"Isatuximab in type I cryoglobulinemia: A prospective pilot study"

ICE STUDY (**I**satuximab in type 1 **C**ryoglobulin**E**mia)

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

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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.

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1 SUMMARY

Full title	Isatuximab in type I cryoglobulinaemia: A prospective pilot study
Acronym/reference	**ICE STUDY (Isatuximab in type 1 CryoglobulinEmia)**
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Sponsor	Assistance Publique-Hôpitaux de Paris
Scientific justification	Cryoglobulinaemia is defined as the presence of immunoglobulins in the serum which reversibly precipitate and form a gel when the temperature drops below 37°C and redissolve upon re-warming. Classification includes three subgroups based on Ig composition. Type I cryoglobulinaemia consists of only one isotype or subclass of immunoglobulin. Types II and III are classified as mixed cryoglobulinaemia (MC) because they include both IgG and IgM components. Overall, cryoglobulinaemia is considered a rare disease (<5/10,000 in the general European and North American population), although prevalence is likely to be higher in some areas such as the Mediterranean Basin. MC vasculitis is a multi-organic disease involving kidneys, joints, skin, and peripheral nerves. In type I cryoglobulinaemic vasculitis, searching for an underlying plasma-cell neoplasms is mandatory. Cryoglobulinaemia composed of IgG is more often found in multiple myeloma or monoclonal gammapathy of unknown significance (MGUS). The course of MC vasculitis varies widely and the prognosis is influenced by both MC-induced damage to vital organs and co-morbidities associated with underlying diseases. Type I cryoglobulinaemic vasculitis is a plasma cell associated disorder at the crossroad between autoimmunity and plasma-cell neoplasm. Treatment should be modulated according to the underlying associated disease and the severity of internal organ involvement. The overall 10-year survival after a diagnosis of cryoglobulinaemic syndrome ranges from 50% to 90% in case of renal involvement. The main therapeutic goal must be the cure of the underlying haematological disease (overwhelmingly plasma-cell neoplasms). The most common neoplasias are multiple myeloma (predominantly associated with type I cryoglobulinaemia and hyperviscosity) in more than 50% of cases. Treating the underlying monoclonal disorder has been associated with improvement/stabilization of cryoglobulinaemic symptoms in most patients with type I cryoglobulinemia, although negativation of serum cryoglobulins was achieved in only half the patients.

	Alkylating agents and bortezomib are the main therapeutic options but are associated with side effects including neuropathy. Patients presenting with symptomatic hyperviscosity require urgent therapeutic intervention using plasma exchange or plasmapheresis to remove cryoglobulins from the circulation. There is no standard of care or international guidelines for treatment of type 1 cryoglobulinemia. Isatuximab is an anti-CD38 monoclonal antibody that has been effective to treat relapsed or refractory multiple myeloma. Autoreactive plasma cells represent a key player in autoimmune disorders and particularly in type I cryoglobulinemia. Type I cryoglobulinemia is a model of plasma cell associated disorder at the crossroad between autoimmunity and plasma-cell neoplasm. However, rituximab fails to target this population and is poorly effective in this condition. Thus, there is an unmeet need for plasma cell targeted therapy in type I cryoglobulinemia. Clonal plasma cells in type I cryoglobulinemia do express surface CD38, providing a rationale for the use of isatuximab in cryoglobulinemia. Although the biology of the clonal plasma cell in type I cryoglobulinemia is distinct from that of AL amyloidosis, they are models of hematological diseases associated with monoclonal Ig and whose tumor mass is low. In AL amyloidosis anti-CD38 targeted therapy was highly efficient as monotherapy in treatment naïve patients and relapsers. Thus, isatuximab represents a highly promising therapy in type I cryoglobulinemia that could be use as monotherapy.
Main objective and primary endpoint	The primary objective is to assess the complete clinical response rate of Isatuximab in type I IgG cryoglobulinemia. <u>Primary endpoint</u>: Complete clinical response rate of cryoglobulinemia vasculitis symptoms at week (W) 20
Secondary objectives and endpoints	**Secondary objectives:** • Safety and tolerability of treatment as assessed by frequency and severity of adverse clinical events • Early complete response rate at W12 • Complete, partial (improvement in some but not all organs involved at baseline) and non clinical (no clinical improvement) response rate at W12 and W20 • Rate of cryoglobulinemia clearance • Rate of negativation of rheumatoid factor activity • Rate of normalization of C4 complement level • Early failure rate at W4 (non clinical response at W4) • Clinical relapse rate and the time to relapse, • Course of plasma cell associated disorder • Evolution of gammaglobulin level • Quality of life scores (SF-36) (Appendix 1), • Rate of infections (severe or not) and other complications • Birmingham Vasculitis Activity Score (BVAS) (Appendix 2) • Immunomonitoring (deep immunophenotyping, cytokines production, spectrometry, Fish analysis, single plasma cell repertoire)

	Secondary endpoints • Safety and tolerability of treatment as assessed by frequency and severity of adverse clinical events at W20 • Complete, partial and non-clinical response rate at W12, and at W20. • Rate of cryoglobulinemia clearance, of negativation of rheumatoid factor activity and of normalization of C4 complement level at W12, and at W20. • Rate of early failures (non-clinical response at W4), • Rate of renal complete remission defined as proteinuria <0.5g/24h or proteinuria/creatininuria <50 mg/mmol, disappearance of hematuria, and glomerular filtration rate ≥ 60ml/min/1.73m² at W12, and at W20. • 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 • Course of plasma cell associated disorder W12, and at W20. • Mean change of gammaglobulin level from baseline to W20 • Quality of life assessed by the mean variation of the SF-36 over the 20 weeks, • Rate of infections (severe or not) and other complications during the 48 weeks of follow-up • Proportion of patients remaining in remission with a BVAS=0 at baseline, W12, and W20. • Evolution of Immunomonitoring (deep immunophenotyping, cytokines production, spectrometry, Fish analysis, single plasma cell repertoire) at baseline, week 12, and week 20
Design of the study	This is a Phase 2 pilot prospective study of 21 patients with type I IgG cryoglobulinemia treated by Isatuximab. Isatuximab will be perform intravenously at 10mg/kg at day 0, week (W)1, W2, W3, and W4 then every 2 weeks for a total of 12 infusions.
Population of study participants	Adult patients with type 1 IgG active cryoglobulinemia vasculitis.
Inclusion criteria	1. Age > 18 years 2. Written informed consent 3. Monoclonal gammopathy of unknown significance (MGUS) with monoclonal IgG component 4. Active cryoglobulinemia vasculitis defined by positive (or history of positive) type I IgG cryoglobulinemia and a clinically active cryoglobulinemia with skin, joint, renal, pulmonary, cardiovascular, muscular, digestive, central and/or peripheral neurological involvement, 5. Treated naïve or relapsers type I cryoglobulinemia patients 6. Affiliated to National French social security system 7. Contraception : a) Male participants: A male participant must agree to use a highly effective method of contraception during the participation period and for at least 5 months after the last dose of study treatment and refrain from donating sperm during this period.

