN PARTICIPANTS CONCERNING A MEDICINAL PRODUCT FOR HUMAN USE

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Coordinating Investigator:
Pr David Saadoun
Department of Internal medicine and clinical Immunology
Centre national de référence des Maladies Autoimmunes et Systémiques rares
Hospital Pitié Salpétrière, 75013 PARIS
Tel. : 01 42 17 80 09 / Email : david.saadoun@aphp.fr

Scientific Director:
Pr Patrice Cacoub
Department of Internal medicine and clinical Immunology
Centre national de référence des Maladies Autoimmunes et Systémiques rares
Hospital Pitié Salpétrière, 75013 PARIS
Tel. : 01 42 17 80 09 / Email : patrice.cacoub@aphp.fr

Sponsor:
AP-HP and by delegation: Clinical Research and Innovation Department (DRCI)
Hôpital Saint-Louis, 1, avenue Claude Vellefaux, 75010 PARIS
DRCI head office project advisor: Elodie SOLER /Tel.: 01 44 84 17 35/Elodie.soler@aphp.fr

Entity responsible for monitoring the trial:
DRCI-URC (Clinical Research Unit) du GH saint Louis Lariboisière, site Saint Louis
Hôpital Saint Louis, 1 avenue Claude Vellefaux, 75010 PARIS
Pr Mathieu RESCHE RIGON
Tel. 01 42 49 97 42 / Email : Matthieu.resche-rigon@univ-paris-diderot.fr
Project referent: Nabil RAKED
Tel. 01 42 49 97 49 / Email : nabil.raked@univ-paris-diderot.fr

Entity responsible for pharmaceutical management:
Département Essais Cliniques (DEC) - AGEPS
7, rue du Fer à Moulin, 75005 PARIS
Pharmacist: Blandine LEHMANN
Project referents: Kévin CARDET / Sabrina ALESSI
Tél : +33 1 46 69 14 02 / Email: blandine.lehmann@aphp.fr

Clinical Research and Innovation Department (DRCI)
Hôpital Saint Louis 75010 PARIS

INTERVENTIONAL RESEARCH PROTOCOL RELATING TO A MEDICINAL PRODUCT FOR HUMAN USE

PROTOCOL SIGNATURE PAGE

Research code number: P180351

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TRIBECA STUDY

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The study will be carried out in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

Coordinating Investigator:
Pr David SAADOUN
Department of Internal Medicine and Clinical Immunology
Centre de référence des maladies autoimmunes et systémiques rares
Hospital Pitie Salpetriere

Date: ...
Signature:

Professeur David SAADOUN
Département de Médecine Interne
et d'Immunologie Clinique DMU 3ID
Centre de Référence Maladies Auto-immmunes Systématiques rares
Maladies Auto-Inflammatoires et Amylose
RRPS 10005176275
FINESS 750100125
APHP - Sorbonne Université
Site Pitié-Salpêtrière
47/83 Bd de l'Hôpital - 75651 PARIS CEDEX 13
Tél 01 42 16 10 51
Fax 01 42 16 10 53

Sponsor
Assistance Publique-Hôpitaux de Paris
Clinical Research and Development Department
Hôpital Saint Louis
1 avenue Claude Vellefaux
75010 PARIS

Date: 31 JAN. 2022
Signature:

P.O. Y. VACHER

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1 SUMMARY

Full title	Multicenter randomized double-blind study comparing the efficacy and safety of belimumab in the treatment of non-infectious active cryoglobulinemia vasculitis compared to placebo
Acronym	TRIBECA: Treatment after RItuximab with BElimumab in Cryoglobulinemia Associated vasculitis
Coordinating Investigator	Pr David SAADOUN Department of Internal medicine and clinical Immunology Centre national de référence des Maladies Autoimmunes et Systémiques rares Hospital Pitié Salpétrière Tel.0142178009 Email : david.saadoun@aphp.fr
Sponsor	Assistance Publique-Hôpitaux de Paris
Scientific justification	Cryoglobulinemia vasculitis is associated with significant morbidity and mortality, and requires therapeutic intervention. The management of noninfectious mixed cryoglobulinemia vasculitis is currently based on corticosteroids, and rituximab. During the last decade, several groups have reported on the efficacy of anti-CD20 monoclonal antibody (rituximab) in patients with cryoglobulinemia vasculitis. Rituximab infusions proved effective on main vasculitis signs, with a complete clinical response in 65-70% of patients. However, cryoglobulinemic vasculitis relapse is noted in up to 40% patients within few days to nineteen months after the last rituximab infusion. We and other have previously shown that serum BLys concentration was correlated with serum cryoglobulin level and with cryoglobulinemia vasculitis and cryoglobulinemia associated B non-Hodgkin's lymphoma. In agreement with data in systemic lupus erythematosus and Sjögren's syndrome, we also observed decrease in BLys binding and in BR3 staining which was correlated with disease severity. Following rituximab serum BLys concentration significantly increased and may favour the survival of autoreactive B cell clones and relapses of cryoglobulinemia vasculitis. A recent study has shown that rituximab does not reset defective early B cell tolerance checkpoints. An obvious solution to prevent the rise in BAFF levels from precipitating a flare of disease following rituximab therapy (and thus to achieve sustained remission of disease) would be to combine rituximab with BAFF blockade. In mice, a combination of B cell depletion and BAFF inhibition removes B cells in the marginal zone and follicular compartments more effectively than either treatment alone. A combination of B cell depletion and BAFF blockade was superior to B cell depletion alone with respect to reducing the numbers of plasmablasts and plasma cells, as well as reducing disease severity, in three different mouse models of lupus. In addition, promising results have been observed in patients with cryoglobulinemia vasculitis treated by rituximab plus

	belimumab and with good safety profile.
Main objective and primary endpoint	To evaluate efficacy of belimumab compared to placebo in patients with non-infectious active cryoglobulinemia vasculitis. Complete clinical response rate of vasculitis symptoms at week (W) 25 with corticosteroid withdrawal (prednisone at 0 mg/day) at week (W) 12.
Secondary objectives and endpoints	**Secondary objectives** • Safety and tolerability of treatments as assessed by frequency and severity of adverse clinical events • Complete, partial (improvement in some but not all organs involved at baseline) and non clinical (no clinical improvement) response rate • Rate of complete renal response • Rate of cryoglobulinemia clearance • Rate of negativation of rheumatoid factor activity • Rate of normalization of C4 complement level • Early failure rate at W5 (non clinical response at W5) • Clinical relapse rate and the time to relapse between the two treatments groups, • Cumulative dose of corticosteroids received between the two treatments groups, • Evolution of gammaglobulin and of CD19+ B cells levels • Quality of life scores (SF-36) (Appendix 1) between the two treatment groups, • Rate of infections (severe or not) and other complications (lymphoma.) • BVAS activity score (Appendix 2) **Secondary endpoints** • Safety and tolerability of treatments as assessed by frequency and severity of adverse clinical events at W25 and at W48 • Complete, partial and non clinical response rate at W13, W25 and at W48. • Complete renal response rate at W13, W25 and W48 • Rate of cryoglobulinemia clearance, of negativation of rheumatoid factor activity and of normalization of C4 complement level at W13, W25 and at W48 • Rate of early failures (non clinical response at W5), • Clinical relapse rate defined by de novo appearance or reappearance of a manifestation attributable to cryoglobulinemia vasculitis during 48 weeks of follow-up, • Rate and time to relapse from baseline to W48 • Cumulative dose of prednisone at W25 and at W48, • Quality of life score SF-36 at baseline,W25 and W48, • Rate of infections (severe or not) and other complications during the 48 weeks of follow-up • Evolution of gammaglobulin and of CD19+ B levels from baseline to W48 • BVAS activity score at baseline, W13, W25 and W48.

Design of the trial	This is a Bayesian Phase II randomized clinical trial that aims at evaluating the best treatment strategy of cryoglobulinemia vasculitis, based on difference in the response rate as measured at week 25 after randomization.
Population of trial subjects	Adult patients with non-infectious active cryoglobulinemia vasculitis.
Inclusion criteria	1. Age ≥ 18 years 2. Written inform consent 3. Active cryoglobulinemia vasculitis, at initiation of rituximab, define by a clinically active vasculitis with skin, joint, renal, peripheral nerve, central neurological, digestive, pulmonary and/or cardiac involvement, and history of positive cryoglobulinemia 4. Affiliated to National French social security system 5. Having received Rituximab as induction therapy within 6 weeks (1 to 4 infusions, dose at the discretion of the investigator) 6. Female subjects of childbearing potential must have a negative serum or urinary pregnancy test at inclusion visit, and confirmed monthly while in study, out to at least 92 days (5 half lives) post last dose. 7. For subjects with reproductive potential (male or female), a willingness to use contraceptive measures adequate to prevent the subject or the subject's partner from becoming pregnant during the study from 2 weeks prior to administration of the 1st dose of study agent until 92 days after the last dose of study agent. Therefore the subjects agree to 1 of the following: a. Complete abstinence from intercourse from 2 weeks prior to administration of the 1st dose of study agent until 92 days after the last dose of study agent (Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are <u>not</u> acceptable methods of contraception) **OR** b. Consistent and correct use of 1 of the following acceptable methods of birth control for 1 month prior to the start of the study agent, during the study, and 92 days after the last dose of study agent o Oral contraceptive, either combined or progestogen alone o Injectable progestogen o Implants of levonorgestrel or etonogestrel o Estrogenic vaginal ring

	○ Percutaneous contraceptive patches ○ Intrauterine device (IUD) or intrauterine system (IUS) with <1% failure rate as stated in the product label ○ Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, “documented” refers to the outcome of the investigator's/designee’s medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject’s medical records ○ Double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository) These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception. 8. HIV negative serology ; negative HBs Ag test and HBc Ab test; HCV negative serology or negative HCV RNA if positive HCV serology within 3 months before inclusion 9. Neutrophils (ANC) >1x109/L,
Exclusion criteria	1. Patient with a vasculitis unrelated to cryoglobulinemia 2. Patient with non active cryoglobulinemia vasculitis, at initiation of rituximab. Patients with inactive vasculitis following rituximab administration may be included. 3. Excluded concomitant medications a. 365 days Prior to Investigational Medicinal Product (Belimumab or placebo):: ○ 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 it is being used b. 180 Days Prior to Investigational Medicinal Product (Belimumab or placebo):: c. Intravenous cyclophosphamide 30 Days Prior to Investigational Medicinal Product (Belimumab or placebo): (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 it is being use) d. Live vaccines within 30 days prior to baseline or concurrently with Investigational Medicinal Product (Belimumab or placebo) 4. Have a history of malignant neoplasm within the last 5 years, other than carcinoma in situ of the cervix or excised basal cell, squamous cell carcinoma of the skin and low-grade hemopathy with no indication for a specific treatment 5. Have a Progressive multifocal leukoencephalopathy 6. Have 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, pose a significant suicide risk 7. Have a history of a primary immunodeficiency 8. Have a significant IgG deficiency (IgG level < 400 mg/dL) and/or significant IgA deficiency (IgA level < 10 mg/dL) according to results obtained within 1 month prior to inclusion visit 9. Have a history of major organ transplant or hematopoietic stem cell/marrow transplant or renal transplant. 10. Infection history: a. Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus,) b. Infection requiring hospitalization and/or use of parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti-parasitic agents) within 60 days of the inclusion visit. 11. Have current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within 365 days prior the inclusion visit 12. Have a historically positive HIV test according to results obtained within 3 months prior to inclusion visit 13. Hepatitis status according to results obtained within 3 months prior to inclusion visit: a. 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 b. Positive test for Hepatitis C RNA 14. Have a history of a hypersensitivity or an anaphylactic reaction to parenteral administration of Belimumab, corticosteroids or any excipients of the treatments administered during the study

	15. If Women of Child Bearing Potential (WCBP) are included please see special instructions in Inclusion criteria 16. Pregnant or breast feeding women 17. Have any intercurrent significant medical or psychiatric illness that the investigator considers would make the candidate unsuitable for the study 18. Patients under legal protection or unable to consent 19. Participation to another interventional study
Investigational medicinal product(s)	Belimumab Benlysta® administered subcutaneously 200 mg weekly from W1 to week 24
Comparator treatment	Placebo of Belimumab administered subcutaneously weekly from W1 to week 24
Risks added by the trial	*Risk C*
Scope of the trial	Phase II prospective randomized, multicentre, double-blind, study: Group I: Belimumab administered subcutaneously 200mg weekly from W1 to week 24. Group II: Placebo of Belimumab administered subcutaneously weekly from W1 to week 24. Randomization will be centralized, stratified on previous treatment history (naive patients versus relapsing patients) and the severity of vasculitis (i.e. extensive skins necrosis, glomerulonephritis, multiple mononeuropathy, myocarditis, digestive or central nervous system specific involvement) in a 1:1 ratio between groups. Both groups will have the same corticosteroid tapering scheme, with an initial dose of 30 mg/day. The following schedule of reduction of prednisone will apply to both groups as long as the disease is inactive: 30 mg/day week (W)0-W2, 20 mg/day W2-W4 15 mg/day W4-W6, 10 mg/day W6-W8, 5 mg/day W8-W10, Between W10-W12 the strategy for stopping glucocorticoids is left to the investigator's discretion Stopping glucocorticoid therapy at W12 At each step, the prednisone dose will be reduced only in the absence of signs of vasculitis activity.
Number of subjects included	48 patients, 24 patients in each arm
Number of sites	Multicentre national study including 20 centres
Duration of the trial	- *Duration of inclusions: 36 months* - *Duration of participation of each patient:12 months* o *Duration of treatment : 24 weeks* - *Total duration: 48 months*

Number of enrolments expected per site and per month	0.06 patient/month/centre
Statistical analysis	This is a Bayesian Phase II randomized clinical trial that aims at evaluating the treatment strategy of cryoglobulinemia vasculitis, based on difference in the response rate as measured at week 25 after randomization. Randomized phase II trials are still poorly used, with still large use of single-arm phase II trial results that are interpreted relative to historical control subjects, introducing selection bias and confounding that may limit the validity of the conclusions. Thus, planning a phase II randomized trial appears a worthy investment considering finite patient and financial resources. This design is adapted to binary outcomes observed at the end of a fixed follow-up period and analyzed using an absolute difference in proportions that has been shown to greatly reduce sample size requirements. We thus used the approach for phase II randomized trials proposed by Simon R, Wittes RE, and Ellenberg SS that aims at controlling the probability of detecting a given difference in response rates. We hypothesize that up to 70% of the patients receiving placebo of belimumab and 85% of those treated by belimumab will achieve a complete remission of cryoglobulinemia vasculitis at week 25 (W25) and with steroid therapy stopped (0 mg/day) at W12.
Sources of funding for the trial	GSK who will also provide belimumab Benlysta® and placebo of belimumab.
Trial will have a Data Monitoring Committee	*Yes*

2 SCIENTIFIC JUSTIFICATION FOR THE TRIAL

2.1 Hypothesis for the study

Cryoglobulinemia vasculitis is associated with significant morbidity and mortality, and require therapeutic intervention [1]. The management of noninfectious mixed cryoglobulinemia vasculitis is currently based on corticosteroids, and rituximab. During the last decade, several groups have reported on the efficacy of anti-CD20 monoclonal antibody (rituximab) in patients with cryoglobulinemia vasculitis. Rituximab infusions proved effective on main vasculitis signs, with a complete clinical response in 65-70% of patients [2]. However, cryoglobulinemic vasculitis relapse is noted in up to 40% patients within few days to nineteen months after the last rituximab infusion. We and other have previously shown that serum BLys concentration was correlated with serum cryoglobulin level and with cryoglobulinemia vasculitis and cryoglobulinemia associated B non Hodgkin's lymphoma [3]. In agreement with data in systemic lupus erythematosus and Sjögren's syndrome we also observed decrease in BLys binding and in BR3 staining which was correlated with disease severity [3]. Following rituximab serum BLys concentration significantly increased and may favour the survival of autoreactive B cell clones and relapses of cryoglobulinemia vasculitis. A recent study has shown that rituximab does not reset defective early B cell tolerance checkpoints [4]. An obvious solution to prevent the rise in BAFF levels from precipitating a flare of disease following rituximab therapy (and thus to achieve sustained remission of disease) would be to combine rituximab with BAFF blockade. In mice, a combination of B cell depletion and BAFF inhibition removes B cells in the marginal zone and follicular compartments more effectively than either treatment alone [5]. A combination of B cell depletion and BAFF blockade was superior to B cell depletion alone with respect to reducing the numbers of plasmablasts and plasma cells, as well as reducing disease severity, in three different mice models of lupus. Cryoglobulinemia is associated with increased risk of developing lymphoid neoplasm mainly marginal zone lymphoma. In addition, promising results have been observed in patients with cryoglobulinemia vasculitis treated by rituximab plus belimumab (unpublished observations) and with good safety profile. This provides a strong rationale for targeting B cell depletion and BAFF blockade in cryoglobulinemia vasculitis. TRIBECA STUDY (Treatment after RItuximab with BElimumab in Cryoglobulinemia Associated vasculitis) is the first double blind randomized controlled study comparing the efficacy and safety of belimumab to that placebo after rituximab in the treatment of non-infectious active cryoglobulinemia vasculitis.