	b) Female participants: A female participant is eligible to participate if she is not pregnant, not breastfeeding, and with at least one of the following conditions: ▪ Not a female of childbearing potential (FCBP), OR ▪ A FCBP who must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 24 hours of starting study medication and must apply a highly effective method of contraception during the participation period and for at least 5 months after the last dose of study treatment and refrain from donating oocyte during this period 8. HIV negative serology; negative HBs Ag test; HCV negative serology or negative HCV RNA if positive HCV serology within 3 months prior inclusion
Exclusion criteria	1. Patient with a vasculitis unrelated to cryoglobulinemia 2. Patient with non-active cryoglobulinemia vasculitis, 3. Patient with diagnosis of multiple myeloma, except indolent myeloma 4. Patient treated with immunosuppressant (e.g alkylating agent, Rituximab, chemotherapy for plasma-cell neoplasms) introduced or increased in the month prior to the inclusion, 5. Live vaccines within 30 days prior to baseline or concurrently with Isatuximab 6. Infection requiring hospitalization and/or use of parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti-parasitic agents) within 60 days prior Day 0. 7. Active tuberculosis 8. HIV positive, positive Ag HbS, positive HCV RNA 9. Any clinically significant, uncontrolled medical conditions that, in the Investigator's opinion, would expose excessive risk to the patient or may interfere with compliance or interpretation of the study results. 10. Hypersensitivity or history of intolerance to steroids, mannitol, pregelatinized starch, sodium stearyl fumarate, histidine (as base and hydrochloride salt), arginine hydrochloride, poloxamer 188, sucrose or any of the other components of study therapy that are not amenable to premedication with steroids and H2 blockers or would prohibit further treatment with these agents. 11. Hypersensitivity to the active substances (isatuximab and premedication) or to any of their excipients 12. Received any investigational drug within 14 days prior to inclusion or within 5 half-lives of the investigational drug, whichever is longer. 13. Participation in another interventional study or being in the exclusion period at the end of a previous study. 14. Vulnerable populations o pregnant or breastfeeding women o Persons deprived of liberty by judicial or administrative decision o Persons under psychiatric care without their consent

	○ Adults subject to a legal protection measure ○ Persons unable to express their consent 15. Neutrophils < 1000/mm^3 16. Platelets < 75000/mm^3
Investigational medicinal product(s)	Isatuximab administered intravenously at 10mg/kg at day 0, W1, W2, W3 and W4 then every 2 weeks for a total of 12 infusions
Comparator treatment	None
Interventions added for the study	Immunomonitoring (deep immunophenotyping, cytokines production, spectrometry, Fish analysis, repertoire and function of single plasma cells) at baseline,12, and week 20 Premedication: - Dexamethasone 40 mg PO or IV (or 20 mg PO or IV in patients ≥75 years of age). - Acetaminophen 650 mg to 1000 mg PO (or equivalent). - Montelukast 10 mg orally 15 to 30 minutes before Isatuximab infusion (and never > 60 minutes) (or equivalent) - Diphenhydramine 25 mg to 50 mg IV or PO (or equivalent).
Risks added by the trial	*Risk D*
Scope of the trial	Phase II prospective multicenter study from the french plasma cell neoplasm and cryoglobulinemia network is composed of hematologists, internists, rheumatologists, dermatologists and nephrologists. All patients will receive subsequently the same therapy. 21 patients with type I IgG cryoglobulinaemia will be treated by Isatuximab. Isatuximab will be administred intravenously at 10mg/kg at day 0, W1, W2, W3 and W4 then every 2 weeks for a total of 12 infusions.
Number of subjects included	21 patients
Number of sites	Multicenter national study including 17 centers
Duration of the trial	- *Duration of inclusions: 30 months* - *Duration of participation of each patient: 12 months* *Total duration: 42 months*
Number of enrolments expected per site and per month	0.04 patient/month/centre
Statistical power and sample size justification:	We used the one-sample multiple testing procedure for Phase II clinical trials (Report Definitions, Fleming, T. R. 1982; Biometrics, Volume 38, pages 143-151) to calculate the sample size. Report Definitions P0 is the maximum response proportion of a poor drug. P1 is the minimum response proportion of a good drug. N is the sample size. If the number of responses ≥ R+1, P0 is rejected. If the number of responses ≤ R, P1 is rejected. Alpha is the probability of rejecting that P ≤ P0 when this is true. Beta is the probability of rejecting that P ≥ P1 when this is true. <u>Summary Statements</u>

	The ICE study requires 21 subjects to decide whether the proportion responding, P, is less than or equal to 0,400 or greater than or equal to 0,700. If the number of responses is 13 or more, the hypothesis that $P \leq 0,400$ is rejected with a target error rate of 0,050 and an actual error rate of 0,035. If the number of responses is 12 or less, the hypothesis that $P \geq 0,700$ is rejected with a target error rate of 0,150 and an actual error rate of 0,148.
Statistical analysis	This is a pilot prospective Phase II clinical trial that aims at evaluating safety and efficacy of Isatuximab in type 1 cryoglobulinemia vasculitis. We hypothesize that up to 70% of the patients receiving Isatuximab will achieve a complete remission of cryoglobulinemia vasculitis at week 20 (W20). Continuous variables (cf variables described in primary and secondary objectives) will be presented with the median and IQR or with the mean ± SEM. Categorical variables will be presented with counts and proportions. Statistical comparisons will be performed by using the Mann-Whitney test for quantitative unpaired data, t-test for quantitative paired data, Kruskal-Wallis for multiple comparisons, Spearman correlation test for correlations. T-test for quantitative paired data analysis will be used to compare immunological changes between day 0 and week 12 and 20 after Isatuximab. All statistical tests will be two-tailed with a significance level of 0.05.
Sources of funding for the trial	Sanofi funds the trial and will provide Isatuximab
Budget	350 000 euros Plus the supply of Isatuximab
Study will have a Data Safety Monitoring Board	Yes

2 SCIENTIFIC JUSTIFICATION FOR THE STUDY

2.1 Hypothesis for the study

Cryoglobulinaemia is defined as the presence of immunoglobulins in the serum which reversibly precipitate and form a gel when the temperature drops below 37°C and redissolve upon re-warming[1]. Classification includes three subgroups based on Ig composition. Type I cryoglobulinaemia consists of only one isotype or subclass of immunoglobulin. Types II and III are classified as mixed cryoglobulinaemia (MC) because they include both IgG and IgM components. Overall, cryoglobulinaemia is considered a rare disease (<5/10,000 in the general European and North American population), although prevalence is likely to be higher in some areas such as the Mediterranean Basin.

MC vasculitis is a multi-organic disease involving kidneys, joints, skin, and peripheral nerves. In type I cryoglobulinaemic vasculitis, searching for an underlying plasma-cell neoplasms is mandatory. Cryoglobulinaemia composed of IgG is more often found in multiple myeloma or monoclonal gammapathy of unknown significance (MGUS). The course of MC vasculitis varies widely and the prognosis is influenced by both MC-induced damage to vital organs and co-morbidities associated with underlying diseases.