2.2 Existing knowledge relating to the condition under investigation

Definition and prevalence of cryoglobulinemia

The presence in the serum of monoclonal or polyclonal immunoglobulins, which precipitate at temperatures below 37°C and redissolve on rewarming, is termed cryoglobulinaemia. Cryoglobulins are the cause of cryoglobulinemic vasculitis, which is part of the systemic vasculitis affecting small vessels (arterioles, capillaries, venules) [6]. The visceral manifestations are polymorphic, with preferential involvement of the skin, joints, peripheral nervous system and kidney. Mixed cryoglobulinemia is defined by the presence of several immunoglobulins. They are divided into type II and type III. Type II mixed cryoglobulinemia accounts for 65% of cases and are composed of two types of Ig, one monoclonal and the other polyclonal. Mixed type III cryoglobulinemias are found in 35% of cases, and are composed of polyclonal IgG and polyclonal IgM complexes. In addition to hepatitis C infection, which is the main cause of mixed cryoglobulinemia, the most frequent etiologies are B lymphoid hemopathies and connective tissues (including Sjögren's syndrome and systemic lupus erythematosus). When the etiological investigation is negative, it is called essential mixed cryoglobulinemia (10% to 30% of all cases).

The prevalence and incidence of non-viral mixed cryoglobulinemic vasculitis is poorly understood, particularly due to the heterogeneity of the causes, clinical presentation and geographic distribution of the disease [7]. A prevalence of 1 case per 100 000 individuals was

reported in an American study. Prevalence appears to be higher in Southern Europe than in the United States.

Pathogenesis

Cryoglobulinemic vasculitis is a systemic vasculitis affecting small vessels, and more rarely those of medium size. Mixed cryoglobulinemia is characterized by a proliferation of B lymphocytic clones producing IgM most often with rheumatoid activity (anti-IgG activity), and constitute a model of vasculitis with immune complexes. In type II mixed cryoglobulinaemia, the formation of large, complement bound, IgM–IgG complexes is a major factor influencing cryoprecipitation. Immune-complex–mediated vasculitis is a major mechanism of tissue injury in cryoglobulinaemia. The monoclonal IgM component generates large immune complexes with IgG and complement fractions, particularly C1q. C1q can bind to receptors on endothelial cells, facilitating immune complex deposition and subsequent vascular inflammation. Intravascular precipitation of cryoglobulin is favored by cold, and mainly affects the skin, peripheral nerve and kidney. Protein solubility can depend on a range of factors, including primary structure and steric conformation which, in turn, depend on temperature, pH, and ionic strength [8]. Scarcity of tyrosine residues, relative abundance of hydrophobic aminoacids, and reduced concentration of galactose and sialic acid in the glycosylated portion of the molecule can increase precipitation. The major role of cryoglobulinemia in the occurrence of these vasculitides is demonstrated by the presence in the vascular wall of territories affected by immunoglobulin molecules and complement fractions. In addition, cutaneous and glomerular lesions similar to those seen in cryoglobulinemic vasculitides can be reproduced in mice after injection of immunoglobulins with cryoglobulin and rheumatoid factor activities. Cryoglobulin and rheumatoid factor are both necessary for the development of cutaneous vasculitis lesions, whereas cryoglobulin activity alone is sufficient for the development of glomerular lesions [9].

Clinical manifestations

The visceral manifestations are polymorphic, with preferential involvement of the skin, joints, peripheral nervous system and kidney. The cutaneous manifestations are the direct consequence of a vasculitis of small vessels (leucocytoclastic vasculitis). The main symptom is vascular purpura, present in 30% to 100% of patients with symptomatic cryoglobulinemia. Joint manifestations are mainly arthralgia affecting large joints, bilateral and symmetrical, non-deforming and non-migratory. Neurological manifestations are present in 9% to 45% of patients. The predominant clinical picture (80% of cases) is that of sensory or distal sensory distal polyneuropathy, predominant in the lower limbs. In 20% of cases, it is a table of mononeuropathy or multiple mononeuropathy mimicking a necrotizing vasculitis of the periarteritis nodosa type. The electromyogram of the four limbs confirms the axonal neuropathy with alteration of the sensory and / or motor potentials, or even of the motor conduction in the form of a sensory-motor axonal polyneuropathy or of a multiple mononeuropathy.

Renal involvement is proliferative glomerular nephropathy, reported in 2% to 50% of cryoglobulinemic patients. The typical form is type I glomerulonephritis membranoproliferative (GNMP), which is associated in more than 80% of cases with type II cryoglobulinemia whose monoclonal component is a rheumatoid IgM. More rarely, mesangio-proliferative glomerulonephritis is observed, notably accompanying type III cryoglobulinemias. The most frequent presentation (40% to 55%) is non-nephrotic proteinuria, associated with microscopic haematuria and variable degree of renal insufficiency. Acute nephrotic syndrome with or without renal failure (20%), rapidly progressive glomerulonephritis (14% to 25%), or chronic renal failure without urinary sediment abnormality (10%) may reveal renal impairment. Arterial hypertension is present in 50% to 80% of cases. Severe chronic renal insufficiency is found in 10% of patients.

Outcome

Cryoglobulinemic vasculitis is a major cause of morbidity and mortality, especially in elderly patients with severe renal impairment. The evolution of cryoglobulinaemic disease varies widely. Patients with cryoglobulinaemic vasculitis have a worse 10-year survival rate compared with the rate in the general population. Risk factors for poor outcomes include male sex, age more than 60 years, glomerulonephritis, gastrointestinal or pulmonary involvement, chronic HCV infection and type II cryoglobulinaemia [10]. Prognosis is influenced heavily by both cryoglobulinaemic damage to vital organs and by underlying diseases and comorbidities. The main complications associated with their progression are infectious complications, complications related to the severity of vasculitis, and non-Hodgkin's lymphoma B. In a retrospective study, severe infections were responsible for half the deaths. Furthermore, a high level of cryoglobulin (> 0.6 g / L) and the presence of vasculitis were significantly associated with the occurrence of B lymphoma. The most common causes of death in cryoglobulinaemic vasculitis are infection, end-stage liver disease, cardiovascular disease, and more rarely vasculitis (i.e. renal involvement with end-stage renal and CNS involvement) and lymphoma/neoplasia.

Treatment options in cryoglobulinemia vasculitis

Cryoglobulinemic vasculitis is associated with significant morbidity and mortality that often warrant therapeutic intervention. The therapeutic management of cryoglobulinemic vasculitis associated with the hepatitis C virus has made enormous progress over the last ten years, and is based above all on the eradication of the virus. Recently, Rituximab in combination with anti-viral C therapy has demonstrated a beneficial effect on vasculitis, particularly in renal-compromised forms, with a satisfactory tolerance profile [11]. On the other hand, the management of non-viral mixed cryoglobulinemic vasculitis remains empirical, based on corticosteroid therapy, plasma exchange and / or immunosuppressive drugs, without any study having precisely evaluated the efficacy and safety of these different therapeutics options, explaining the lack of clear and consensual recommendations. Analysis of the retrospective data shows an improvement in non-viral cryoglobulinemic vasculitis by corticosteroids and/or immunosuppressive treatments, but also highlights the numerous side effects of these long-term treatments.

Rituximab

During the last decade, several groups have reported on the efficacy of anti-CD20 monoclonal antibody (rituximab) in patients with cryoglobulinemic vasculitis. Rituximab is an interesting therapy in patients with cryoglobulinemic vasculitis as it targets B-cell arm of autoimmunity. In a literature review, 13 references reported a total number of 57 cases [12]. Patients had a cryoglobulinemia vasculitis secondary to chronic active HCV infection in 75.4% or an essential mixed cryoglobulinemia in 24.6%. Most patients (48/57) received 4 weekly consecutive i.v. infusions of 375 mg/m^2 of rituximab. The mean follow up after rituximab infusions lasted 9.7 months (range, 3 to 24). Rituximab infusions proved effective on main vasculitis signs, with a complete clinical response in 24/33 (73%) patients for skin involvement, 16/30 (53%) for arthralgia, 9/25 (36%) for neuropathy, and 9/13 (70%) for glomerulonephritis. Cryoglobulinemic vasculitis relapse was noted in 13/36 (36.1%) patients within few days to nineteen months (mean 6.7 months) after the last rituximab infusion. There was no significant difference in the efficacy of rituximab therapy whether patients presented with HCV-induced or essential cryoglobulinemia vasculitis. Ferri et al reported 87 patients (HCV infection in 92% of cases) with active cryoglobulinemic vasculitis treated by rituximab [13]. A significant clinical improvement was observed regardless the presence/absence of associated HCV infection. Complete/partial remission of pre-treatment active manifestations was observed in 74% of skin purpuric lesions, up to 87% of non-healing vasculitic leg ulcers, and 44% of the peripheral neuropathy. De Vita et al. reported the results of a multicenter phase III randomized controlled trial in 57 patients with cryoglobulinemia vasculitis (including 53 HCV-positive patients), comparing conventional treatment (i.e. one of the followings: azathioprine or cyclophosphamide; or plasmapheresis) and rituximab. None of the HCV-positive patients received concomitant antiviral therapy, because it had previously failed

(n=28) or was not indicated (n=25). Survival of treatment at 12 months (i.e., the proportion of patients who continued taking their initial therapy) was statistically higher in the rituximab group (64.3% versus 3.5%, P<0.0001), and the Birmingham Vasculitis Activity Score decreased only after treatment with rituximab, indicating the absence of efficacy of conventional treatment in cryoglobulinemia vasculitis patients [14]. Sneller et al. reported the results of a single-center, open-label, randomized controlled trial of rituximab compared to conventional immunosuppressive therapy (glucocorticoids, cyclophosphamide, plasma exchanges or methotrexate) for HCV- cryoglobulinemia vasculitis patients in whom antiviral therapy had failed to induce remission. A total of 24 patients were enrolled (12 in each treatment group). Remission at month 6 was statistically higher in the rituximab group (83% versus 8%, P<0.0001). The median duration of remission for rituximab-treated patients was 7 months, and the safety profile was good.

Belimumab

Belimumab is a recombinant, human, immunoglobulin G 1 lambda (IgG1λ) monoclonal antibody that binds and antagonizes the biological activity of soluble B lymphocyte stimulator (BLyS) protein, a member of the tumor necrosis factor (TNF) ligand superfamily that promotes the survival of B lymphocytes. BLyS inhibits B cell apoptosis and stimulates the differentiation of B cells into immunoglobulin-producing plasma cells. BLyS can bind to 3 receptors, BLyS receptor 3 (BR3), transmembrane activator–1 and calcium modulator and cyclophilin ligand-interactor (TACI), and B-cell maturation antigen (BCMA). These receptors are expressed predominantly on B cells. Increased levels of BLyS are associated with autoimmune disease phenotypes. Mice transgenic for BLyS have increased numbers of peripheral B cells, production of autoantibodies, proteinuria and glomerulonephritis [15]. In humans with systemic lupus erythematosus (SLE), Sjogren's syndrome and cryoglobulinemia vasculitis, elevated BLyS levels have been found to be positively correlated with elevated autoantibody levels, immunoglobulin IgG, and disease activity [3, 16]. Inhibition of BLyS activity with soluble BLyS receptors (TACI-Fc or BR3-Fc) administered to New Zealand Black/New Zealand White (NZB/NZW) F1 mice, which develop a lethal, SLE-like autoimmune syndrome, slowed disease progression, and improved survival.

By neutralizing the activity of BLyS, belimumab inhibits survival of B cells and other biomarkers including reductions in circulating immunoglobulins (IgG, IgA, and IgM) and anti-double stranded DNA(dsDNA) antibodies and normalization of serum complement levels. Over 5000 individuals with SLE have been treated with belimumab in clinical studies. The observation that antagonism of BLyS by treatment with belimumab results in reductions of B cells, serum immunoglobulins and in particular, reduction of a variety of serum autoantibodies suggests that belimumab may have therapeutic benefit in other B cell-mediated autoimmune diseases in which BLyS may have a role. Diseases which are characterized by autoantibody production or excess antibody levels in which elevated levels of BLyS have been observed, and in some cases, shown to be correlated with disease activity include: cryoglobulinemia vasculitis, Sjogren's Syndrome, idiopathic thrombocytopenic purpura (ITP), anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitides, chronic graft versus host disease (GVHD), chronic antibody-mediated allograft rejection, Waldenstrom's macroglobulinemia.

2.3 Summary of relevant pre-clinical and clinical trials

Belimumab in Combination with Rituximab

Clinical Trials using Belimumab in Combination with Rituximab are ongoing in Sjogren's syndrome (NCT02631538), in immune thrombocytopenia (NCT03154385) and in Lupus nephritis (NCT02260934).

TRIBECA STUDY (Treatment after RItuximab with BElimumab in Cryoglobulinemia Associated vasculitis) is the first double blind randomized controlled study comparing the efficacy and safety of belimumab to placebo in the treatment of non-infectious active cryoglobulinemia vasculitis. The current first line therapy for active cryoglobulinemia vasculitis

is rituximab but it failed to demonstrate sustainable remission over 65-70 %. Following rituximab serum BLys concentration significantly increased and may favour the survival of autoreactive B cell clones and relapses of cryoglobulinemia vasculitis. Cryoglobulinemia is associated with increased risk of developing lymphoid neoplasm mainly marginal zone lymphoma. In mice, a combination of B cell depletion and BAFF inhibition removes B cells in the marginal zone compartments more effectively than either treatment alone. In addition, promising results have been observed in patients with cryoglobulinemia vasculitis treated by rituximab plus belimumab and with good safety profile. This provides a strong rationale for targeting B cell depletion and BAFF blockade in cryoglobulinemia vasculitis.

2.4 Description of the population of trial subjects and justification for the choice of subjects

This is a Bayesian Phase II randomized clinical trial that aims at evaluating the best treatment strategy of cryoglobulinemia vasculitis, based on difference in the response rate as measured at week 25 after randomization.
Randomized phase II trials are still poorly used, with still large use of single-arm phase II trial results that are interpreted relative to historical control subjects, introducing selection bias and confounding that may limit the validity of the conclusions. Thus, planning a phase II randomized trial appears a worthy investment considering finite patient and financial resources. This design is adapted to binary outcomes observed at the end of a fixed follow-up period and analyzed using an absolute difference in proportions that has been shown to greatly reduce sample size requirements.
We thus used the approach for phase II randomized trials proposed by Simon R, Wittes RE, and Ellenberg SS that aims at controlling the probability of detecting a given difference in response rates. We hypothesize that up to 70% of the patients receiving placebo of belimumab and 85% of those treated by belimumab will achieve a complete remission of cryoglobulinemia vasculitis at week 25 (W25) and with steroid therapy stopped (0 mg/day) at W12. Thus, based on binomial distributions under the assumed response rate of the control arm (here, p=0.70), this allowed to randomly allocate two groups of 24 patients to detect a 0.15 difference in response rates with a 0.90 probability.

2.5 Name and description of the investigational medicinal product(s)

After the collection of their free and informed consent, eligible patients with active non-infectious active cryoglobulinemia vasculitis will be randomized into one of 2 groups at the randomization visit (W0):

Group I: 1-ml pre-filled syringes containing 200 mg of belimumab, Benlysta® sterile solution for subcutaneous injection
Group II: 1-ml pre-filled syringes containing 200 mg of placebo of belimumab, sterile solution for subcutaneous injection

2.6 Description and justification of the dosage, route of administration, administration schedule and treatment duration

Group I: Belimumab Benlysta® administered subcutaneously 200mg weekly from week 1 to week 24.
Group II: Placebo of Belimumab administered subcutaneously weekly from week 1 to week 24.