Type I cryoglobulinaemic vasculitis is a plasma cell associated disorder at the crossroad between autoimmunity and plasma-cell neoplasm. Treatment should be modulated according to the underlying associated disease and the severity of internal organ involvement. The overall 10-year survival after a diagnosis of cryoglobulinaemic syndrome ranges from 50% to 90% in case of renal involvement. The main therapeutic goal must be the cure of the underlying haematological disease (overwhelmingly plasma-cell neoplasms).

The most common neoplasias are multiple myeloma (predominantly associated with type I cryoglobulinaemia and hyperviscosity) in more than 50% of cases. Treating the underlying monoclonal disorder has been associated with improvement/stabilization of cryoglobulinaemic symptoms in most patients with type I cryoglobulinaemia, although negativation of serum cryoglobulins was achieved in only half the patients. Alkylating agents and bortezomib are the main therapeutic options but are associated with side effects including neuropathy[2]. Patients presenting with symptomatic hyperviscosity require urgent therapeutic intervention using plasma exchange or plasmapheresis to remove cryoglobulins from the circulation.

There is no standard of care or international guidelines for treatment of type I cryoglobulinemia. Isatuximab is an anti-CD38 mAb that has been effective to treat relapsed or refractory multiple myeloma. Autoreactive plasma cells represent a key player in in type I cryoglobulinemia. Type I cryoglobulinemia is a model of plasma cell associated disorder at the crossroad between autoimmunity and plasma-cell neoplasm. However, rituximab fails to target this population and is poorly effective in this condition[3]. Thus, there is an unmeet need for plasma cell targeted therapy in type I cryoglobulinemia. Clonal plasma cells in type I cryoglobulinemia do express surface CD38, providing a rationale for the use of isatuximab in cryoglobulinemia. Although

the biology of the clonal plasma cell in type I cryoglobulinemia is distinct from that of AL amyloidosis, they are models of hematological diseases associated with monoclonal Ig and whose tumor mass is low. In AL amyloidosis anti-CD38 targeted therapy was highly efficient as monotherapy in treatment naïve patients and relapsers[4]. Thus, isatuximab represents a highly promising therapy in type I cryoglobulinemia that could be use as monotherapy.

2.2 Description of knowledge relating to the condition in question

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)[5]. The visceral manifestations are polymorphic, with preferential involvement of the skin, joints, peripheral nervous system and kidney.

The prevalence and incidence of non-viral mixed cryoglobulinemic vasculitis is poorly understood[6]. 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

Type I cryoglobulinemia is a systemic vasculitis affecting small vessels, and more rarely those of medium size[7]. Cryoglobulinemia is characterized by a proliferation of plasma cell clones that express surface CD38 and producing IgG. In type I cryoglobulinaemia, the formation of large, complement bound, IgG complexes is a major factor influencing cryoprecipitation. Immune-complex–mediated vasculitis is a major mechanism of tissue injury in cryoglobulinaemia.

The monoclonal IgG component generates large immune complexes 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. 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), whose monoclonal component is a IgG. 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

Type I cryoglobulinemia 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[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, and complications related to the severity of vasculitis. In a retrospective study, severe infections were responsible for half the deaths. The most common causes of death in type I cryoglobulinaemia 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.

2.3 Summary of relevant pre-clinical experiments and clinical trials

Type I cryoglobulinemia is associated with significant morbidity and mortality that often warrant therapeutic intervention. The main therapeutic goal must be the cure of the underlying haematological disease (overwhelmingly plasma-cell neoplasms). The most common neoplasias are multiple myeloma (predominantly associated with type I cryoglobulinaemia and hyperviscosity) in more than 50% of cases. Treating the underlying monoclonal disorder has been associated with improvement/stabilization of cryoglobulinaemic symptoms in patients with type I cryoglobulinaemia, although negativation of serum cryoglobulins was achieved in only half the patients[11,12]. Alkylating agents and bortezomib are the main therapeutic options but are associated with side effects including neuropathy. Patients presenting with symptomatic hyperviscosity require urgent therapeutic intervention using plasma exchange or plasmapheresis to remove cryoglobulins from the circulation. There is no standard of care or international guidelines for treatment of type I cryoglobulinemia. Clonal plasma cells in type I cryoglobulinemia do express surface CD38, providing a rationale for the use of isatuximab in cryoglobulinemia.

2.4 Description of the population to be studied and justification for the choice of participants

This is a pilot prospective Phase II clinical trial that aims at evaluating safety and efficacy of Isatuximab in type 1 cryoglobulinemia vasculitis. We hypothesize that up to 70% of the patients receiving Isatuximab will achieve a complete remission of cryoglobulinemia vasculitis at week 20 (W20).

2.5 Identification and description of the investigational medication or medications

After the collection of their free and informed consent, eligible patients will receive Isatuximab administered intravenously at 10mg/kg at day 0, W1, W2, W3 and W4 then every 2 weeks for a total of 12 infusions.

2.6 Summary of the known and foreseeable benefits and risks for the research participants

The majority of patients with type I cryoglobulinemia fail to achieve a complete response to standard chemotherapy, and almost all patients eventually experience relapse and/or progression of organ involvement. Alkylating agents and bortezomib are the main therapeutic options but are associated with side effects including neuropathy. There is no standard of care or international guidelines for treatment of type I cryoglobulinemia. Additional well-tolerated treatment options are needed. Autoreactive CD38+ plasma cells represent a key player in in

type I cryoglobulinemia. Isatuximab is an immunoglobulin (Ig) G1 monoclonal antibody (mAb) that selectively binds to the human cell surface antigen molecule classified as cluster of differentiation (CD). Isatuximab targets CD38 expressed in hematological malignancies and is able to destroy CD38 expressing tumor cells in vitro through several mechanisms, including: DCC, ADCP, CDC, and direct apoptosis. Isatuximab binding to CD38 expressed on immune cells triggers immunomodulatory functions. For instance, isatuximab can activate NK cells and increase their lytic activity. Isatuximab can also induce the polarization of monocytes to an M1 phenotype and restore the proliferative potential of conventional T cells repressed by regulatory T cells (Tregs). Isatuximab has been effective to treat relapsed or refractory multiple myeloma without unexpected toxicity. Thus, isatuximab represents a highly promising therapy in type I cryoglobulinemia that could be used as monotherapy.

Reported side effects that may or may not be related to single agent isatuximab IV or that could possibly be caused by other medications or by disease, include the following:

- Observed in more than 10% of the patients: Infusion related reaction, Fatigue, Nausea, Anemia, Cough, Upper respiratory tract infection, Diarrhea, Headache, Dyspnea, Back pain, Vomiting, Pyrexia, Chills, Decreased appetite, Constipation, Chest discomfort, and Peripheral edema.
- Observed in 5 to 10% of the patients: Insomnia, Arthralgia, Bone pain, Flushing, Pain in extremity, Thrombocytopenia, Pneumonia, Dizziness, Nasal congestion, Musculoskeletal chest pain, Abdominal pain, Epistaxis, Wheezing, Bronchitis, Hypercalcemia, Musculoskeletal pain, Myalgia, Decreased weight, Increased blood creatinine, Hypertension, Hypokalemia, Pain, Urinary tract infection, Acute kidney injury, Asthenia, Dysgeusia, Oropharyngeal pain, Peripheral sensory neuropathy, Productive cough, and Rhinorrhea.