2.7 Summary of the known and foreseeable benefits and risks for the study participants

The management of cryoglobulinemia vasculitis remains largely empirical. There is a strong immunological rationale for immunomodulation with B-cell depletion and BAFF inhibition in cryoglobulinemia vasculitis. Immunomodulatory activity of rituximab associated with belimumab has the potential to be effective in cryoglobulinemia vasculitis and preliminary safety results are encouraging. This is the first randomized study on synergistic B cell immunomodulation in the therapeutic management of noninfectious mixed cryoglobulinemia vasculitis. It will validate the treatment of naïve and relapsing patients. This study will also assess the complete withdrawal of corticosteroids following a five-month period of treatment compared with a strategy never validated using the maintenance of low dose corticosteroids (<10 mg/d) or an immunosuppressive therapy. This study could confirm the superiority of rituximab and belimumab association compared to rituximab associated with placebo in terms of efficacy and steroid sparing. It could improve the management of patients with non-infectious mixed cryoglobulinemia vasculitis. The expected benefit is both individual, in improving quality of life for patients with cryoglobulinemia vasculitis and collective, in reducing costs of hospitalization, and side effects of immunosuppressants.

Major side effects of corticosteroids (e.g. osteoporosis, abnormal behavior, infection, diabetes…) are related to the cumulative dose administered. Although, relapses, progression and exacerbation of the symptoms of cryoglobulinemia vasculitis may appear with steroids tapering.

The most frequently reported adverse events of Belimumab in lupus patients (incidence ≥ 5% among patients treated with Belimumab in combination with standard therapy and ≥ 1% compared to placebo arm) were: nausea, diarrhea, fever, stuffy or runny nose and sore throat, persistent cough, trouble sleeping, leg or arm pain, depression, headache, and pain, redness, itching, or swelling at the site of injection. The proportion of patients who discontinued treatment due to adverse events was 7% for Benlysta-treated patients and 8% for placebo-treated patient. Exceptionally, cases of progressive multifocal leukoencephalopathy have been described in lupus patients.

3 OBJECTIVES

3.1 Primary objective

To evaluate the efficacy of belimumab compared to placebo in patients with non-infectious active cryoglobulinemia vasculitis .

3.2 Secondary objectives

- Safety and tolerability of treatments as assessed by frequency and severity of adverse clinical events
- Complete (remission of all affected organs involved at baseline and the absence of clinical relapse), partial (improvement in some but not all organs involved at baseline) and non clinical (no clinical improvement) response rate
- Rate of complete renal response
- Rate of cryoglobulinemia clearance
- Rate of negativation of rheumatoid factor activity
- Rate of normalization of C4 complement level
- Early failure rate at W5 ((non clinical response at W5))
- Clinical relapse rate and the time to relapse between the two treatments groups,
- Cumulative dose of corticosteroids received between the two treatments groups,
- Evolution of gammaglobulin levels and of CD19+ B cells levels

- Quality of life scores (SF-36) between the two treatment groups,
- Rate of infections (severe or not) and other complications (lymphoma...)
- BVAS activity score.

4 DESCRIPTION OF THE TRIAL

4.1 Concise description of the primary and secondary endpoints

4.1.1 Primary endpoint

Complete clinical response rate of vasculitis symptoms at W25 with corticosteroid withdrawal (prednisone at 0 mg/day) at week (W) 12.

The complete clinical response is defined by the remission of all affected organs involved at baseline and the absence of clinical relapse.

- The skin and articular remissions are evaluated clinically (disappearance of purpura and/or ulcers, disappearance of arthritis).
- Renal remission is evaluated biologically (proteinuria <0.5g/24h or proteinuria/creatininuria <50 mg/mmol) .
- Neurological remission is evaluated clinically (any improvement of pains and paresthesia by visual analogue scales, any stabilization or improvement of muscular testing in case of motor impairment at baseline) and electrophysiologically (stabilization or improvement of electromyogram abnormalities at W25 compared to baseline).
- Digestive remission is evaluated clinically (improvement of abdominal pain and other gastrointestinal symptoms), by endoscopy (improvement of potential gastrointestinal lesions seen at baseline) and/or by Xray (improvement of any abnormalities found on baseline imaging). Complete remission of all baseline abnormalities is required to define digestive remission.
- Cardiac remission is evaluated clinically (improvement of chest pains and other cardiac events), electrically (disappearance of abnormalities indicating acute myocardial suffering on EKG) and biologically (normalization of muscular enzymes). Complete remission of all baseline abnormalities is required to define cardiac remission.
- Central nervous system remission is evaluated clinically (stabilization or improvement of central nervous system manifestation) and by MRI (stabilization or disappearance of vasculitis sign)
- Pulmonary remission is evaluated clinically (improvement of dyspnea and disappearance of hemoptysis) and by chest scan (improvement of vasculitis sign)

Patients with no clinical response at W5 will be defined as early treatment failure (failure for the principal judgment criteria); unblinded, the optimal treatment will be performed by the physician in charge of the patient.
Patients with clinical relapse (defined as de novo appearance or recurrence of a manifestation due to the cryoglobulinemia vasculitis) between W5 and W25 will be considered in failure according to the primary endpoint. For severe relapses, unblinded the optimal treatment will be performed by the physician in charge of the patient and therapeutic management will be at the discretion of the investigator according to standard of care. Patients with moderate or mild relapse will be treated by an increase of the corticosteroids without breaking the double-blind.

A severe flare-up is defined by the appearance or reappearance of one of the following signs:

- Extensive skin necrosis with loss of substance
- Specific cardiac involvement of vasculitis (documented by EKG, troponin and MRI)

- Specific digestive impairment of vasculitis (documented by imaging and/or endoscopy)
- Affection of the central nervous system specific to vasculitis (documented by cerebral MRI)
- Multiple mononeuropathy clinically defined by asymmetrical motor impairment of 2 or more nerve trunks. (documented by electromyogram)
- Severe renal impairment defined as a doubling of creatinine levels from the usual value or a glomerular filtration rate according to MDRD of less than 30 ml/min/1.73m2 (in the absence of prior history of creatinine levels) and after excluding other causes of renal impairment.

Other flare up [appearance or reappearance of purpura, arthritis, sensory neuropathy documented by electromyogram and/or glomerulonephritis (proteinuria>1g/24h after excluding other causes of proteinuria)] will be defined as moderate or mild at the discretion of the investigator.

4.1.2 Secondary endpoints

- Safety and tolerability of treatments as assessed by frequency and severity of adverse clinical events from baseline to W25 and at W48
- Complete, partial and non clinical response rate at W13, W25 and at W48.
- Complete renal response rate at W13, W25 and W48 defined by : proteinuria <0.5g/24h or proteinuria/creatininuria <50 mg/mmol, disappearance of hematuria and glomerular filtration rate by MDRD > 60 ml/min/1.73 m².
- Rate of cryoglobulinemia clearance, negativation of rheumatoid factor activity and of normalization of C4 complement level at W13, W25 and at W48,
- Rate of early failures (non clinical response at W5),
- Clinical relapse rate defined by de novo appearance or recurrence of a manifestation attributable to cryoglobulinemia vasculitis during 48 weeks of follow-up,
- Rate and time to relapse from baseline to W48
- Cumulative dose of prednisone at W25 and at W48,
- Evolution of gammaglobulin and of CD19+ B levels from baseline to W48
- Quality of life score SF-36 at baseline, W25 and W48,
- Rate of infections (severe or not) and other complications during the 48 weeks of follow-up
- BVAS activity score at baseline, W13, W25 and W48.

4.1.3 Design of the trial

The experimental design is a multicentric randomized controlled clinical trial stratified on previous treatment history (naive patients versus relapsing patients) and the severity of cryoglobulinemia vasculitis (i.e. extensive skins necrosis, glomerulonephritis, multiple mononeuropathy, myocarditis, digestive or central nervous system specific involvement) in a 1:1 ratio between groups with evaluation of the primary assessment criteria at week 25.

The primary assessment criteria and the final measures of corticosteroid sparing will be reviewed by an endpoint adjudication committee blinded of the randomization. This committee will have the role of validating under blind conditions the following assignments: complete remission, treatment failure and relapse of the disease.

The RCT will use an adaptive Bayesian design for phase II randomized national multicentre clinical trial that aims at comparing a new treatment to a reference based on a binary endpoint (i.e. complete clinical response at week 25), which offers greater flexibility and simplicity of inference to the monitoring for patient safety and evidence of efficacy of small randomized trials.

- Week 0: Day of Inclusion and Randomization in a 1:1 ratio

Group I: Belimumab administered subcutaneously 200mg weekly from week 1 to week 24.
Group II: placebo of Belimumab administered subcutaneously weekly from week 1 to week 24.

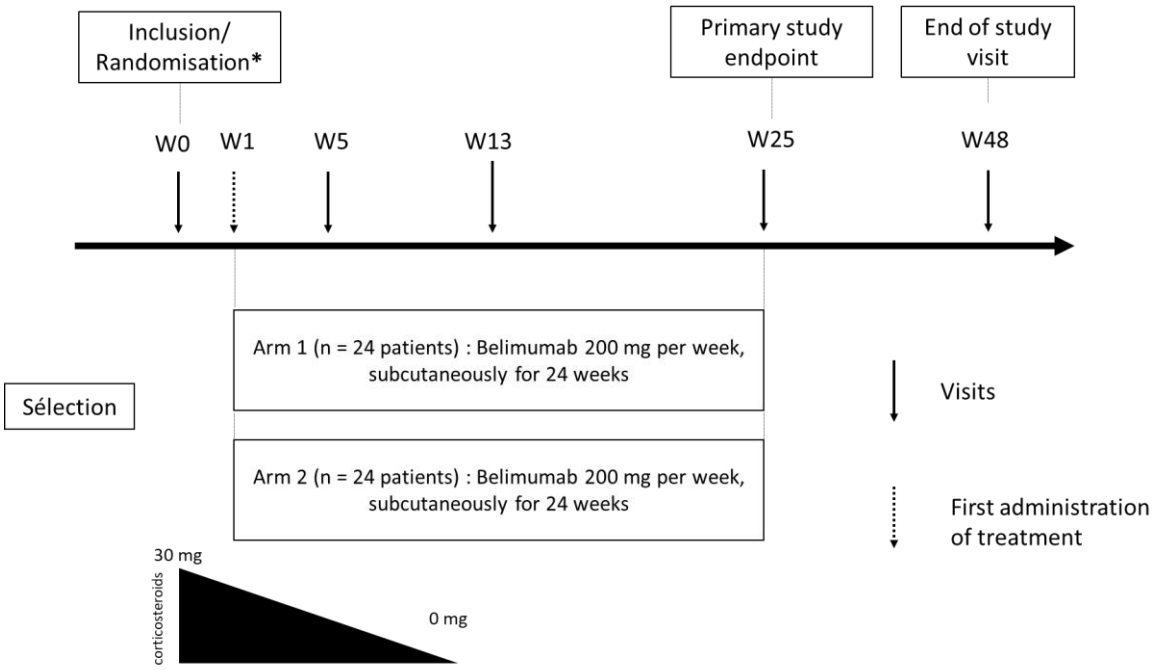
Both groups will have the same corticosteroid tapering scheme, with an initial dose of 30 mg/day. The following schedule of reduction of prednisone will apply to both groups as long as the disease is inactive:
30 mg/day week (W)0-W2,
20 mg/day W2-W4
15 mg/day W4-W6,
10 mg/day W6-W8,
5 mg/day W8-W10,
Between W10-W12 the strategy for stopping glucocorticoids is left to the investigator's discretion,

Stopping glucocorticoid therapy at W12
At each step, the prednisone dose will be reduced only in the absence of signs of vasculitis activity. In case of minimal to moderate relapse, the dose of prednisone will be re-increased to the previous level, and the new dose should be maintained for 4 weeks before resuming the regimen of corticosteroid decay.

First administration of belimumab or placebo for patients who satisfy all entry criteria including informed consent will be done within 7 days (+/-2 days) at visit W1 after inclusion/randomisation.

- Week 5: evaluation of clinical response
- Week 25: Evaluation of primary assessment criteria
- Week 13, 25 and 48: Evaluation of secondary assessment criteria

Figure 1. Scheme of the study



*Due to pharmaceutic deliverance of belimumab and its placebo, the fisrt injection will occur within 7 days +/-2 days after randomization

4.1.4 Number of participating sites

Multicentre national study including 20 centres.

4.1.5 Identification of the subjects

The subjects participating in this study will be identified as follows:
Site number (3 digits) - Sequential selection number for the site (4 digits) - surname initial - first name initial
This reference number is unique and will be used for the entire duration of the trial.

4.1.6 Randomisation

When selected, the patient eligibility will be evaluated from inclusion and non-inclusion criteria. Once the consent will be signed by the patient and investigator, the patient will be included and randomised by connecting the eCRF. The patient identification number will be allocated.
Randomization of patients will be centralized and carried out using a computerized system in the eCRF website according to a predefined randomization list. Distribution in the two groups will be made in a 1:1 ratio.
The randomization list will be designed by the Sponsor/designee, and stratified on previous treatment history (naive patients versus relapsing patients) and the severity of cryoglobulinemia vasculitis (i.e. extensive skins necrosis, glomerulonephritis, multiple mononeuropathy, myocarditis, digestive or central nervous system specific involvement); between the two arms.
Each list will be based on permutation blocks, the size of which will be unknown to practitioners involved in patient accrual.
All inclusion and non-inclusion criteria will be checked before randomization.

4.1.7 Unblinding procedures

The investigating doctor may request unblinding for any reason he considers essential, by contacting:

- **In emergency cases** at the poison control centre at Fernand Widal Hospital, Telephone: **+33 (0)1 40 05 48 48.**
- **Apart from an emergency situation** at the DRCI (Clinical Research and Innovation Department) to the DRCI project advisor whose contact information are listed on the protocol cover page :Project Manager Elodie SOLER, Tel. 01 44 84 17 35

5 PROCEDURE FOR THE TRIAL

5.1 Inclusion/randomisation visit

The Inclusion/randomisation visit takes place *at week 0*.

Whose consent must be obtained	Who informs the individual and collects their consent	When is the individual informed	When is the individual's consent collected
the subject	*the investigator*	*During*	*After time reflexion during*

participating in the trial	*internal medicine, nephrologist or Rheumatologist*	*Inclusion/randomisation visit*	*Inclusion/randomisation visit*

The Inclusion/randomisation visit will be carried out by the physician who is responsible for the patient during the Study.

During this visit, the investigator will:

- verify the eligibility criteria,
- interview the patient and record:
- medical, surgical and therapeutic histories,
- histories of undercurrent disease and current treatments,
- perform a physical examination including a search for active lesions of cryoglobulinemia vasculitis, vital signs assessed and recorded at baseline
- Suicidality assessed at baseline (Some autoimmune diseases have an increased risk of suicidal behavior and/or ideation [Bachen, 2009; imonen, 2003;Stenager, 1992]. For this reason in studies of patients with autoimmune disease, patients should be clinically assessed for suicidal ideation and/or behavior at each visit.)
- Progressive multifocal leukoencephalopathy (PML) evaluation
- perform complete blood count with platelets, serum electrolytes, liver function tests (AST, ALT, GGT, total bilirubin, PAL), LDH, total cholesterol and triglycerides, glycemia, CRP, protein electrophoresis, creatinine, proteinuria, or proteinuria/creatininuria, creatininuria, hematuria, CD19 level, cryoglobulin, rheumatoid factor and C4 level and for women, and ECG
- Assess the results of serum IgG, IgA and IgM obtained within 1 month prior to inclusion
- Assess the results of HIV, HVB and HCV serologies (and HCV PCR if positive serology) , obtained within 3 months prior to inclusion
- Assess the results of the specific exam for vasculitis evaluation (depending on organ involvement at baseline):
    - electromyogram
    - digestive endoscopy and/or abdominal scanner
    - cardiac: troponin, echocardiography and/or cardiac MRI with gadolinium injection),
    - pulmonary: CT scan
    - Central nervous system: cerebral MRI

  Electromyogram, CT scan, cerebral MRI, digestive exploration and cardiac exploration has to be obtained within 3 months prior inclusion in case of clinical signs of specific impairment. If present at baseline, exploration must be done at W25
- inform the patient about the protocol, and give them the information and consent form
- collect the free and informed written consent of the patient
- ßHCG for women of childbearing potential WCBP (urinary or plasmatic)
- If all eligibility criteria are met the investigator will complete the Study Inclusion Form listing the eligibility criteria
- Ensure the randomization on CleanWeb, an online randomization system
- Quality of life assessment BVAS

Inclusion may occur on the day of the last injection of Rituximab.
The first shipment of belimumab or its placebo to each pharmacy will be made after the randomisation of a patient in a centre.