Isatuximab IV may cause infusion reactions, which typically occur within 24 hours from the start of an infusion, and most commonly during the first infusion. The most frequent symptoms of infusion reactions associated with isatuximab include chills, shortness of breath, nausea, chest discomfort, flushing, cough, and headache. Although usually mild-to-moderate and always reversible either spontaneously or with treatment, infusion reactions can also be severe or even life threatening. Serious infusion reactions (such as throat tightness, difficulty in breathing, lowered blood pressure, or severely increased blood pressure) are known to occur at any time during the administration of monoclonal antibodies, including isatuximab.

Considering the risks of relapse with classical therapeutic strategies, the potentially serious side effects of bortezomib and alkylating agents, Isatuximab, by specifically targeting plasma cells involved in cryoglobulin production, appears to be a promising therapy with a favorable benefit-risk ratio.

3 OBJECTIVES

3.1 Primary objective

The primary objective is to assess the complete clinical response rate of Isatuximab in type I IgG cryoglobulinaemia.

3.2 Secondary objectives

- Safety and tolerability of treatment as assessed by frequency and severity of adverse clinical events
- Early complete response rate at W12
- Complete, partial (improvement in some but not all organs involved at baseline) and non-clinical (no clinical improvement) response rate at W12 and W20
- Rate of cryoglobulinemia clearance
- Rate of complete remission of glomerulonephritis at W12 and W20
- Rate of negativation of rheumatoid factor activity
- Rate of normalization of C4 complement level
- Early failure rate at W4 (non-clinical response at W4)
- Clinical relapse rate and the time to relapse,
- Course of plasma cell associated disorder
- Evolution of gammaglobulin level
- Quality of life scores (SF-36) (Appendix 1),
- Rate of infections (severe or not) and other complications
- BVAS activity score (Appendix 2)
- Immunomonitoring (deep immunophenotyping, cytokines production, spectrometry, Fish analysis, single plasma cell repertoire)

4 STUDY DESIGN

4.1 Study endpoints

4.1.1 Primary endpoint

Complete clinical response rate of cryoglobulinemia vasculitis symptoms at week (W) 20.

The complete clinical response is defined by the remission of all affected organs involved at baseline and the absence of clinical relapse according to the international guidelines [11, 12].

- The skin and articular remissions are evaluated clinically (disappearance of purpura, ulcers and/or critical ischemic lesions, disappearance of arthritis).
- Renal remission is evaluated biologically (proteinuria <0.5g/24h or proteinuria/creatininuria <50 mg/mmol,).

- Peripheral 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 W20 compared to baseline).
- Central neurological remission is evaluated clinically (stabilization or improvement of central neurological symptoms) and by cerebral angio-MRI (stabilization or improvement of vessel wall thickening and intramural contrast uptake, of FLAIR lesion, and/or of leptomeningeal enhancement).
- 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.
- Pulmonary remission is evaluated clinically (improvement of dyspnea, cough, and/or respiratory distress), and by CT-scan (improvement in intra-alveolar hemorrhages)
- Muscular remission is evaluated clinically (disappearance of muscular pain and stabilization or improvement of muscular testing in case of motor impairment at baseline) and biologically (normalization of CPK if elevated at baseline)

Patients with no clinical response at W4 will be defined as early treatment failure (failure for the primary endpoint).

Patients with clinical relapse (defined as de novo appearance or recurrence of a manifestation due to the cryoglobulinemia vasculitis) between W4 and W20 will be considered in failure according to the primary endpoint.

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/1.73m^2 (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.
Therapeutic management of flare-up will be at the discretion of the investigator according to standard of care.

4.1.2 Secondary endpoints

- Safety and tolerability of treatment as assessed by frequency and severity of adverse clinical events at W20
- Complete, partial and non-clinical response rate at W12, and at W20.
- Rate of cryoglobulinemia clearance, of negativation of rheumatoid factor activity and of normalization of C4 complement level at W12, and at W20.
- Rate of early failures (non-clinical response at W4)
- Rate of renal complete remission defined as proteinuria < 0.5g/24h or proteinuria/creatininuria < 50 mg/mmol, disappearance of hematuria, and glomerular filtration rate ≥ 60ml/min/1.73m² at W12 and W20.
- Clinical relapse rate defined by de novo appearance or reappearance of a manifestation attributable to cryoglobulinemia vasculitis during 20 weeks of follow-up,
- Rate and time to relapse from baseline to W48
- Course of plasma cell associated disorder W12, and at W20.

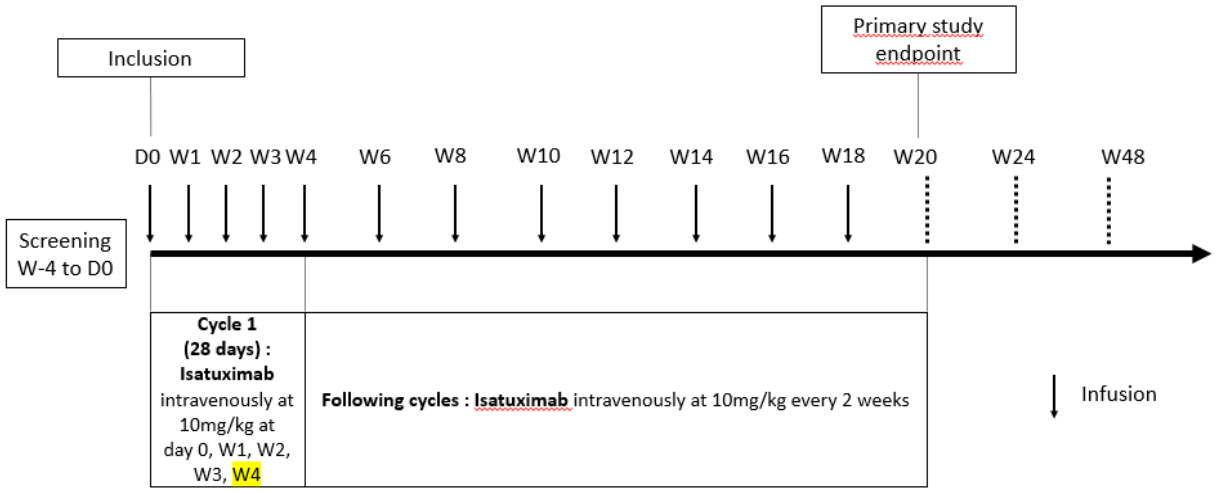
- Mean change of gammaglobulin level from baseline to W20
- Quality of life assessed by the mean variation of the SF-36 over the 20 weeks study period,
- Rate of infections (severe or not) and other complications during the 48 weeks of follow-up
- proportion of patients remaining in remission with a BVAS=0at baseline, W12, and W20.
- Evolution of Immunomonitoring (deep immunophenotyping, cytokines production, spectrometry, Fish analysis, single plasma cell repertoire) at baseline, week 12, and week 20

4.2 Description of research methodology

4.2.1 Design of the study

Phase II prospective multicenter study from the french plasma cell neoplasm and cryoglobulinemia network is composed of hematologists, internists and nephrologists.