5.2 Start of treatment visit (W1)

The first subcutaneous injection of belimumab or its placebo will be administered within 7 days +/-2 and then weekly until week 24.
The first injection should be under the supervision of a healthcare professional in the center. Injections should comply with the information patient sheet and SmPC of Benlysta®

Group I (n=24 patients): Belimumab administered subcutaneously 200mg weekly from W1 to week 24.
Group II (n=24 patients): Placebo of Belimumab administered subcutaneously weekly from W1 to week 24.

5.3 Follow-up visits

Monitoring should continue for all patients until the end of the Study according to the schedule, even if they discontinue treatment. Consultations at these visits will be with the patient's usual Study doctor. Patients in both Arms will be reviewed at weeks 5 (+/- 3 days), 13 (+/- 3 days), 25 (+/- 3 days) and 48 (+/- 7 days),

- A physical examination will be performed by the patient's Study physician at each visit, vital signs assessed and recorded at each visit
- The investigator will look for signs of complications including :
    - Progressive multifocal leukoencephalopathy (PML) resulting in neurological deficits, including fatal cases, has been reported in Systemic lupus erythematous (SLE) patients receiving immunosuppressant pharmacotherapy, including belimumab. A diagnosis of PML should be considered in any subject presenting with new-onset or deteriorating neurological signs and symptoms. The subject should be referred to a neurologist or other appropriate specialist for evaluation. If PML is confirmed, study agent should be discontinued and consideration should be given to stopping immunosuppressant therapy. If PML is suspected, this should be immediately reported to the sponsor. The appropriateness of continuing study agent, while the case is being assessed, should be discussed.
    - Suicidality assessed at every visit
- Every month until W25:
    - complete blood count with platelets,
    - serum electrolytes, and creatinin
    - liver function tests (AST, ALT, GGT, total bilirubin, PAL),
    - LDH, total cholesterol and triglycerides, glycemia,
    - CRP,
    - protein electrophoresis,
    - proteinuria, creatininuria, hematuria,
    - ß-HCG (urinary) for WCBP every month and at least 4 months (5 half lives) post last dose.
- Serum IgG, IgM, and IgA and CD19 levels at W13 , W25 and W 48.
- At W5, W13, W25 and W48: cryoglobulin rheumatoid factor and C4 level and ECG will be performed.
- Quality of life assessment SF-36 and BVAS score assessement at W13, W25 and W48
- Other exams according to others active cryoglobulinemia vasculitis manifestations (i.e. cardiac (troponin, echocardiography +/- cardiac MRI with gadolinium injection), digestive (X-ray, endoscopy), neurological (electromyogram....) have to be done at week 25 If present at baseline.

A nurse from the investigating center will perform the biological tests at W5, W13, W25 and W48 using a routine standard method during consultation.

In case of clinical relapse, biological tests, dosage of cryoglobulinemia, C4 level, rheumatoid and CD19 level will be done.

Additional visits will take place if there are clinical signs indicating a possible flare up of the disease.

Increased Monitoring Criteria with Continued Therapy

Criteria

- If ALT ≥5xULN and <8xULN and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 2 weeks

OR

- ALT ≥3xULN and <5xULN and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 4 weeks

Required Actions

Report the event to GSK the sponsor immediately without delay when the investigator becomes aware,of the abnormality to discuss subject safety

Subject can continue study treatment

Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline

If at any time subject meets the liver chemistry stopping criteria, proceed as described above for Required Actions and Follow up Assessments following ANY Liver Stopping Event

If ALT decreases from ALT 5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly

If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

5.4 End of study visit: Week 48

The end of study visit will be done at week 48. The biological tests and exams will be performed according the assessment

After this visit all subjects will be followed after the study according to their usual routine hospital care every 3 months until one year.

5.5 Expected length of participation, chronology and duration of the study.

The total duration of the Study will be 48 months (4 years).

The duration of the inclusion phase will be 36 months.

The duration of participation of each patient will be of 12 months.

The duration of experimental treatment of each patient will be 24 weeks for all patients. After 24 weeks the treatment will be left to the discretion of the physician in charge of the patient.

5.6 Table summarising the chronology of the study

Weeks (W)	Inclusion / randomisation visit W0	W1 +/- 2 days	W5 +/-3 days	W9 +/- 3 days	W13 +/- 3 days	W17 +/- 3 days	W21 +/- 3 days	W25§ +/- 3 days	W48 +/- 7 days
Information	®								
Inclusion/randomization visit (Oral and written Information about the protocol and Signature of informed consent)	®								
Inclusion and non-inclusion Criteria	®								
HIV, HVB and HCV serologies (and HCV PCR if positive serology), obtained within 3 months prior inclusion	X								
beta-hCG for women of childbearing age§	®		®	®	®	®	®	®	
Randomization	®								
Physical exam,	X		X		X			X	X
Biological tests#	X		X	X	X	X	X	X	X
Evaluation of the efficacy			X		X			X	X
Evaluation of the safety including suicidal risk and PML evaluation	X		®		®			®	®
Quality of life questionnaire SF-36 BVAS score	®				®			®	®
Dosage of cryoglobulinemia, C4 level, rheumatoid factor and ECG	X		X		X			X	X
Electromyogram**	X							X	
Other exams according to others active cryoglobulinemia vasculitis manifestations (i.e. cardiac or digestive)**	X							X	
Serum IgG, IgM and IgA and CD19 levels	X				X			X	X
Dispensation of treatment		®*			®				

§Primary end point

® = Specific for research

* The first shipment of belimumab or its placebo to each pharmacy will be made after the randomisation of a patient in a centre. The first subcutaneous injection of belimumab or its placebo will be administered within 7 days +/-2 and then weekly until week 24.

**Electromyogram, pulmonary CT scan, cerebral MRI, digestive exploration and cardiac exploration has to be obtained within 3 month prior inclusion in case of clinical signs of specific impairment. If present at baseline, exploration must be done at W25

Biological tests included complete blood count with platelets, serum electrolytes, liver function tests (AST, ALT, GGT, total bilirubin, PAL), LDH, total cholesterol and triglycerides,), glycemia, creatinine, proteinuria or proteinuria/creatininuria, creatininuria, hematuria, CRP and protein electrophoresis will be performed every months. In case of clinical relapse, biological tests, dosage of cryoglobulinemia, C4 level, rheumatoid and CD19 level will be done. **§** ßHCG (urinary or plasmatic) for WCBP at inclusion visit then every month (urinary) during treatment and at least 92 days (5 half lives) post last dose

5.7 Distinction between standard care and research

Procedures and treatments carried out as part of the research	Procedures and treatments associated with care	Procedures and treatments added because of the research
Treatments	- oral prednisone - Reduction of corticosteroid regimen - supportive treatment to reduce the adverse effects associated with the use of steroids - Rituximab intravenously 6 weeks prior inclusion	- Belimumab 200mg/week SC for 24 weeks - Placebo of Belimumab 200mg/week SC for 24 weeks
Consultations	- visit at week 5, 13, 25 and 48	
Blood samples	- Biological tests at each visit - Cryoglobulinemia, C4 and rheumatoid factor at W0, W5, W13, W25 and W48 - Serum IgG, IgM and IgA and CD19 levels at baseline, W13 W25 and W48.- Biological tests, dosage of cryoglobulinemia, C4 level, rheumatoid and CD19 level will be done in case of clinical relapse.	- BHCG (plasmatic or urinary) at baseline and every month until at least 92 days (5 half lives) post last dose
Imaging	- ECG: before starting treatment and at W5, W13, W25 and W48 - Electromyogram If neurological manifestation within 3 months prior inclusion and W25, Other exams according to others active cryoglobulinemia vasculitis manifestations (i.e. cardiac echocardiography and cardiac MRI with gadolinium injection, GI endoscopy and CT scan, central nervous system MRI..)	
Others		- QOL questionnaires at W0, W13, 25 and 48 weeks

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

The eligibility criteria will be checked at the inclusion/randomization visit. Patients meeting the following criteria may be included in the study:

1. Age > 18 years
2. Written inform consent
3. Active cryoglobulinemia vasculitis, at initiation of rituximab, define by a clinically active vasculitis with skin, joint, renal, peripheral nerve, central neurological, digestive, pulmonary and/or cardiac involvement , and history of positive cryoglobulinemia
4. Affiliated to National French social security system
5. Having received Rituximab as induction therapy within 6 weeks (1 to 4 infusions, dose at the discretion of the investigator)
6. Female subjects of childbearing potential must have a negative serum or urinary pregnancy test at inclusion visit, and confirmed monthly while in study, out to at least 92 days (5 half lives) post last dose.
7. For subjects with reproductive potential (male or female), a willingness to use contraceptive measures adequate to prevent the subject or the subject's partner from becoming pregnant during the study from 2 weeks prior to administration of the 1st dose of study agent until 92 days after the last dose of study agent. Therefore the subjects agree to 1 of the following:
   a. Complete abstinence from intercourse from 2 weeks prior to administration of the 1st dose of study agent until 92 days after the last dose of study agent (Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception)
   OR
   b. Consistent and correct use of 1 of the following acceptable methods of birth control for 1 month prior to the start of the study agent, during the study, and 92 days after the last dose of study agent

      - Oral contraceptive, either combined or progestogen alone
      - Injectable progestogen
      - Implants of levonorgestrel or etonogestrel
      - Estrogenic vaginal ring
      - Percutaneous contraceptive patches
      - Intrauterine device (IUD) or intrauterine system (IUS) with <1% failure rate as stated in the product label
      - Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, "documented" refers to the outcome of the investigator's/designee's medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject's medical records

- Double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository)

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

8. HIV negative serology ; negative HBs Ag test and HBc Ab test; HCV negative serology or negative HCV RNA if positive HCV serology within 3 months before inclusion
9. neutrophils (ANC) >1x109/L

6.2 Exclusion criteria

Subjects will be not included from the study if they meet any of the following criteria:

1. Patient with a vasculitis unrelated to cryoglobulinemia
2. Patient with non active cryoglobulinemia vasculitis, at initiation of rituximab. Patients with inactive vasculitis following rituximab administration may be included.
3. Excluded concomitant medications:
    a. 365 days Prior to Investigational Medicinal Product (Belimumab or placebo)::
        - 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 it is being used
    b. 180 Days Prior to Investigational Medicinal Product (Belimumab or placebo)::
        - Intravenous cyclophosphamide
    c. 30 Days Prior to Investigational Medicinal Product (Belimumab or placebo): (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 it is being use
    d. Live vaccines within 30 days prior to baseline or concurrently with Investigational Medicinal Product (Belimumab or placebo)
4. Have a history of malignant neoplasm within the last 5 years, other than carcinoma in situ of the cervix or excised basal cell, squamous cell carcinoma of the skin and low-grade hemopathy with no indication for a specific treatment
5. Have 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, pose a significant suicide risk
6. Have a Progressive multifocal leukoencephalopathy
7. Have a history of a primary immunodeficiency
8. Have a significant IgG deficiency (IgG level < 400 mg/dL) and/or significant IgA deficiency (IgA level < 10 mg/dL) according to results obtained within 1 month prior to inclusion visit
9. Have a history of major organ transplant or hematopoietic stem cell/marrow transplant or renal transplant
10. Infection history:
    a. Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus
    b. Infection requiring hospitalization and/or use of parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti-parasitic agents) within 60 days of the inclusion visit.
11. Have current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within 365 days prior to the inclusion visit
12. Have a historically positive HIV test according to results obtained within 3 months prior to inclusion visit
13. Hepatitis status according to results obtained within 3 month prior to inclusion visit :

a. 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
b. Positive test for Hepatitis C RNA

14. Have a history of a hypersensitivity or an anaphylactic reaction to parenteral administration of Belimumab, corticosteroids or any excipients of the treatments administered during the study
15. If Women of Child Bearing Potential (WCBP) are included please see special instructions in Inclusion criteria
16. Pregnant or breast feeding women
17. Have any intercurrent significant medical or psychiatric illness that the investigator considers would make the candidate unsuitable for the study
18. Patients under legal protection or unable to consent
19. Participation to another interventional study

6.3 Recruitment procedure

The French national reference center for rare systemic and autoimmune diseases located in the Pitie Salpetriere hospital, Paris is a leading center in the field of cryoglobulinemia vasculitis with a cohort of more than 500 patients. With the French cryoglobulinemia vasculitis network, we recently conducted a study on management of noninfectious mixed cryoglobulinemia vasculitis and recruited 242 patients. We are working in close collaboration with French neurologist, nephrologist, dermatologist and rheumatologist including those from Pitie Salpetriere hospital, in Paris.

	Number of subjects
Total number of subjects to be included	48
Number of sites	20
Enrolment period (months)	36
Number of subjects/site	2
Number of subjects/site/month	**0.06**

6.4 Termination rules

6.4.1 Criteria and procedures for prematurely terminating the study treatment

Several situations are possible

- Temporary suspension of treatment: the investigator must document the reason for suspending and resuming the treatment in the participant's source file and the case report form (CRF)
- Premature discontinuation of treatment, but the participant remains enrolled in the study until the end of their participation
- Premature discontinuation of treatment and withdrawal from the study

The investigator must:

- Document the reason(s)

- Collect the assessment criteria at the time of ending participation in the study, if the participant agrees
- Schedule a follow-up for the participant, particularly in case of a serious adverse event.

6.4.2 Temporary interruption of the study treatment

Non-injection of the study treatment is permitted in the event of an intercurrent event requiring suspension of treatment, at the investigator's discretion. The continuation of the protocol treatment is possible if 2 or less injections have not been performed in this case.
The reason for interruption should be documented in the patient's study record.

6.4.3 Permanent termination of the study treatment

A subject must be discontinued the treatment for any of the following reasons:

- Severe infection define by :
  - tuberculosis, pneumocystis, or cytomegalovirus,
- Progressive multifocal leukoencephalopathy.
  - If PML is confirmed, study agent should be discontinued and consideration should be given to stopping immunosuppressant therapy.
- Serum IgG levels <250 mg/dL associated with a severe or serious infection.
  - If a subject experiences any IgG levels < 250 mg/dL not associated with severe or serious infection, increased vigilance for infection is required. Clinical judgment should be applied with respect to the appropriateness of continuing study therapy in these subjects.
- Neoplasia
- Serious Hypersensitivity or Infusion Reactions ≥ grade 3 CTCAE
- Clinically significant, potentially life-threatening (Grade 4) adverse event (AE) that the investigator believes is definitely, possibly or probably related to study agent,

- **Stopping / withdrawal criteria. Benlysta should be discontinued:**

✓ **Liver chemistry stopping criteria:Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).**

- ALT Absolute: ALT ≥ 8xULN
- ALT Increase:
  - ALT ≥ 5xULN but <8xULN persists for ≥2 weeks
  - ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
- Bilirubin: ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin)
  - Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury
  - All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
- INR: ALT ≥ 3xULN and INR>1.5, if INR measured
- Cannot Monitor:
  - ALT ≥ 5xULN but <8xULN and labs cannot be monitored weekly for ≥2 weeks

○ ALT ≥ 3xULN but <5xULN and labs cannot be monitored weekly for ≥4 weeks

Symptomatic: ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

○ New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)

Required Actions, Monitoring, and Follow up Assessments following ANY Liver Stopping Event

Actions:

- Immediately discontinue study treatment
- Report the event to the sponsor immediately without delay when the investigator becomes aware,
- Perform liver event follow up assessments (as stated below)
- Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below)
- Do not restart/rechallenge subject with study treatment

Monitoring:

For bilirubin or INR criteria:

- Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hours
- Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline
- A specialist or hepatology consultation is recommended
- For All other criteria:
- Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24-72 hours
- Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline

Follow Up Assessments:

- Viral hepatitis serology (Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody)
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin≥2xULN
- Obtain complete blood count with differential to assess eosinophilia
- Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
- Record use of concomitant medications including acetaminophen, herbal remedies, other over the counter medications
- Record alcohol use

<u>For bilirubin or INR criteria:</u>

- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins)
- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009])

Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.
Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

Participants will continue to be monitored for the study according the timetable visits of protocol except in case of the subject withdraws consent and lost to follow-up.
The decrease and continuation of corticosteroids will be left to the discretion of the investigator.