All patients will receive subsequently the same therapy.



21 patients with type I cryoglobulinaemia will be treated by Isatuximab. Isatuximab will be administred intravenously at 10mg/kg at day 0, W1, W2, W3 and W4 then every 2 weeks for a total of 12 infusions.

4.2.2 Number of participating sites

Multicenter national study including 17 centres

- Recruitment centres: patients will be recruited in hospital (consultation or hospitalisation), from non-hospital services (general practitioners or specialists) or among outpatients.

4.2.3 Identification of participants

The participants in this research will be identified as follows:

Site number. (3 digits) - Sequential enrolment 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 study.

5 IMPLEMENTATION OF THE STUDY

Before any examination or intervention related to the study may be carried out, the investigator must obtain the *freely given, informed and written consent of the participant, or of his/her legal representative* where applicable.

Individuals liable to participate in studies stipulated in line 1° of article L. 1121-1 of the *Code de la Santé Publique* (French Public Health Code) benefit from a preliminary medical examination adapted to the study.

5.1 Screening visit

A screening visit will take place within 4 weeks prior to inclusion visit.

Whose consent must be obtained	Who informs the individuals and collects their consent	At what point the individuals are informed	At what point the consent is obtained
The subject participating in the trial	The investigator internal medicine, haematologist, nephrologist, dermatologist or rheumatologist	During screening visit	After time reflexion during screening visit

The screening visit will be carried out by the physician who is responsible for the patient during the study. During this visit, the investigator will:

- Inform the patient about the protocol, and give him the information and consent form,
- Collect the free and informed written consent of the patient,
- Interview the patient and record: age, gender, weight, height, ethnicity (required to calculate the MDRD formula[13]), medical and surgical history, current and past treatments, history of vasculitis, smoking, alcohol, drug use
- Perform a physical examination including a search for active lesions of vasculitis
- Perform complete blood count with platelets, serum electrolytes, liver function tests (AST, ALT, GGT, PAL, total bilirubin, albumin), ESR, CRP, ferritin, cholesterol, triglyceride, LDH, glycemia, creatinine, proteinuria on 24h or proteinuria/creatininuria, cytobacteriological examination of the urine (CBEU) : hematuria, leukocyturia, urinary tract infection; gammaglobulin, , haptoglobuline, orosomucoïde, fibrinogen levels; cryoglobulinemia, rheumatoid factor activity, C4 complement level and ECG,
- Assess the results of HIV, HVB and HCV serologies, obtained within 3 months prior to screening visit, the results of which will be communicated directly or through a physician chosen by the subject prior to giving consent.
- Assess the results of specific exams for vasculitis evaluation (depending on organ involvement at baseline):

- Electromyogram obtained within 3 months prior to screening visit in case of peripheral neurological involvement;
- Digestive endoscopy and/or abdominal X-ray obtained within 3 months prior to screening visit in case of digestive involvement;
- Troponin and cardiac MRI with gadolinium injection, obtained within 3 months prior to screening visit in case of cardiac involvement;
- TDM in case of pulmonary involvement obtained within 3 months prior to screening visit;
- CPK in case of muscular impairment

- Perform blood typing (A; B, O, Rh) and indirect antiglobulin test if not done before (in routine care).

5.2 Inclusion visit

The Inclusion visit takes place at day 0, within 4 weeks after screening visit.

The Inclusion visit will be carried out by the physician who is responsible for the patient during the Study. During this visit, the investigator will:

- Perform a physical examination
- For childbearing women, urine or plasmatic pregnancy test will be performed (beta-HCG dosage)
- Verify the eligibility criteria,
- If all eligibility criteria are met the investigator will complete the Study Inclusion Form listing the eligibility criteria
- Perform immunomonitoring (deep immunophenotyping, cytokines production, spectrometry, Fish analysis, single plasma cell repertoire)
- Perform Quality of life Assessment (SF-36).
- Perform BVAS assessment
- Provide the first treatment
- Provide the patient with a patient card

For the APHP centers, immunomonitoring will be centralized in the Immunopathology and Immunotherapy of Autoimmune and Inflammatory Diseases Laboratory of Professor Saadoun (INSERM UMRS 959) in la Pitié-Salpêtrière Hospital. The transportation of these samples is to do at room temperature.

Immunomonitoring requires an additional blood sample of 40 mL, collected during the routine care blood sampling at D0, S12 and S20: 5 EDTA tubes of 6 mL (no less), and 2 dry tubes.

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 investigator. Patients will be reviewed at each infusion at W1, W2, W3, W4, W6, W8, W10, W12, W14, W16 and W18 and at follow up visits at W20, W24 and W48 and will have:

- A physical examination will be performed by the patient's Study investigator at each visit before treatment administration in order to follow tolerance
- At each visit total blood count, platelets, serum electrolytes, creatinine, ESR, CRP, ferritin, glycemia, fibrinogen, haptoglobin, orosomucoid, and liver function tests (AST, ALT, GGT, PAL, total bilirubin, albumin), LDH, cholesterol, triglyceride, creatinine, proteinuria on 24h or proteinuria/creatininuria, cytobacteriological examination of the urine (CBEU): hematuria, leukocyturia, urinary tract infection; gammaglobulin level will be measured.
- Cryoglobulinemia, rheumatoid factor activity and C4 complement level at W12, and at W20
- For childbearing women, urine pregnancy test will be performed monthly for the duration of the treatment and a period of 5 months after the last dose of study treatment
- Quality of life Assessment (SF-36) at 20 weeks.
- BVAS assessment at W12 and W20
- Immunomonitoring (deep immunophenotyping, cytokines production, spectrometry, Fish analysis, single plasma cell repertoire) at week 12 and week 20
- Specific exams for vasculitis evaluation will be performed at week 20 in case of organ involvement at baseline: electromyogram in case of peripheral neurological involvement; digestive endoscopy and/or abdominal X-ray in case of digestive involvement; troponin and cardiac MRI with gadolinium injection in case of cardiac involvement.
- An electrocardiogram will be performed at week 12 and 20.
- CPK at W20 if elevated at screening

5.4 Last study visit

After W20, all subjects will be followed after the study according to their usual routine hospital care. Study is completed for a patient at W48.