6.4.4 Criteria and procedure for premature withdrawals and exits from the study

- Participants may exit the study at any time and for any reason.
- The investigator can temporarily or permanently withdraw a subject from the study for any safety reason or if it is in the subject's best interests. Participants lost to follow-up: the participant cannot be located. The investigator must make every effort to reconnect with the participant (and document his attempts in the source file), at least to determine whether the participant is alive or dead

If a participant exits the study prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used.
- If a participant exits the study prematurely, and if the participant agrees, state the procedure and schedule for collecting the data required by the protocol (primary endpoint, secondary endpoints, safety assessment) (NB: this must be stated in the information and consent form)
- State how premature exit from the study will affect the participant's ongoing care (state exactly what the participant will be offered).
- In case of serious adverse events, see the corresponding section on vigilance

The case report form must list the various reasons why the participant has discontinued the study:
- ☐ Lack of efficacy
- ☐ Adverse reaction
- ☐ Another medical issue
- ☐ Personal reasons of the participant
- ☐ Explicit withdrawal of consent
- ☐ Lost to follow-up

6.4.5 Follow-up of participants following premature withdrawal from the study

If a subject exits the trial this will in no way affect the standard care received for his/her condition.
In case of severe adverse events, the investigator must notify the sponsor and monitor the subject for 12 months following the premature termination of treatment. If treatment is stopped prematurely due to a serious adverse event, a serious adverse event report will be sent by email (eig-vigilance.drc@aphp.fr) to the sponsor. The serious adverse reaction will be monitored until it is resolved.
If a Data Safety Monitoring Board has been created, the committee can specify and/or validate the follow-up methods.

6.4.6 Procedure for replacing participants, if applicable

In case of patient withdrawal, patient will not be replaced.

6.4.7 Full or partial discontinuation of the study

AP-HP as the sponsor or the Competent Authority (ANSM) can prematurely discontinue all or part of the study, temporarily or permanently, further to the recommendations of the Data Safety Monitoring Board in the following situations:

- first of all, if suspected unexpected serious adverse reactions (SUSARs) are observed in one of the treatment arms or if there is a discrepancy in the serious adverse reactions between the two treatment arms, requiring a reassessment of the benefit-risk ratio for the study.

Similarly, AP-HP, as the sponsor, or the Competent Authority (ANSM) may decide to prematurely discontinue the study due to unforeseen issues or new information about the product, in light of which the objectives of the study or clinical programme are unlikely to be achieved.

AP-HP as sponsor reserves the right to permanently suspend enrolment at any time if it appears that the inclusion objectives are not met.

If the study is prematurely discontinued for safety reasons, the decision and justification will be provided by the sponsor (AP-HP) to the Competent Authority (ANSM) and to the CPP (Research Ethics Committee) within a period of 15 days, along with recommendations from the Data Safety Monitoring Board *(if applicable)* in the case of substantial modification.

7 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

7.1 Description of the investigational medicinal product(s)

The treatment administered will be belimumab, Benlysta® or Placebo which will be provided by Glaxo-SmothKline. Treatments should be stored in the refrigerator (between + 2° C and + 8° C).

7.1.1 Investigational medicinal product 1: Benlysta® 200 mg

Presentation: Treatments will be presented in numbered boxes, labelled for this study according to the Good Manufacturing Practices under the responsibility of the Clinical Trial Department of AGEPS (Agence Générale des Equipements et Produits de Santé). Each numbered box will contain 1-ml pre-filled serynges containing 200 mg of belimumab, sterile solution for subcutaneous injection, for a 3 months period of treatment.

Posology for clinical trial: Belimumab will be administered subcutaneously 200mg weekly (each week, on the same day +/-1 day) from week 1 to week 24.

7.1.2 Investigational medicinal product 2: Placebo of Benlysta® 200 mg

Presentation: Treatments will be presented in numbered, labelled for this study according to the Good Manufacturing Practices under the responsibility of the Clinical Trial Department of AGEPS (Agence Générale des Equipements et Produits de Santé). Each numbered box will contain 1-ml pre-filled serynges of Placebo of belimumab, sterile solution for subcutaneous injection, for a 3 month period of treatment.

Posology for clinical trial: Placebo of belimumab will be administered subcutaneously 200mg weekly (each week, on the same day +/- 1 day) from week 1 to week 24.

7.2 Description of Additional medicinal product(s) (treatments required to conduct the study)

Both groups will have the same corticosteroid tapering scheme, with an initial dose of 30 mg/day. The following schedule of reduction of prednisone will apply to both groups as long as the disease is inactive:
30 mg/day week (W)0-W2,
20 mg/day W2-W4
15 mg/day W4-W6,
10 mg/day W6-W8,
5 mg/day W8-W10,
Between W10-W12 the strategy for stopping glucocorticoids is left to the investigator's discretion,
Stopping glucocorticoid therapy at W12

7.3 Description of traceability elements accompanying the investigational medicinal product(s)

The shipments to the hospital pharmacies will be insured by the Clinical Trial Department of AGEPS.

Supply:
Shipment to hospital pharmacy, for each patient, will be made after randomisation (receipt of 2 numbered boxes for each patient 1 week after the randomisation visit).

***Re supply*:**
Automatic orders via eCRF: number of boxes adapted to real consumption.

The hospital pharmacist (with respect to usual procedures) will confirm receipt in writing of all batches of study medication sent and maintain an accurate accounting of them.

Storage:
Treatments should be stored in the refrigerator (between + 2° C and + 8° C).
Keep the package in the outer carton in order to protect from light.
The treatment must not be frozen.
In order to keep treatment at the appropriate temperature on their way home, patients will receive an isothermal bag.

Dispensing:
Pharmacies will dispense numbered box for each patient on the basis of a specific prescription.

The dispensing traceability will be insure with the peel-off label present on each and affixed on the prescription.

Administration:
The first injection should be under the supervision of a healthcare professional in the center.
Injections should comply with the information patient sheet and SmPC of Benlysta®

Investigators/site personnel should be aware of the risk of hypersensitivity reactions,

which may present as injection related systemic reactions, and monitor subjects closely. The healthcare professional must provide proper training in subcutaneous technique and education about signs and symptoms of hypersensitivity reactions. A patient may subsequently self-inject or a patient caregiver may administer belimumab after the healthcare professional determines that it is appropriate

c. "In the post-marketing setting, delayed onset of symptoms of acute hypersensitivity reactions has been observed with intravenous belimumab. Subjects should remain under clinical supervision for 3 hours after completion of the first injection. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment. This may include, but is not limited to, monitoring vital signs and observing any untoward reactions.
    - After the first injection and at the discretion of the investigator, subjects who are adequately trained may self-administer all subsequent doses at home. Comprehensive written instructions on injection technique are required to be provided to the study subject by the investigator (Appendix 3). After the first dose, subjects who do not feel adequately trained with self-injection may return to the site for further training. Patients should not administer the study agent until they receive proper training in subcutaneous injection technique.

d. Subjects should be made aware of the potential risk of delayed onset acute hypersensitivity, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention in event of its development. For further information, see the belimumab IB

The administration traceability will be insure with the peel-off label present on each box and affixed to the patient booklet to ensure the traceability of the administration.

Accountability and destruction: will be accounted by the CRA at the end of the study. After completion, double blind boxes (unused, returned…) might be returned to AGEPS for a central destruction.

7.4 Authorised and prohibited treatments (medicinal, additional medicinal, surgical), including rescue medications

7.4.1 Authorised treatments

All treatments taken by the patient during the trial but not prescribed in the Protocol will be considered "treatments other than Study treatments". Whether allowed or not, they must be reported on the appropriate page of the CRF. The risks and benefits of using such drugs must be carefully assessed for all included patients.

To reduce the adverse effects associated with the use of steroids, the following supportive treatment will be administered routinely starting on W 0:

- a potassium supplement (DIFFU K, 1 capsule 3 times/day)
- a calcium/vitamin D supplement (CACIT D3, 1 g/day)
- a bisphosphonate, in the absence of contra-indications, either Actonel (risedronate) at 35 mg/week or Fosamax (alendronate) at 70 mg/week to be taken on an empty stomach with a large glass of water then remaining sitting or standing for 30 minutes.
- a diet low in fat, salt and rapidly-absorbed sugars.

7.4.2 Prohibited treatments

Immununosuppressive or immunomodulatory therapies (azathioprine, mycophenolate mofetil, methotrexate, cyclophosphamide, plaquenil, ciclosporin, tacrolimus, bortezomib) are

contraindicated for the duration of the study. The use of these treatments implies that this is a primary failure of the TRIBECA trial or a clinical relapse, to be taken into account in the analysis of the results.
Live attenuated vaccines, are contraindicated for the duration of the study.

Treatment used with precaution

Warfarin
Enzyme-inducing anti-convulsants
Digoxin
CYP3A Inhibitors
Fluoroquinolones
Non-steroidal anti-inflammatory drugs

7.5 Method for monitoring compliance with the treatment

Treatment administration will be done in ambulatory. Patients will complete a booklet to record the real date and time of each administration during 24 weeks, and potential side-effects and comments. This booklet will be kept in the patient's medical records.

According a monitoring plan, compliance will be monitored.

8 EFFICACY ASSESSMENT

8.1 Description of efficacy endpoints assessment parameters

- Complete clinical response

The complete clinical response is defined by the remission of all affected organs involved at baseline and the absence of clinical relapse.

- The skin and articular remissions are evaluated clinically (disappearance of purpura and/or ulcers, disappearance of arthritis).
- Renal remission is evaluated biologically (proteinuria <0.5g/24h or proteinuria/creatininuria <50 mg/mmol,
- Neurological remission is evaluated clinically (any improvement of pains and paresthesia by visual analogue scales, any stabilization or improvement of muscular testing in case of motor impairment at baseline) and electrophysiologically (stabilization or improvement of electromyogram abnormalities at W25 compared to baseline).
- Digestive remission is evaluated clinically (improvement of abdominal pain and other gastrointestinal symptoms), by endoscopy (improvement of potential gastrointestinal lesions seen at baseline) and/or by Xray (improvement of any abnormalities found on baseline imaging). Complete remission of all baseline abnormalities is required to define digestive remission.
- Cardiac remission is evaluated clinically (improvement of chest pains and other cardiac events), electrically (disappearance of abnormalities indicating acute myocardial suffering on EKG) and biologically (normalization of muscular enzymes). Complete remission of all baseline abnormalities is required to define cardiac remission.

- Partial clinical response

The partial clinical response is defined by the improvement and / or remission of more than half of the organ involvement present at baseline and the absence of clinical relapse.

- No clinical response

Patients with no clinical response at W5 will be defined by worsening of ulcers or cutaneous necrosis, worsening peripheral neurological involvement or by persistence of active renal involvement defined by persistence of proteinuria> 1.5 g / 24h or proteinuria/creatininuria >150 mg/mmol.
For patients with early treatment failure, blindness can be removed and optimal treatment chosen by the clinician in charge of the patient. These patients will be considered to be failing in the primary endpoint.
Patients with no clinical response at W5 will be defined as early treatment failure (failure for the principal judgment criteria); unblinded, the optimal treatment will be performed by the physician in charge of the patient.

- Relapse

Relapse is defined as de novo appearance or recurrence of a manifestation of cryoglobulinemia vasculitis between W5 and W25 will be considered as a relapser.

Patients with clinical relapse between W5 and W25 will be considered in failure according to the primary endpoint. For severe relapses, unblinded the optimal treatment will be performed by the physician in charge of the patient. Patients with moderate or mild relapse will be treated by an increase of the corticosteroids without breaking the double-blind.
Patients in clinical relapse will be considered to be failing in the primary endpoint.

- Immunological response

The complete immunological response is defined by the disappearance of cryoglobulinemia and / or the normalization of the C4 fraction of the complement at W25.
The partial immunological response is defined as a decrease> 50% in the rate of cryoglobulinemia and / or an increase> 50% in the C4 fraction of the complement at W25.

9 SPECIFIC STUDY COMMITTEES

9.1 Steering Committee

- Committee members: Pr D Saadoun, Dr Vautier, Pr M Resche-Rigon, N Raked, E Soler, a DEC AGEPS representative.
- Roles:
  - *Define the overall structure of the study, coordinate information, determine the initial methodology and oversee the study.*
  - *Propose procedures to be followed during the study, acknowledging any recommendations from the Data Safety Monitoring Board, if applicable. The DRCI sponsor retains decision-making authority.*
- Operating procedures: This committee will meet *every 6 months.*

9.2 Scientific Committee

- Members of the committee:

This committee will consist of the Coordinating Investigators (Pr Saadoun, Dr Vautier CHU Pitié-Salpétrière), a representative of the associated centers (Pr Gilles Kaplanski, CHU La Conception, Marseille), and a representative of the sponsor (Pr Mathieu Resche Rigon, Hôpital Saint Louis, Clinical Research Unit). The management committee will meet *every 6*

months to *determine the objective, write the protocol, recommend changes to the protocol during the trial,* assess Study recruitment, to provide scientific answers to questions from investigators, and to consider operational aspects of the trial and the recommendations of the committee for the evaluation of adverse events.

9.3 Endpoint Adjudication Committee

This committee will have the role of validating under blind conditions the following assignments: complete remission, treatment failure and relapse of the disease. It will consist of persons external to the Study: Clinicians specializing in the pathology under consideration: It will meet at the end of the study. The will reviewed data at baseline, and at week 13 and 25.

10 SAFETY ASSESSMENT - RISKS AND BURDEN ADDED BY THE STUDY

10.1 Recording and reporting adverse events

10.1.1 Definitions

According to Article R.1123-46 of the *Code de la Santé Publique* (French Public Health Code):

- **Adverse event**

Any untoward medical occurrence in a study participant, which does not necessarily have a causal relationship with the study or with the product subject to the study.

- **Adverse reaction**

An adverse event occurring in a study involving human participants when this event is related to the study or to the product being studied.

- **Adverse reaction to an investigational medicinal product**

Any untoward and unwanted reaction to an investigational medication regardless of the dose administered.

- **Serious adverse event or reaction**

Any adverse event or reaction that results in death, threatens the life of the participant enrolled in the study, requires hospitalisation or prolongs existing hospitalisation, causes a severe or long-term disability or handicap, or results in a congenital abnormality or deformity, and in the case of a medication, regardless of the dose administered.

- **Unexpected adverse reaction to an investigational medicinal product**

Any adverse reaction to the product whose nature, severity, frequency or outcome is inconsistent with the standard safety information described in the summary of the product characteristics, or in the investigator's brochure if the product is not authorised.

According to Article R.1123-46 of the Code de la Santé Publique and the guidelines for sponsors of clinical trials (ANSM):

- **Emerging safety issue**

Any new information that may lead to a reassessment of the risk/benefit ratio of the trial or of the product under investigation, modifications in the investigational medicinal product use, the conduct of the clinical trial or the clinical trial documents, or a suspension, interruption or modification of the clinical trial or of similar trials.
For studies involving the first administration of a health product in healthy volunteers: any serious adverse reaction.
Examples:

a) any clinically significant increase in the frequency of an expected serious adverse reaction;
b) suspected unexpected serious adverse reactions in patients who have terminated their participation in the clinical trial which have been notified to by the investigator to the sponsor , as well as potential follow-up reports;
c) any new fact relating to the conduct of the clinical trial or the development of the investigational medicinal product, if the new fact is likely to affect participant safety
Examples:

- a serious adverse event likely to be related to the trial's interventions and diagnostic procedures and which may impact the conduct of the clinical trial,
- a significant risk for the trial participants such as a lack of efficacy of the investigational medicinal product used in the treatment of a life-threatening disease,
- significant safety results from a recently completed study on animal subjects (such as a carcinogenicity study),
- the premature termination, or temporary suspension, of a trial conducted with the same investigational medicinal product in another country, for safety reasons
- an unexpected serious adverse reaction related to a non-investigational medicinal product required to conduct the trial, (e.g.: "challenge agents", rescue treatment)

d) recommendations from the Data Safety Monitoring Board (DSMB), if applicable, if they are relevant to the safety of the participants
e) any unexpected serious adverse reaction reported to the sponsor by another sponsor of a clinical trial carried out in a different country but relating to the same medication

10.1.2 The role of the investigator

All serious and non-serious adverse events must be reported in the eCRF.

The investigator must **assess the seriousness of each adverse event** and record all serious and non-serious adverse events in the case report form (eCRF*).*
The investigator must **document** serious adverse events **as thoroughly as possible** and provide a definitive medical diagnosis, if possible.

The investigator must **assess the intensity** of the adverse events by using the *Common Terminology Criteria for Adverse Events [National Cancer Institute]*

The investigator must assess the **causal relationship** between the serious adverse events and the investigational medicinal product(s) or the study procedure(s).

The method used by the investigator is based on the WHO Uppsala Monitoring Centre method and uses the following 4 causality terms:

- Certain
- Probable/likely
- Possible
- Unlikely (not excluded)

Their definition is presented in the following table (excerpt from WHO-UMC causality categories, version dated 17/04/2012).

Table: WHO-UMC causality categories (excerpt)

Causality term	Assessment criteria*
Certain	· Event or laboratory test abnormality, with plausible time relationship to drug intake ** · Cannot be explained by disease or other drugs · Response to withdrawal plausible (pharmacologically, pathologically) · Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) · Rechallenge satisfactory, if necessary
Probable / Likely	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Unlikely to be attributed to disease or other drugs

Causality term	Assessment criteria*
	· Response to withdrawal clinically reasonable · Rechallenge not required
Possible	· Event or laboratory test abnormality, with reasonable time relationship to drug intake ** · Could also be explained by disease or other drugs · Information on drug withdrawal may be lacking or unclear
Unlikely	· Event or laboratory test abnormality, with a time to drug intake ** · that makes a relationship improbable (but not impossible) · Disease or other drugs provide plausible explanations

*All points should be reasonably complied with
** Or study procedures

10.1.2.1 Serious adverse events that require the investigator to notify the sponsor without delay

As per article R.1123-49 of the *Code de la Santé Publique* (French Public Health Code), the investigator notifies the sponsor without delay on the day the investigator becomes aware of any serious adverse event which occurs during a study that meets the description in line 1° of Article L.1121-1 of the Code de la Santé Publique, with the exception of any event which is listed in the protocol and, if applicable, in the investigator's brochure as not requiring notification.

A serious adverse event is any untoward medical occurrence that:

1- results in death
2- is life-threatening to the participant enrolled in the study
3- requires hospitalisation or prolongation of existing hospitalisation
4- results in persistent or significant disability/incapacity
5- is a congenital anomaly/birth defect

10.1.2.2 Specific features of the protocol

10.1.2.2.1 Other events that require the investigator to notify without delay the sponsor

- Adverse events deemed "medically significant"

- Serious Hypersensitivity or Infusion Reactions ≥ grade 3 CTCAE
- Severe infection define by :
  - tuberculosis, pneumocystis, or cytomegalovirus,
- Other infections, including herpes zoster and opportunistic infections ≥ grade 3 CTCAE
- Progressive multifocal leukoencephalopathy.
  - If PML is confirmed, study agent should be discontinued and consideration should be given to stopping immunosuppressant therapy.
- Serum IgG levels <250 mg/dL associated with a severe or serious infection.
  - If a subject experiences any IgG levels < 250 mg/dL not associated with severe or serious infection, increased vigilance for infection is required. Clinical judgment should be applied with respect to the appropriateness of continuing study therapy in these subjects.
- Neoplasia
- Suicidal thought, intent or behaviour
- Malignancy
- Relapse
- Liver chemistry stopping criteria: (cf paragraph 6.4.3 : permanent termination)

Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and

scientific judgement of the investigator are to be recorded as AEs or SAEs. However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

The investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of these adverse events, according to the same modalities and within the same timeline as for serious adverse events (see above).

- Adverse events of particular interest

- Progressive multifocal leukoencephalopathy.
  - If PML is confirmed, study agent should be discontinued and consideration should be given to stopping immunosuppressant therapy.

The investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of these adverse events, according to the same modalities and within the same timeline as for serious adverse events (see above).

- In utero exposure

The investigator must notify the sponsor **without delay on the day the investigator becomes aware** of any pregnancy that occurs during the study, even if it is not associated with an adverse event.
If the investigational medicinal product is genotoxic, every case of maternal or paternal exposure must be notified.

Notification is required if the exposure involves:
- the mother,
- the father if the experimental medication is genotoxic.

The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

*10.1.2.2.2 **Serious adverse events that do not require the investigator to notify without delay the sponsor***

These serious adverse events are only recorded in the case report forms**.** A data retrieval of the case report forms will be implemented for serious adverse events every 6 months and for every DSMB meeting by URC Saint-Louis and will be sent to the vigilance department by mail (expertisecsi.drc@aphp.fr).

- **Common side effects of belimumab :**
  - Nausea, diarrhea , vomiting, constipation, headache, migraine, pyrexia, hair loss, infections < grade 3 and without complications
  - Insomnia
  - Upper respiratory tract and urinary tract infections < grade 3
  - Dizziness (< grade 3)
  - Skin rash (< grade 3)
  - Headache, fever, hair loss (< grade 3)
  - Hypersensitivity reaction: fever, chills, chest pain, flushing of the face, nasal congestion (< grade 3)
  - hepatic toxicity < grade 3 without clinical symptomatology, and not leading to definitive or provisional IMP withdrawal

- Aplasia and febrile aplasia, neutropenia, febrile neutropenia, leucopenia, thrombopenia and anemia < grade 3 without infectious complications

- **Serious Adverse Events related to prednisone:** all adverse events listed in the SmPC of the corticoid administered, except those leading to death or life threatening.

- **Normal and natural course of the condition:**

- *scheduled hospitalisation for monitoring the condition under investigation*
- *hospitalisation for routine treatment or for monitoring of the condition under investigation, not associated with a deterioration in the participant's condition*
- worsening of the *condition studied* (progression)
- Emergency inpatient hospitalisation upon enrollment or prolongation of hospitalisation upon enrollment for monitoring the condition under investigation

- **Special circumstances:**

Hospitalisations which do not need to be reported without delay by the investigator:
- *Hospitalisation for a pre-existing illness or condition*
- *Hospitalisation for a medical or surgical treatment scheduled prior to the study*
- *Admission for social or administrative reasons*
- *Emergency care (< 12 hours)*

- ***Adverse events potentially related to treatments prescribed as part of the care provided during the study follow-up***

The investigator must report these adverse events to the relevant regional pharmacovigilance centre, *Centre Régional de Pharmacovigilance* (CRPV).

- Adverse Events related to MRI or CT Scan:

- Related to contrast product : Allergy, allergic shock< grade 4, renal insufficiency< grade 4
- claustrophobia
- panic attack
- Nausea, vomiting
- vasovagal attack< grade 4
- anxiety, fear, distress

- Adverse events related to endoscopy: perforation and its complications and hemorrhagia grade ≤3

10.1.2.3 Period during which SAEs must be notified without delay by the investigator to the sponsor

The investigator must notify the sponsor without delay of any serious adverse events as defined in the corresponding section:
- from the date on which the participant begins treatment with an investigational medicinal product (belimumab)
- throughout the whole follow-up period required for the trial (48 weeks)
- until 4 months after the end of the participant's treatment with the investigational medicinal product.
- indefinitely, if the SAE is likely to be due to the investigational medicinal product or to the study interventions (e.g. serious reactions that could appear at long term after exposure to the medication, such as cancers or congenital abnormalities)

10.1.2.4 Procedures and deadlines for notifying the sponsor

The initial notification of an SAE must be provided in a written report signed by the investigator using a SAE notification form specific to the study and intended for this purpose (in the case report form).

Each item in this form must be completed by the investigator so that the sponsor can carry out the appropriate analysis.

The initial notification to the sponsor of a serious adverse event must be quickly followed by an additional detailed written report (or reports) so that the case outcome may be monitored by the Safety Department or to provide further information.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results from additional examinations, etc.). These documents must be non-identifying. In addition, the documents must include the following: study acronym, number and participant's initials.

Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the participant has left the study.

The initial notification, the SAE follow-up reports and all other documents must be sent to the sponsor's Safety Department by email (eig-vigilance.drc@aphp.fr). It should be noted that it is possible to send SAE reports to the Safety Department by fax to +33 (0)1 44 84 17 99 only in the event of a failed attempt to send the SAE report by email (in order to avoid duplication).

For studies which use e-CRFs

- the investigator completes the SAE notification form in the e-CRF, then validates, prints, and signs the form before sending it by email;
- if it is not possible to connect to the e-CRF, the investigator should complete, sign, and send the SAE notification form to the Safety Department. As soon as the connection is restored, the SAE notification form in the e-CRF must be duly completed.

The investigator must respond to all requests from the sponsor for additional information.
For all questions relating to the notification of an adverse event, the Safety Department can be contacted via email: vigilance.drc@aphp.fr.

For cases of *in utero* exposure, the investigator will complete the Notification and Follow-up form for a pregnancy occurring during participation in a study".
The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy is terminated, and must notify the sponsor of the outcome of the pregnancy using this form.
If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, pregnancy termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAEs.
The initial pregnancy notification, the SAE follow-up reports, and any other documents will be sent to the sponsor according to the same procedures specified herein.
If it was the father who was exposed, the investigator must obtain the pregnant woman's permission before collecting information about the pregnancy.

Special rules for trials involving the administration of a radioactive product (e.g. PET scan): if a subject develops secondary cancer/cancer or develops a hereditary deficiency following

exposure to ionising radiation, the investigator shall complete the special form for reporting cancer**.**

10.1.3 Role of the sponsor

The sponsor, represented by its Safety Department, shall continuously, throughout the trial, assess the safety of each investigational medicinal product throughout the study.

10.1.3.1 Analysis and declaration of serious adverse events

The sponsor assesses:

- the **seriousness** of all adverse events reported,
- the **causal relationship** between these events and each investigational medicinal product and/or study procedures and any other treatments,

All serious adverse events which the investigator and/or the sponsor reasonably believe may have a causal relationship with the investigational medicinal product are classed as suspected serious adverse reactions.

- the **expectedness assessment** of the serious adverse reactions

Any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the summary of product characteristics, or in the investigator's brochure if the product is not authorised, is considered unexpected.
The sponsor, represented by its safety Department, assesses the expectedness/unexpected nature of the serious adverse reaction based on the information described below**.**

❖ For serious adverse events likely to be related to the investigational medicinal product(s):
- refer to the SmPC for belimumab or placebo
- For serious adverse events likely to be related to additional medicinal products (treatments required for the trial): refer to the SmPC for Prednisone,.

❖ Adverse Events related to MRI or CT Scan and which are expected are:
- Allergy, allergic shock, renal insufficiency (cf SmPC of contrast agent administered)
- claustrophobia
- panic attack
- Nausea, vomiting
- vasovagal attack
- anxiety, fear, distress

❖ Adverse events related to endoscopy and which are expected are: perforation and its complications (pneumoperitoneum, hemoperitoneum) and hemorrhagia

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs), within the regulatory time frame, to the ANSM (French Health Products Safety Agency).
- The sponsor must send the initial report without delay upon learning of the unexpected serious adverse reaction if it is fatal or life-threatening, or otherwise within 15 days from receipt of any other type of unexpected serious adverse reaction;
- All additional, relevant information must be declared by the sponsor in the form of follow-up reports within a period of 8 calendar days starting from when the sponsor had this information.

Any suspected unexpected serious adverse reaction must also be declared electronically using the Eudravigilance European adverse drug reactions database managed by the European Medicines Agency (EMA).

The sponsor must notify all the investigators involved about any information that could adversely affect the safety of the trial subjects.

Specific case of serious adverse events of special interest.
The sponsor may be required to declare serious adverse events of special interest, in accordance with the same procedures and deadlines as for SUSARs..

Special rules for double blind trials
After unblinding by the sponsor and if the patient is receiving the product under investigation: the case will be reported without delay as a suspected unexpected serious adverse reaction.
If the patient is receiving the comparator product: the sponsor will reassess the unexpected nature of the adverse reaction based on the reference document for the comparator product identified in the protocol.
In exceptional situations, if the study involves a condition with a high mortality and/or morbidity rate, and if the ANSM grants permission at the request of the sponsor as part of the clinical trial authorisation application, the methods for unblinding and for reporting suspected unexpected serious adverse reactions can be modified. These methods will then be defined thoroughly in the study protocol.

10.1.3.2 Analysis and declaration of other safety data

This means any new information that prompts a reassessment of the risk/benefit ratio of the trial or of the product under investigation, or which could be sufficient to consider changes to the use of the product, the trial procedures or trial documentation, or the suspension, cancellation or amendment of the research trial or of other similar trials. For trials involving the first administration or use of a health product in healthy volunteers: any serious adverse reaction.

The sponsor will inform the competent authority and the Research Ethics Committee without delay upon knowledge of any emerging safety issue and, if applicable, describe what measures have been taken.

Following the initial declaration of any emerging safety issue, the sponsor will address to competent authorities any additional relevant information about the emerging safety issue in the form of a follow-up report, which must be sent no later than 8 days after learning of the information.

10.1.3.3 Annual safety report

Once a year for the duration of the clinical study, the sponsor must produce an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:
- a safety analysis for the research participants,
- a description of the patients included in the study (demographic profile etc.)
- a list of all the suspected serious adverse reactions that occurred during the period covered by the report,
- summary tables of all the serious adverse events that have occurred since the start of the study,

The report must be delivered no later than 60 days after the anniversary of the date on which the ANSM authorised the trial.

10.1.4 Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) may be established by the sponsor. Its primary mission is to monitor safety data. It can have other missions, such as monitoring efficacy data (especially if the protocol includes interim analyses).
The sponsor is responsible for justifying the creation or absence of such a committee to the Competent Authority (ANSM) and to the CPP (Research Ethics Committee).

A DSMB will be established for this trial. The DSMB must hold its first meeting before the first participant is enrolled and ideally before the protocol is submitted to the competent authority and the CPP (Research Ethics Committee).
All missions as well as the specific operating procedures of the DSMB are described in the study's DSMB charter.

The DSMB will operate in accordance with the sponsor's procedures. The DSMB works in an advisory capacity only and the sponsor retains all decision-making authority.

11 DATA MANAGEMENT

11.1 Data collection procedures

The investigator will permit the sponsor's representatives to monitor the study at the frequency defined in the contract, depending on enrolment at each center.
Case Report Forms (CRFs) and related source documents will be reviewed in detail during monitoring visit (completeness, adherence to the guidelines, accuracy compared to source documents). The sponsor's representative will also review regulatory documents, drug storage and accountability.
The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by sponsor's monitors or representatives of other regulatory agencies.

11.2 Identification of data recorded directly in the CRFs which will be considered as source data

11.3 Right to access source data and documents

11.3.1.1 Data access

In accordance with GCP:
- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures or inspections by the competent authority
- the investigators will ensure the persons in charge of monitoring, quality control and auditing or inspecting the interventional study involving human participants have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

11.3.1.2 Source documents

Source documents are defined as any original document or item that can prove the existence or accuracy of a data or a fact recorded during the study. These documents will be kept in accordance with the regulations in force by the investigator or by the hospital in the case of a hospital medical file.

11.3.1.3 Data confidentiality

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the Code de la Santé Publique [French Public Health Code]) will take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular their identity and the results obtained.

These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the Code Pénal [French Criminal Code]).
During and after the research involving human participants, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be rendered non-identifying.
Under no circumstances shall the names and addresses of the participants involved be shown.
Only the participant's initials will be recorded, accompanied by an encoded number specific to the study indicating the order of enrolment.
The sponsor will ensure that each participant has given written permission for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

11.4 Data processing and storage of research documents and data

11.4.1 Identification of the data processing manager and the location(s)

Data will be collected on an E-CRF, with data entry performed in each centre by Clinical research assistants (CRA) and/or physicians.
Monitoring of the data will be performed by CRA under the superivison of the URC and DRCI.
Statistical analysis will be performed by Pr Matthieu Resche-Rigon, Saint Louis hospital, Paris.

11.4.2 Data entry

Data entry will be carried out on electronic media via a web browser.

11.5 Data Ownership

AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

12 STATISTICAL ASPECTS

12.1 Planned statistical methods, including the timetable for any planned interim analyses

This is a Bayesian Phase II randomized clinical trial that aims at evaluating the treatment strategy of non infectious cryoglobulinemia vasculitis, based on difference in the response rate as measured at week 25 after randomization.

Randomized phase II trials are still poorly used, with still large use of single-arm phase II trial results that are interpreted relative to historical control subjects, introducing selection bias and confounding that may limit the validity of the conclusions. Thus, planning a phase II randomized trial appears a worthy investment considering finite patient and financial resources (Sharma 2011).

Moreover, we chose to design the trial as a Bayesian clinical trial, for three main reasons. First, this allows incorporating information outside the trial that results in a decrease in required sample size due to such "fictive" observations. Secondly, Bayes designs are particularly well-suited for adaptive designs, given inference is based on accumulated data along the trial, allowing interim and sequential analyses without any inflation of type I error or biased estimation (Wang 2016). Third, this design is adapted to binary outcomes observed at

the end of a fixed follow-up period and analyzed using an absolute difference in proportions that has been shown to greatly reduce sample size requirements.