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

Duration of enrolment period	30 months
The length of participation for participants, of which:	12 months
• Treatment duration:	18 weeks
• Duration of follow-up period:	30 weeks
Total study duration:	42 months

5.6 Table or diagram summarising the chronology of the study

Actions	Screening W-4 to D0	Inclusion D0	W1 +/- 1 day	W2+/- 1 day	W3 +/- 1 day	W4 +/- 1 day	W6 +/- 3 days	W8 +/- 3 days	W10 +/- 3 days	W12 +/- 3 days	W14 +/- 3 days	W16 +/- 3 days	W18 +/- 3 days	**W20 +/- 3 days End of study §**	**W24 +/- 3 days**	**W48 +/- 7 days**
Information	X®															
Informed consent	X®															
Verification of inclusion and exclusion criteria	X®	X®														
History	X															
Clinical examination	X	X®	X®	X®	X®	X	X®	X®	X®	X	X®	X®	X®	X®	X	X
Pregnancy test (urinary or blood)*		X®				X®		X®		X®		X®		X®	X®	
ECG	X									X				X		
Biological tests **	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electromyogram ***	X													X		
Other exams according to active cryoglobulinemia vasculitis manifestations ***	X													X		
Immunomonitoring ****		X®								X®				X®		
QOL questionnaires (SF-36)		X®												X®		
BVAS		X®								X®				X®		
Dispensation of treatments		X®	X®	X®	X®	X®	X®	X®	X®	X®	X®	X®	X®			
Adverse events			X®	X®	X®	X®	X®	X®	X®	X®	X®	X®	X®	X®	X®	X®

* For childbearing women, urine or blood pregnancy test will be performed **monthly** for the duration of the treatment and a period of 5 months after the last dose of study treatment
** Complete blood count with platelets, serum electrolytes, liver function tests (AST, ALT, GGT, PAL, total bilirubin, albumin), LDH, cholesterol, triglycerides, ESR, CRP, ferritin, creatinine, glycemia, and for women, ß-HCG (urinary or plasmatic), proteinuria on 24h or proteinuria/creatininuria, cytobacteriological examination of the urine (CBEU): hematuria, leukocyturia and urinary tract infection; gammaglobulin, fibrinogen, haptoglobine, orsomucoïd level at each visit. Cryoglobulinemia, rheumatoid factor activity, C4 complement level at baseline, W12 and W20
CPK at screening in case of muscular impairment, and at W20 and W48 (if elevated at screening); HIV, HVB and HCV serologies within 3 months prior to screening.
Blood typing (A; B, O, Rh) and indirect antiglobulin test at screening visit if not done before (in routine care).
*** Electromyogram must have been performed within 3 months prior to screening visit and repeated at W20 in case of peripheral neurological involvement.
TDM in case of pulmonary involvement obtained within 3 months prior to screening visit in case of cardiac involvement.
Other exams according to other active cryoglobulinemia vasculitis manifestations are to be performed at baseline and W20 in case of specific organ involvement
**** Deep immunophenotyping, cytokines production, spectrometry, Fish analysis, single plasma cell repertoire (5 EDTA tubes of 6 mL and 2 dry tubes, for APHP sites only)

§ primary endpoint
® added for <u>research purposes</u>

5.7 Distinction between standard of care and study

Interventions, procedures and treatments carried out for research purposes	**Interventions, procedures and treatments associated with <u>standard care</u>**	**Interventions, procedures and treatments added for <u>research purposes</u>**
Treatments		• Isatuximab 10mg/kg at day 0, W1, W2, W3 and W4 then every 2 weeks for 20 weeks • Premedication: – Dexamethasone 40 mg PO or IV (or 20 mg PO or IV in patients ≥75 years of age). – Acetaminophen 650 mg to 1000 mg PO (or equivalent). – Montelukast 10 mg orally 15 to 30 minutes (and never > 60 minutes) (or equivalent). – Diphenhydramine 25 mg to 50 mg IV or PO (or equivalent).
Visits	Screening visit, visit at W4, W12, W24 and W48	Visits at D0, W1, W2, W3, W6, W8, W10, W14, W16, W18, W20
Blood samples	- Complete blood count with platelets, serum electrolytes, liver function tests (AST, ALT, GGT, PAL, total bilirubin, albumin), LDH, CRP, ferritin, creatinine, proteinuria on 24h or proteinuria/creatininuria, gammaglobulin levels ESR, cholesterol, triglyceride, LDH, glycemia, cytobacteriological examination of the urine (CBEU) : hematuria, leukocyturia, urinary tract infection, at each visit. - Cryoglobulinemia, rheumatoid factor activity, C4 complement level at baseline, W12 and W20 - Blood typing (A, B, O, Rh) and indirect antiglobulin test if not done before	- Deep immunophenotyping, cytokines production, spectrometry, Fish analysis, single plasma cell repertoire at baseline, W12 and W20 - ß-HCG (urinary or plasmatic) monthly for the duration of treatment until 5 months after the last dose of treatment
Imaging	- Electromyogram at baseline and W20 in case of peripheral neurological involvement - Other exams according to other active cryoglobulinemia vasculitis manifestations at baseline and W20 in case of specific organ involvement - ECG: at screening, week 12 and 20	
Others		- QOL questionnaires at D0, and 20 weeks - BVAS at D0, W12 and W20

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

1. Age > 18 years
2. Written informed consent
3. Monoclonal gammopathy of unknown significance (MGUS) with monoclonal IgG component
4. Active cryoglobulinemia vasculitis defined by positive (or history of positive) type I IgG cryoglobulinemia and a clinically active cryoglobulinemia with skin, joint, renal, pulmonary, cardiovascular, muscular, digestive, central and/or peripheral neurological involvement
5. Treated naïve or relapsers type I cryoglobulinemia patients
6. Affiliated to National French social security system
7. Contraception:

   a) Male participants: A male participant must agree to use a highly effective method of contraception during the participation period and for at least 5 months after the last dose of study treatment and refrain from donating sperm during this period.

   b) Female participants: A female participant is eligible to participate if she is not pregnant, not breastfeeding, and with at least one of the following conditions:

   - Not a female of childbearing potential (FCBP), OR

   - A FCBP who must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 24 hours of starting study medication and must apply a highly effective method of contraception during the participation period and for at least 5 months after the last dose of study treatment and refrain from donating oocyte during this period
8. HIV negative serology; negative HBs Ag test; HCV negative serology or negative HCV RNA if positive HCV serology within 3 months prior inclusion.

6.2 Exclusion criteria

1. Patient with a vasculitis unrelated to cryoglobulinemia
2. Patient with non-active cryoglobulinemia vasculitis,
3. Patient with diagnosis of multiple myeloma except indolent multiple myeloma
4. Patient treated with immunosuppressant (e.g alkylating agent, Rituximab, chemotherapy for plasma-cell neoplasms) introduced or increased in the month prior to the inclusion,
5. Live vaccines within 30 days prior to baseline or concurrently with Isatuximab
6. Infection requiring hospitalization and/or use of parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti parasitic agents) within 60 days prior Day 0.
7. Active tuberculosis
8. HIV positive, positive Ag HbS, positive HCV RNA

9. Any clinically significant, uncontrolled medical conditions that, in the Investigator's opinion, would expose excessive risk to the patient or may interfere with compliance or interpretation of the study results.
10. Hypersensitivity or history of intolerance to steroids, mannitol, pregelatinized starch, sodium stearyl fumarate, histidine (as base and hydrochloride salt), arginine hydrochloride, poloxamer 188, sucrose or any of the other components of study therapy that are not amenable to premedication with steroids and H2 blockers or would prohibit further treatment with these agents.
11. Hypersensitivity to the active substances (isatuximab and premedication) or to any of their excipients
12. Received any investigational drug within 14 days prior to inclusion or within 5 half-lives of the investigational drug, whichever is longer.
13. Participation in another interventional study or being in the exclusion period at the end of a previous study.
14. Vulnerable populations
    - pregnant or breastfeeding women
    - Persons deprived of liberty by judicial or administrative decision
    - Persons under psychiatric care without their consent
    - Adults subject to a legal protection measure
    - Persons unable to express their consent
15. Neutrophils < 1000/mm^3
16. Platelets < 75000/mm^3

6.3 Recruitment procedure

	Number of participants
Total number of participants to be included	21
Number of centres	17
Enrolment period (months)	30
Number of participants/centre	1.5
Number of participants/centre/month	**0.04**

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.

In the case of severe adverse events, the investigator must notify the sponsor and follow up the participant for 7 months following the premature discontinuation of treatment. Notification of a serious adverse event must be sent by email (eig-vigilance.drc@aphp.fr) to the sponsor. The serious adverse event 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.

6.4.2 Criteria and procedure for premature withdrawal of a participant from the study

- Participants may exit the study at any time and for any reason.
- If, during the course of his/her participation in the study, the participant presents one of the following exclusion criteria, then the study product/procedure must be discontinued but the participant will continue to be monitored for the study:
    - Vasculitis flare
    - Neutropenia < 500 PNN/mm^3
    - Severe infusion reaction (≥ grade 3 or 4) leading to suspension of at least 2 infusions of Isatuximab
- The investigator can temporarily or permanently withdraw a participant from the study for any safety reason or if it is in the participant's best interests.
- Participant 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

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

If a participant discontinues the study, this will in no way affect their usual care for their condition. In the event of serious adverse events following premature discontinuation of treatment and participation of the patient in the study; see section 6.4.1

6.4.4 Full or partial discontinuation of the study

AP-HP as 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 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.

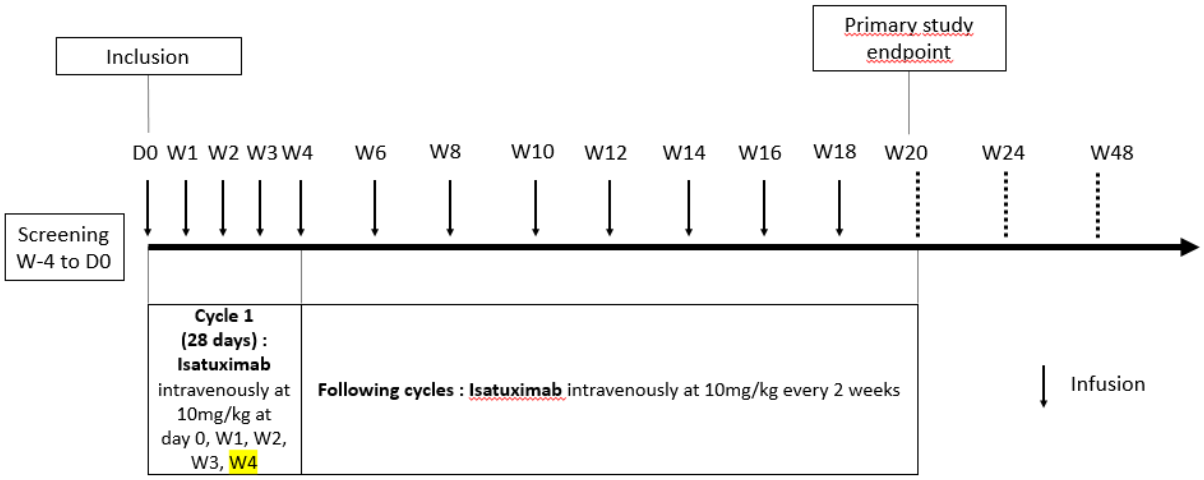
If the study is prematurely discontinued for safety reasons, the decision and justification will be provided by the sponsor (AP-HP) to the Competent Authority (ANSM) and to the CPP (Research Ethics Committee) within a period of 15 days, along with recommendations from the Data Safety Monitoring Board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

7 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

7.1 Description of the investigational medicinal product(s)

7.1.1 Investigational medicinal product 1

Isatuximab administered intravenously at 10mg/kg at day 0, W1, W2, W3 and W4 then every 2 weeks for a total of 12 infusions.



Isatuximab is available for parenteral administration as a sterile, non-pyrogenic, injectable, colorless to slightly yellow, 20 mg/mL concentrate for solution for infusion, essentially free of visible particles.

It is supplied as two presentations:

- 30 mL Type I colorless clear glass vials fitted with elastomeric closures. Each vial contains a nominal content of 500 mg of isatuximab. The fill volume has been established to ensure removal of 25 mL.
- 6 mL Type I colorless clear glass vials fitted with elastomeric closures. Each vial contains a nominal content of 100 mg of isatuximab. The fill volume has been established to ensure removal of 5 mL.

The pH of the solution is about 5.7 to 6.3. The solution contains the following excipients: water for injection, sucrose, histidine (as base and hydrochloride salt), and polysorbate 80.

The concentrated solution is diluted in 0.9% sodium chloride solution or dextrose 5% solution before use.

Based on available stability data, the 20 mg/mL concentrate for solution for infusion is stable for at least 36 months when stored according to conditions specified in the clinical supplies' labelling.

The preparation of the infusion solution should be performed under aseptic conditions.
- Calculate the dose (mg) of solution to be diluted according to the patient's weight.
- Remove the appropriate volume of solution to be diluted and dilute it in an infusion bag with 250 ml 9 mg/ml (0.9%) sodium chloride or 5% glucose solution to achieve the concentration of isatuximab suitable for infusion.

Study intervention name Isatuximab	Isatuximab
Dosage formulation	Concentrate for solution for intravenous infusion
Unit dose strength(s)/Dosage level(s)	20 mg/mL (500 mg/25 mL and 100 mg/5 mL) of isatuximab in 20 mM histidine, 10% (w/v) sucrose and 0.02% (w/v) polysorbate 80 at pH 6.0
Route of administration	Intravenous infusion
Dosing instructions	10mg/Kg weekly cycle 1 (D0, W1, W2, W3 and W4), 10mg/kg every two weeks thereafter (combination therapy)
Packaging and labelling	Study intervention will be provided in 30 mL and 6 mL glass vials fitted with elastomeric closure. Each glass vial will be labelled as required per country requirement.

Administration:

	Volume of dilution	Initial flow rate	no infusion reactions	Increase in flow rate	Maximum flow rate
First infusion	250 ml	25 ml/hour	During 60 minutes	25 ml/hour every 30 minutes	150 ml/hour
Second infusion	250 ml	50 ml/hour	During 30 minutes	50 ml/hour for 30 minutes, and then increase by 100 ml/hour every 30 minutes.	200 ml/hour
Next infusions	250 ml	200 ml/hour			200 ml/hour

Administration adjustments should be made if patients experience infusion reactions:

- In patients who experience Grade 2 (moderate) infusion reactions, a temporary interruption in the infusion should be considered and additional symptomatic medicinal products can be administered. After improvement to grade ≤1 (mild), Isatuximab infusion may be resumed at half of the initial infusion rate under close monitoring and supportive care, as needed. If symptoms do not recur after 30 minutes, the infusion rate may be increased to the initial rate, and then increased incrementally, as shown previously.