12.2 Hypotheses for calculating the required number of subjects, and the result

Given the uncertainty in the belimumab alone in non infectious cryoglobulinemia vasculitis at this early stage of evaluation, and the fact that the severe population focused in this trial is not very large in size, the selection approach to planning sample size was worthy of consideration.

We thus used the approach for phase II randomized trials proposed by Simon R, Wittes RE, and Ellenberg SS (1985) that aims at controlling the probability of detecting a given difference in response rates. Based on binomial distributions under the assumed response rate of the control arm (here, p=0.70), this allowed to randomly allocate two groups of 24 patients to detect a difference in response rates with a 0.90 probability of correct selection. This appeared preferable to planning a trial on hypotheses either non-consistent with the literature based on a too pejorative success rate on control arm, or overoptimistic regarding the expected effect size in the experimental arm.

This design is not powered based on standard type I and type II error rates like a randomized phase III trial would be. Rather, sample size is based on the smallest expected relative risk, the minimal clinically important difference, and the probability desired for choosing the “true” best arm if the minimal clinically important difference is exceeded.

12.3 State whether subjects who exit the study prematurely will be replaced and in what proportion.

Analysis will be in intent-to-treat. All patients withdrawn will be considered as treatment failures. Nevertheless, in case of dropout during the inclusion phase of the trial, a new patient will replaced the withdrawn patients.

12.4 Statistical criteria for termination of the study.

We will use a Bayesian inference framework, where $\pi_k = P(Y = 1|A = k)$ denotes the probability of response in the arm A=k (k=1,2). Using a beta Be(a_k,b_k) prior for π_k, the posterior probability of π_k is still a beta distribution given by Be(a_k+y_k,b_k+$n_k - y_k$) due to the natural conjugate property of the beta family for binomial sampling.
In our setting, the inefficacy of the drug will be first assessed by comparison to some historical minimal value of interest, sometimes called the “minimum required treatment response rate”. It has been set at 0.70 in this trial. Thus, we will compute for each arm
$P(\pi_k < 0.70|y_{ki}, n_{ki})$ (1)

Of note, if the true response rate in the Belimumab arm is 0.85, $P(\pi_k < 0.70|y_{ki}, n_{ki})$ should be below 0.05.

However, in randomized phase II settings, the selection of a new drug is mostly based on evaluating the potential benefits of the experimental treatment over the control arm (Whitehead 2014). Thus, one may consider dropping a new drug from further studies only if there is a rather low posterior probability that this drug is beneficial over the control by some targeted minimal level. This will be done by computing the value of the posterior probability of the difference in response rates between the experimental arm and the control (Xie 2012):

$P(\pi_k - \pi_0 > \Delta|y_{ki}, n_{ki})$

π_0 Being the probability in the placebo arm and $\Delta = 0$. In this study if π_0=0.7 and π_0=0.85 this probability should be above 0.90.

Calculations will be based using a_k=0.5 an b_k=0.5 for both arms. Sensitivity analyses will be performed using a_k=0.7 an b_k=0.3 for the placebo arm and using a_k=0.85 an b_k=0.25 for the Belimumab arm.

12.5 Analyses

All patients characteristics will be described within each treatment group by their frequency and percentage for categorical characteristics and by their median and Interquartile range for quantitative variables.

Secondary endpoint

- Safety and tolerability of treatments as assessed by frequency and severity of adverse clinical events at W25 and at W48. Frequencies will be estimated within each group with their 95%CI and compared using Fisher tests.
- Complete, partial and non clinical response rate at W13, W25 and at W48 will be analyzed as the primary outcomes.
- Complete renal response rate at W13 and W25
- Rate of cryoglobulinemia clearance, of negativation of rheumatoid factor activity and of normalization of C4 complement level at W13, W25 and at W48 will be estimated within each group with their 95%CI and compared using Fisher tests.
- Rate of early failures (non clinical response at W5) will be estimated within each group with their 95%CI and compared using Fisher tests.
- Clinical relapse rate defined by de novo appearance or reappearance of a manifestation attributable to cryoglobulinemia vasculitis during 48 weeks of follow-up will be estimated within each group with their 95%CI and compared using Fisher tests.
- Rate and time to relapse from baseline to W48 will be estimated using Kaplan Meier estimator and compared using Logrank tests.
- Cumulative dose of prednisone at W25 and at W48 will be estimated within each group with their 95%CI.
- Mean change of gammaglobulin and CD19+ B cells levels from baseline to W48 will be estimated within each group with their 95%CI and compared using Wilcoxon tests.
- Quality of life score SF-36 at baseline, W25 and W48, will be estimated within each group with their 95%CI. Impact of time on Quality of life score SF-36 will be assessed using linear random effect model. comparaisons between groups will be assessed by testing interaction term between time and treatment group
- Rate of infections (severe or not) and other complications during the 48 weeks of follow-up will be estimated within each group with their 95%CI and compared using Fisher tests.
- BVAS activity score at baseline, W13, W25 and W48 will be estimated within each group with their 95%CI. Impact of time on BVAS activity score will be assessed using linear random effect model. Comparisons between groups will be assessed by testing interaction term between time and treatment group

12.6 Method for taking into account missing, unused or invalid data

All the effort will be done to avoid missing data in the outcomes. All causes of study dropouts will consider the patients as failures.

In case of missing outcome the primary analysis will be performed considering missing outcome as treatment failures. A sensitivity analysis will be performed by multiple imputation of the missing outcome using a multiple imputation by chained equation algorithm.

12.7 Management of modifications made to the analysis plan for the initial strategy.

All modifications of the initial plan will be submitted.

12.8 Selection of populations

All the patients randomized in the trial will be analysed in the arm to which he(she) has been allocated to. This is the main principle of intent-to-treat analysis to avoid treatment selection biases in the estimation of treatment effect.

13 QUALITY CONTROL AND ASSURANCE

Every research project involving human participants managed by AP-HP is ranked according to the projected risk incurred by study participants using the classification system specific to AP-HP sponsored interventional research involving human participants.

13.1 General organisation

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the study. The sponsor must implement a quality assurance system to best monitor the implementation of the study in the investigation centres.

For this purpose, the sponsor shall assign Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the study locations, after having carried out the initial visits.
The purpose of monitoring the study, as defined in Good Clinical Practices (GCP section 5.18.1), is to verify that:

- the rights, safety and protection of the research participants are met
- the data reported are exact, complete and consistent with the source documents
- the study is carried out in accordance with the protocol in force, the GCPs and the statutory and regulatory provisions in force

13.1.1 Strategy for site opening

The strategy for opening the centres established for this study is determined using the appropriate monitoring plan. It will be performed by the CRA from the URC-DRCI from Saint Louis hospital.

13.1.2 Scope of site monitoring

In the case of this level C risk study the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Therefore, in agreement with the coordinating investigator, the sponsor has determined the logistical score and impact, resulting in a study monitoring level to be implemented: level Intermediate.

13.2 Quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the good completion of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI (Clinical Research and Innovation Department) and in accordance with Good Clinical Practices as well as the statutory and regulatory requirements.

The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits carried out by the Clinical Research Associate. During these visits, the following elements will be reviewed depending on the monitoring level:

- written consent
- compliance with the study protocol and with the procedures defined therein
- quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the treatments used

13.3 Case Report Form

All information required by the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Any missing data must be coded.
Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given a document offering guidance on using this tool.
When the investigators complete the case report form via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. To this end, the investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment.
A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the study. The investigator must archive a copy of the authenticated document that was issued to the sponsor.

13.4 Management of non-compliances

Any events that occur as a result of non-compliance – by the investigator or any other individual involved in running the study – with the protocol, standard operating procedures, good clinical practices or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.

These non-compliances will be managed in accordance with the sponsor's procedures.

13.5 Audits/inspections

The investigators agree to consent to the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. These audits and inspections cannot be refused on the grounds of medical secrecy.
An audit can be carried out at any time by individuals appointed by the sponsor and independent of those responsible for the research. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage and monitor the study agree to comply with the sponsor's requirements and with the competent authority regarding study audits or inspections.

The audit may encompass all stages of the study, from the development of the protocol to the publication of the results, including the storage of the data used or produced as part of the study.

13.6 Principal Investigator's commitment to assume responsibility

Before starting the study, each investigator will give the sponsor's representative a copy of his/her updated personal curriculum vitæ, signed and dated less than one year, with his/her RPPS number (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals). The CV must include any previous involvement in clinical research and related training.

Each investigator will commit to comply with legislation and to conduct the study in line with GCP, in accordance with the Declaration of Helsinki.

The Principal Investigator at each participating site will sign a commitment of responsibility (standard DRCI document) which will be sent to the sponsor's representative.
The investigators and their staff will sign a delegation of duties form specifying each person's role and will provide their CVs.

14 ETHICAL AND LEGAL CONSIDERATIONS

14.1 Methods for informing and obtaining consent from the research participants

In accordance with Article L1122-1-1 of the Code de la Santé Publique (French Public Health Code), no interventional research involving human participants can be carried out on a person without his/her freely given and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of the aforementioned Code.

A reflection period is given to the individual during the inclusion/randomisation visit between the time when he or she is informed and when he or she signs the consent form.

The person's freely-given, written, informed consent will be obtained by the principal investigator or a physician representing the investigator before the person is enrolled in the study at inclusion/randomisation visit.

A copy of the information note and consent form, signed and dated by the research participant and by the principal investigator or the physician representing the investigator will be given to the individual prior to their participation in the study. The principal investigator or the physician representing him/her will keep a copy.

At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

In addition, the investigator will specify in the person's medical file the person's participation in the research, the procedures for obtaining his/her as well as the methods used for providing information for the purpose of collecting it. The investigator will retain one copy of the signed and dated consent form.

14.2 Prohibition from participating in another clinical study or exclusion period set after the study,

An exclusion period of participation after the participant has finished this study is defined in the context of this research. It will last for 1 month (more than 5 half-life of Belimumab)

The participant may not enrol in another interventional study protocol involving human participants for the duration of his or her participation without consulting with the physician monitoring him or her in the context of the study.

The participants can however participate in other non-interventional studies

14.3 Compensation for participants

Each participant will receive financial compensation for the travel fees for the W1 visit (100 euros maximum) that he or she will receive at the end of the study.

14.4 Registration on the National Register of study participants to studies involving human participants concerning the products mentionned in Article L. 5311-1 of the Code de la santé publique

Non applicable.

14.5 Authorisation for the research location

The study will be carried out in treatment units on individuals presenting a clinical condition for which the units are specialised and who require interventions that are routinely performed at those units. Therefore, the research location does not require specific authorisation.

14.6 Legal obligations

14.6.1 The sponsor's role

Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this study and, by delegation, the DRCI (Clinical Research and Innovation Department) carries out the study's missions in accordance with Article L.1121-1 of the Code de la Santé Publique (French Public Health Code). Assistance Publique - Hôpitaux de Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case, notification will be sent to the investigator.

14.7 Request for approval from the CPP (Research Ethics Committee)

Prior to starting the study, AP-HP, as sponsor, must obtain for this interventional study involving human participants concerning a medicinal product for human use, approval from the appropriate CPP (Research Ethics Committee), within the scope of its authority and in accordance with in force legislation and regulatory requirements.

14.8 Request for authorisation from the ANSM

Prior to starting the study, AP-HP, as sponsor, must obtains authorisation from the ANSM (French Health Products Safety Agency) for the interventional study involving human participants concerning a medicinal products for human use, within the scope of the ANSM's authority and in accordance with in force legislation and regulatory requirements.

14.8.1 Procedures relating to data protection regulations

The computer file used for this research is implemented in accordance with French (amended “Informatique et Libertés” law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.

This research is governed by the CNIL (French Data Protection Agency) “Reference Methodology for processing personal data used within the scope of health research” (amended MR-001). AP-HP, as sponsor of the research, has signed a declaration of compliance with this “Reference Methodology”

14.9 Amendments to the research

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, approval from the CPP (Research Ethics Committee) and authorisation from the ANSM within the scope of their respective authorities, before the amendment can be implemented.
The information note and the consent form can be revised if necessary, in particular in case of a substantial amendment to the study or if adverse reactions occur.

14.10 Final study report

The final report for the research involving human participants referred to in Article R1123-67 of the Code de la Santé Publique (French Public Health Code) is written and signed by the sponsor and the investigator. A report summary drafted according to the reference plan of the competent authority must be sent to the competent authority within a period of one year following the end of the study, i.e., the end of the participation of the last participant in the study.

14.10.1 Archiving

Specific documents for an interventional study involving human participants concerning a medicinal product for human use will be archived by the investigator and the sponsor for *15 years* after the end of the research.

This indexed archiving includes, in particular:

- A sealed envelope for the investigator containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- A sealed envelope for the sponsor, containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- "Study" binders for the Investigator and the sponsor, including (non-exhaustive list) :
  - the successive versions of the protocol (identified by the version number and its date), and any appendices
  - the ANSM authorisations and CPP (Research Ethics Committee) decisions
  - any correspondence
  - the enrolment list or register
  - the appendices specific to the research
  - final study report
- The data collection documents

15 FUNDING AND INSURANCE

15.1 Funding sources

The funding source is GlaxoSmithKline.

15.2 Insurance

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own public liability, as well as the public liability for all the physicians involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the participant enrolled and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator. Compensation cannot be refused on the grounds of a third-party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique-Hôpitaux de Paris (AP-HP) has taken out insurance with HDI-GLOBAL SE through the insurance broker BIOMEDIC-INSURE for the full study period, which covers its own public liability and that of any collaborator (physician or research staff), in accordance with Article L.1121-10 of the Code de la Santé Publique (French Public Health Code).

16 PUBLICATION

The author(s) of any publication relating to this study must include the AP-HP among their affiliations and name the sponsor AP-HP (DRCI) and the source of funding, if funded by a call for tenders (e.g. national or regional PHRC); a copy of the publication must be sent to the sponsor (see below for rules governing affiliation, and naming the sponsor and funders).

16.1 Mention of AP-HP affiliation for projects sponsored or managed by AP-HP

- If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is not important
- However, if the trial is funded by an internal call for tenders at the AP-HP, the first affiliation must be "AP-HP"
- Each of these affiliations must be identified by an address and separated by a semicolon
*- The AP-HP institution must feature under the acronym "**AP-HP**" first in the address, specifically followed by: **AP-HP**, hospital, department, city, postcode, France*

16.2 Mention of the sponsor AP-HP (DRCI) in the acknowledgements of the text

"The sponsor was Assistance Publique – Hôpitaux de Paris (Direction de la Recherche Clinique et de l'Innovation)"

16.3 Mention of the financial backer in the acknowledgements of the text

"The study was funded by a grant from GlaxoSmithKline."

This study has been registered on the http://clinicaltrials.gov/ website under registration number NCT04629144.

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18 LIST OF ADDENDA

18.1 List of Investigators

See enclosed document.

18.2 Serious Adverse Events report form

See enclosed document.

18.3 SCP of Benlysta®

SCP obtained from the EMA website
*(*https://www.ema.europa.eu/en/medicines/human/EPAR/benlysta)

18.4 Appendix 1. SF36 scale

9 Echelles de qualité de vie

Evaluer la qualité de vie d'un individu permet de juger du degré de répercussion d'un traumatisme sur la santé (troubles de santé mentale) et sur le fonctionnement social ou au travail. Ceci permet d'évaluer également le besoin de soins des individus. Plusieurs outils standardisés existent à l'heure actuelle.

Le Medical Outcome Study Short Form (MOS-SF–36)

Auteur(s) : Ware et al.

Type : Echelle d'auto-évaluation

Objectifs : Evaluer la qualité de vie liée à la santé

Caractéristiques : Cette échelle est issue de la « Medical Outcome Study [5]» (Ware and Sherbourne 1992). L'outil original était constitué de 149 items ; l'échelle dérivée n'en contient plus que 36.

Le SF-36 doit sa notoriété à un projet international (International Quality of Life Assessment) qui a adapté et validé cet outil dans 15 pays différents, dont la France (Leplege, Ecosse et al. 1998). Il s'agit d'une échelle de qualité de vie générique qui explore la santé physique, émotionnelle et sociale. On n'y trouve ni le bien-être matériel, ni les valeurs, ni la satisfaction globale de la vie. Le SF-36 évalue 8 dimensions de la santé : l'activité physique, la vie et les relations avec les autres, les douleurs physiques, la santé perçue, la vitalité, les limitations dues à l'état psychique, les limitations dues à l'état physique et la santé psychique. Pour chaque échelle, on obtient un score variant de 0 à 100, les scores tendant vers 100 indiquant une meilleure qualité de vie. A partir de ces huit échelles, il est possible de calculer deux scores synthétiques qui ont été identifiés par analyse factorielle : un score agrégé de santé physique et un score agrégé de santé mentale.

Mode de passation, cotations, scores : Il s'agit d'un auto-questionnaire rempli par le sujet (en 8 à 15 minutes) en fonction de son ressenti par rapport à son état au cours des 4 dernières semaines. Les algorithmes de traitement des scores sont disponibles sur le site internet suivant : http://www.snof.org/melody/interface/qualite

Des données de référence ont été publiées pour la population française. Ces données peuvent servir de normes afin d'interpréter des résultats d'études de qualité de vie. Elles ont

[5] Medical Outcome Study : étude d'observation comprenant une enquête transversale (sur 20 000 patients) et une enquête longitudinale qui s'est déroulée sur 4 années consécutives

été recueillies par la société SOFRES Médicale auprès d'un échantillon de 3 617 individus (Leplege 2001).

Population cible : L'échelle a été utilisée dans différents types de population : patients souffrant de maladies chroniques graves (cancer, VIH) ou d'autres maladies chroniques (asthme, diabète, arthrite, polyarthrite rhumatoïde…). Le SF-36 se prête aux enquêtes en population générale car son spectre de mesure permet de mesurer aussi des différences entre des états de santé globalement bons. Le SF-36 peut être administré à des personnes de plus de 14 ans (Leplege 2001).

Qualités métrologiques : Le SF-36 présente des coefficients de Cronbach compris entre 0,80 et 0,92 pour les différentes sous-échelles selon les études. Tous les items ont une corrélation avec leur propre échelle supérieure à 0,4 et la plupart du temps, cette corrélation est significativement supérieure à celle observée avec les autres échelles.

Le taux de succès pour la validité discriminante est de 99,3 %, ce qui signifie que les dimensions physique et mentales présentent extrêmement peu de corrélation.

Langues : 15 langues dont l'anglais et le français. La traduction et l'adaptation culturelle en français ont été réalisées dans le cadre du projet IQOLA par Leplege et al. (1995). La procédure de traduction a suivi le schéma du projet.

Intérêts et limites : Selon certains auteurs, ce questionnaire est complexe car il comporte des instructions assez longues et spécifiques, qui peuvent causer des problèmes dans certaines populations (personnes ayant un faible niveau d'éducation par exemple). Si le SF-36 convient bien à des personnes vivant indépendamment, il n'est pas idéal pour un usage en milieu hospitalier.

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Nom de l'outil	SF-36
Type d'outil	Echelle d'auto-évaluation
Objectifs	Evaluation de la qualité de vie
Population cible	Population générale, patients
Administration	Autoévaluation
Période de temps sur laquelle porte les échelles	Dernier mois
Langues / traduction	15 langues dont anglais et français / Leplege et al.

Questionnaire : SF-36

Consigne : *Les questions qui suivent portent sur votre santé, telle que vous la ressentez. Ces informations nous permettront de mieux savoir comment vous vous sentez dans votre vie de tous les jours.*

Veuillez répondre à toutes les questions en entourant le chiffre correspondant à la réponse choisie, comme il est indiqué. Si vous ne savez pas très bien comment répondre, choisissez la réponse la plus proche de votre situation.

1. Dans l'ensemble, pensez-vous que votre santé est :

Excellente

Très bonne

Bonne

Médiocre

Mauvaise

2. Par rapport à l'année dernière à la même époque, comment trouvez-vous votre état de santé en ce moment ?

Bien meilleur que l'an dernier

Plutôt meilleur

A peu près pareil

Plutôt moins bon

Beaucoup moins bon

SF36

1. Dans l'ensemble, pensez-vous que votre santé est :

Cochez la case qui correspond à votre choix

- Excellente ❑
- Très bonne ❑
- Bonne ❑
- Médiocre ❑
- Mauvaise ❑

2. **Par rapport à l'année dernière à la même époque**, comment trouvez-vous votre état de santé **en ce moment** ?

Cochez la case qui correspond à votre choix

- Bien meilleur que l'an dernier ❑
- Plutôt meilleur ❑
- A peu près pareil ❑
- Plutôt moins bon ❑
- Beaucoup moins bon ❑

3. Voici une liste d'activités que vous pouvez avoir à faire dans votre vie de tous les jours. Pour chacune d'entre elles indiquez si **vous êtes limité(e) en raison de votre état de santé actuel**

Cochez la case qui correspond à votre choix, une par ligne

Liste d'activités	oui, beaucoup limité(e)	oui, un peu limité(e)	non, pas du tout limité(e)
a. **Efforts physiques importants** tels que courir, soulever un objet lourd, faire du sport	❑	❑	❑
b. **Efforts physiques modérés** tels que déplacer une table, passer l'aspirateur, jouer aux boules	❑	❑	❑
c. Soulever et porter les courses	❑	❑	❑
d. Monter **plusieurs étages** par l'escalier	❑	❑	❑
e. Monter **un étage** par l'escalier	❑	❑	❑
f. Se pencher en avant, se mettre à genoux, s'accroupir	❑	❑	❑
g. Marcher **plus d'1 km** à pied	❑	❑	❑
h. Marcher **plusieurs centaines de mètres**	❑	❑	❑
i. Marcher **une centaine de mètres**	❑	❑	❑
j. Prendre un bain, une douche ou s'habiller	❑	❑	❑

4. Au cours de ces **4 dernières semaines**, et en raison de votre **état physique**

Cochez la case qui correspond à votre choix, une par ligne

	OUI	NON
a. Avez-vous réduit **le temps passé** à votre travail ou à vos activités habituelles	❑	❑
b. Avez-vous **accompli moins** de choses que vous auriez souhaité	❑	❑
c. Avez-vous dû arrêter de faire **certaines choses**	❑	❑
d. Avez-vous eu des **difficultés** à faire votre travail ou toute autre activité (par exemple, cela vous a demandé un effort supplémentaire)	❑	❑

5. Au cours de ces **4 dernières semaines**, et en raison de votre **état émotionnel** (comme vous sentir triste, nerveux(se) ou déprimé(e))

Cochez la case qui correspond à votre choix, une par ligne

	OUI	NON
a. Avez-vous réduit **le temps passé** à votre travail ou à vos activités habituelles	❑	❑
b. Avez-vous **accompli moins** de choses que vous auriez souhaité	❑	❑
c. Avez-vous eu des **difficultés** à faire ce que vous aviez à faire **avec autant de soin et d'attention** que d'habitude	❑	❑

6. Au cours de ces **4 dernières semaines** dans quelle mesure votre état de santé, physique ou émotionnel, vous a t-il gêné(e) dans votre vie sociale et vos relations avec les autres, votre famille, vos amis, vos connaissances ?

Cochez la case qui correspond à votre choix

- Pas du tout ❑
- Un petit peu ❑
- Moyennement ❑
- Beaucoup ❑
- Enormément ❑

7. Au cours de ces **4 dernières semaines**, quelle a été l'intensité de vos **douleurs physiques** ?

Cochez la case qui correspond à votre choix

- Nulle ❑
- Très faible ❑
- Faible ❑
- Moyenne ❑
- Grande ❑
- Très grande ❑

8. Au cours de ces **4 dernières semaines**, dans quelle mesure vos douleurs physiques vous ont-elles limité(e) dans votre travail ou vos activités domestiques ?

Cochez la case qui correspond à votre choix

- Pas du tout ❑
- Un petit peu ❑
- Moyennement ❑
- Beaucoup ❑
- Enormément ❑

9. Les questions qui suivent portent sur comment vous vous êtes senti(e) **au cours de ces 4 dernières semaines**. Pour chaque question, veuillez indiquer la réponse qui vous semble la plus appropriée. **Au cours de ces 4 dernières semaines**, y a-t-il eu des moments où :

Cochez la case qui correspond à votre choix, une par ligne

	en permanence	très souvent	souvent	quelquefois	rarement	jamais
a. Vous vous êtes senti(e) dynamique ?	❑	❑	❑	❑	❑	❑
b. Vous vous êtes senti(e) très nerveux (se) ?	❑	❑	❑	❑	❑	❑
c. Vous vous êtes senti(e) si découragé(e) que rien ne pouvait vous remonter le moral ?	❑	❑	❑	❑	❑	❑
d. Vous vous êtes senti(e) calme et détendu(e) ?	❑	❑	❑	❑	❑	❑
e. Vous vous êtes senti(e) débordant(e) d'énergie ?	❑	❑	❑	❑	❑	❑
f. Vous vous êtes senti(e) triste et abattu(e) ?	❑	❑	❑	❑	❑	❑

(Suite de la question 9)

	en permanence	très souvent	souvent	quelquefois	rarement	jamais
g. Vous vous êtes senti(e) épuisé(e) ?	❑	❑	❑	❑	❑	❑
h. Vous vous êtes senti(e) heureux (se) ?	❑	❑	❑	❑	❑	❑
i. Vous vous êtes senti(e) fatigué(e) ?	❑	❑	❑	❑	❑	❑

10. Au cours de ces **4 dernières semaines** y a t-il eu des moments où votre **état de santé, physique ou émotionnel**, vous a gêné(e) dans votre vie sociale et vos relations avec les autres, votre famille, vos amis, vos connaissances ?

Cochez la case qui correspond à votre choix

- En permanence ❑
- Une bonne partie du temps ❑
- De temps en temps ❑
- Rarement ❑
- Jamais ❑

11. Indiquez, pour **chacune** des phrases suivantes, dans quelle mesure elles sont vraies ou fausses dans votre cas :

Cochez la case qui correspond à votre choix, une par ligne

	totalement vraie	plutôt vraie	Je ne sais pas	plutôt fausse	totalement fausse
a. Je tombe malade plus facilement que les autres	❑	❑	❑	❑	❑
b. Je me porte aussi bien que n'importe qui	❑	❑	❑	❑	❑
c. Je m'attends à ce que ma santé se dégrade	❑	❑	❑	❑	❑
d. Je suis en excellente santé	❑	❑	❑	❑	❑

18.5 Appendix 2.BVAS score

BVAS 2003 (adaptation française - GFEV)

BIRMINGHAM VASCULITIS ACTIVITY SCORE 2003

NOM :
Prénom :
Date :

Si toutes les manifestations représentent une maladie chronique active, mais** faiblement (smoldering grumbling disease) **et qu'il n'y aucune manifestation nouvelle récente ou d'aggravation franche, cocher la case dans le coin en bas à droite.

Les scores indiqués pour chacune des manifestations sont ceux pour une maladie active récemment (poussée ou aggravation récente, c'est-à-dire survenue dans les dernières semaines – 1ère colonne) / « chronique », avec signes d'activité persistants, depuis plusieurs semaines, «forme grumbling » (2ème colonne – à ne comptabiliser que si la case du bas est cochée). Les séquelles (maladie non active) présentes depuis plus de 3 mois ne sont pas comptabilisées et doivent être appréciées par le VDI.

	Récent / Persistant
1. Signes généraux	|__| **(maxi. 3 / 2)** |__|
Myalgies	☐ 1 / 1 ☐
Arthralgies ou arthrites	☐ 1 / 1 ☐
Fièvre ≥ 38°C	☐ 2 / 2 ☐
Amaigrissement ≥ 2 kg	☐ 2 / 2 ☐
2. Signes cutanés	|__| **(maxi 6 / 3)** |__|
Nécrose	☐ 2 / 1 ☐
Purpura	☐ 2 / 1 ☐
Ulcération(s)	☐ 4 / 1 ☐
Gangrène	☐ 6 / 2 ☐
Autre(s) lésion(s) liée(s) à la vascularite	☐ 2 / 1 ☐
3. Atteintes muqueuses et oculaires	|__| **(maxi 6 / 3)** |__|
Ulcération buccale / granulome	☐ 2 / 1 ☐
Ulcération génitale	☐ 1 / 1 ☐
Inflammation lacrymale ou salivaire	☐ 4 / 2 ☐
Exophtalmie	☐ 4 / 2 ☐
Episclérite	☐ 2 / 1 ☐
Conjonctivite / blépharite / kératite	☐ 1 / 1 ☐
Baisse progressive d'acuité visuelle / vue trouble	☐ 3 / 2 ☐
Baisse brutale d'acuité visuelle / cécité	☐ 6 / - -
Uvéite	☐ 6 / 2 ☐
Vascularite rétinienne Thrombose / hémorragie / exsudats rétiniens	☐ 6 / 2 ☐
4. Signes ORL	|__| **(maxi 6 / 3)** |__|
Epistaxis / croûtes nasales / ulcération ou granulome nasal	☐ 6 / 3 ☐
Sinusite	☐ 2 / 1 ☐
Sténose sous-glottique	☐ 6 / 3 ☐
Baisse d'audition de transmission (conduction)	☐ 3 / 1 ☐
Baisse d'audition de perception (sensorielle)	☐ 6 / 2 ☐
5. Signes pulmonaires	|__| **(maxi 6 / 3)** |__|
Wheezing / sibilants	☐ 2 / 1 ☐
Nodule(s) / Nodule(s) excavé(s)	☐ 3 / - -
Epanchement pleural	☐ 4 / 2 ☐
Infiltrat pulmonaire radiologique	☐ 4 / 2 ☐
Sténose endobronchique	☐ 4 / 2 ☐
Hémorragie intra-alvéolaire	☐ 6 / 4 ☐
Détresse respiratoire	☐ 6 / 4 ☐

	Récent / Persistant
6. Signes cardiaques	|__| **(maxi 6 / 3)** |__|
Disparition d'un pouls	☐ 4 / 1 ☐
Atteinte valvulaire	☐ 4 / 2 ☐
Péricardite	☐ 3 / 1 ☐
Angor	☐ 4 / 2 ☐
Cardiomyopathie	☐ 6 / 3 ☐
Insuffisance cardiaque congestive	☐ 6 / 3 ☐
7. Atteinte digestive	|__| **(maxi 9 / 6)** |__|
Péritonite	☐ 9 / 3 ☐
Diarrhée sanglante	☐ 9 / 3 ☐
Douleur abdominale (angor digestif)	☐ 2 / 6 ☐
8. Atteinte rénale	|__| **(maxi 12 / 6)** |__|
HTA	☐ **4 / 1** ☐
Protéinurie > 1 +	☐ **4 / 2** ☐
Hématurie > 10 GR / champ	☐ **6 / 3** ☐
Créatininémie 125–249 µmol/l	☐ 4 / 2 ☐
Créatininémie 250–499 µmol/l	☐ 6 / 3 ☐
Créatininémie > 500 µmol/l	☐ **8 / 4** ☐
Augmentation de la Créatininémie > 30% ou diminution de la clairance de la créatinine > 25%	☐ 6 / - -
9. Atteinte neurologique	|__| **(maxi 9 / 6)** |__|
Céphalées	☐ 1 / 1 ☐
Méningite	☐ 3 / 1 ☐
Confusion, trouble de la conscience	☐ 3 / 1 ☐
Convulsions (non liées à l'HTA)	☐ 9 / 3 ☐
Atteinte médullaire (myélite)	☐ 9 / 3 ☐
Accident vasculaire cérébral	☐ 9 / 3 ☐
Atteinte de(s) paire(s) crânienne(s)	☐ 6 / 3 ☐
Neuropathie périphérique sensitive	☐ 6 / 3 ☐
Neuropathie périphérique motrice	☐ 9 / 3 ☐

10. Autre atteinte spécifique récente ☐ / ancienne ☐

Préciser : ……

COCHER CETTE CASE SI **TOUTES** LES ATTEINTES NOTEES SONT ANCIENNES ET PERSISTANTES, et non récentes ou aggravées. ☐

TOTAL = ……

(= somme des items actifs.
Si cette somme est = 0, faire la somme des items persistants)

18.6 Appendix 3. Patient subcutaneous self-dosing instructions (pre-filled syringe)

1) Remove a syringe from the kit allowing it to warm to room temperature for no longer than 30 minutes.

2) Visually inspect the medication in the syringe. Only use the syringe if the:
   - liquid is clear and free of particles.
   - liquid is colorless to light yellow in appearance.

3) Obtain the following:
   - alcohol swab
   - sterile gauze
   - container for syringe disposal

4) Wash your hands thoroughly with soap and water.

5) Choose an injection site: either left or right side of the abdomen or upper thigh. Choose a different site for each injection.

Injectable Areas