- If symptoms do not resolve rapidly or do not improve to Grade ≤1 after interruption of Isatuximab infusion, recur after initial improvement with appropriate medicinal products, or require hospitalization or are life-threatening (Grade ≥3), treatment with Isatuximab should be permanently discontinued and additional supportive therapy should be administered, as needed.

In case of a missed infusion (due to medical reasons, toxicity, missed visit..), the treatment will be continued normally at the next visit. No postpone or delay will be applied for the study.

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

Premedication should be used prior to isatuximab infusion with the following medications to reduce the risk and severity of infusion reactions (IRs):

- Dexamethasone 40 mg PO or IV (or 20 mg PO or IV in patients ≥ 75 years of age).
- Acetaminophen 650 mg to 1000 mg PO (or equivalent).
- Montelukast 10 mg orally 15 to 30 minutes (and never > 60 minutes) (or equivalent).
- Diphenhydramine 25 mg to 50 mg IV or PO (or equivalent).

An LRA such as montelukast is an optional pre-medication agent that can also be used to mitigate the risk of IRs.

The recommended premedication agents should be administered 15 to 60 minutes prior to starting an isatuximab infusion. Patients who do not experience an IR upon their first 4 administrations of isatuximab may have their need for subsequent premedication reconsidered. In accordance with the public health code L.1121-16-1, the costs related to the administration of these auxiliary drugs will be borne by the sponsor.
Prophylaxis against Pneumocystis Jirovecii is recommended for all patients.

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

Supply:

2 orders will be made for each patient:

- At screening visit (2 to 4 weeks before inclusion), site will order for cycle 1: D0, W1, W2, W3 injections (4 injections in total)
- At W1 visit, site will order for cycles 2, 3 and 4: W4, W6, W8, W10, W12, W14, W16 and W18 injections (8 injections in total)

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:

Isatuximab should be stored in the refrigerator (between + 2° C and + 8° C), and not be frozen. Unopened vials of Isatuximab should be kept in the original package to be protected from the light. The unopened vials have a 3-year shelf life.
Chemical and physical in-use stability of Isatuximab infusion solution has been demonstrated for 48 hours at 2°C - 8°C, followed by 8 hours (including the infusion time) at room temperature. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions. No protection from light is required for storage in the infusion bag.

Dispensing:

Pharmacies will dispense Isatuximab for each patient on the basis of a specific prescription. The dispensing traceability will be insured by the pharmacists who will manually enter the quantities, batch numbers and expiration dates of the drugs dispensed on the prescription.

Administration:

Treatment administration will be done during hospitalization and compliance will be monitored.

Nurses will complete a booklet to record administration. In the booklet, the nurses will note every injection during 20 weeks (i.e. 12 administrations in total) and it will be kept in the patient's medical records + eCRF.

Accountability and destruction:

At the end of the study, accountability must be ensured by the CRA. After completion, vials (unused, returned…) will be destructed by the local hospital pharmacy only with the promoter's authorization.

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

Prohibited treatments will include, with the exception of premedication intended to reduce the risk and severity of reactions to injections with isatuximab:

- Any other immunosuppressive or immunomodulatory agent administered for the control of vasculitis or any other inflammatory disorders,
- plasmapheresis
- corticosteroids

In the event of infusion-related reactions, all necessary supportive treatments will be authorized.

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 according to the international guidelines.

- The skin and articular remissions are evaluated clinically (disappearance of purpura and/or ulcers, disappearance of arthritis).
- Renal remission is evaluated biologically (proteinuria <0.5 g/24h or proteinuria/creatininuria <50 mg/mmol).
- Peripheral neurological remission is evaluated clinically (any improvement of pains and paresthesia by visual analogue scales, any improvement of muscular testing in case of motor impairment at baseline) and electrophysiologically (improvement of electromyogram abnormalities at W20 compared to baseline).
- Central neurological remission is evaluated clinically (stabilization or improvement of central neurological symptoms) and by cerebral angio-MRI (stabilization or improvement of vessel wall thickening and intramural contrast uptake, of FLAIR lesion, and/or of leptomeningeal enhancement)

- 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.
- Pulmonary remission is evaluated clinically (improvement of dyspnea, cough, and/or respiratory distress), and by CT-scan (improvement in intra-alveolar hemorrhages)
- Muscular remission is evaluated clinically (disappearance of muscular pain and stabilization or improvement of muscular testing in case of motor impairment at baseline) and biologically (normalization of CPK if elevated at baseline)

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 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).

Relapse: Relapse is defined as de novo appearance or recurrence of a manifestation of cryoglobulinemia vasculitis between W4 and W20 will be considered as a relapser.
Patients with clinical relapse between W4 and W20 will be considered in failure according to the primary endpoint.

Immunological response: The complete immunological response is defined by the disappearance of cryoglobulinemia at W20.
The partial immunological response is defined as a decrease> 50% in the rate of cryoglobulinemia at W20.

9 SAFETY ASSESSMENT - RISKS AND BURDEN ADDED BY THE STUDY

9.1 Recording and reporting adverse events

9.1.1 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

9.1.2 The role of the investigator

The investigator must **assess the seriousness of each adverse event** and record all serious and non-serious adverse events in the case report form (CRF or 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 a rating scale for adverse events appended to the protocol

- *Common Terminology Criteria for Adverse Events [National Cancer Institute]*

The investigator must **assess the causal relationship** between serious adverse events and the investigational medicinal product(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 to occur	· 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 recognised 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 · 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

9.1.2.1 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

9.1.2.2 Specific features of the protocol

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

- Adverse events deemed "medically significant", including adverse events of special interest: The investigator must notify the sponsor without delay on the day the investigator becomes aware of these adverse events, in the same manner and within the same deadline as for serious adverse events (see above). These events may include:
  - Vasculitis flare
  - Major vasculitis relapse
  - Infusion related reactions of grade 3 and 4

- Infections/ neutropenia ≥ grade 3 CTCAE
- Symptomatic overdose
- Second primary malignancy

- 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 (maternal or paternal exposure), even if it is not associated with an adverse event.

- Exposure while breastfeeding: Exposure while breastfeeding occurs if an infant or a child may have been exposed to a medicinal product via the breast milk of a mother being treated with an investigational medicinal product.

Even if it is not associated with an adverse event, the investigator must notify the sponsor without delay on the day the investigator becomes aware of the exposure while breastfeeding.

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

These serious adverse events are only recorded in the case report forms.

- *Normal and natural course of the condition*:
- planned hospitalisation for monitoring the condition under investigation [no deterioration in the participant's condition compared to baseline],
- hospitalisation for routine treatment or for monitoring of the condition under investigation, not associated with a deterioration in the participant's condition,
- emergency hospitalisation at inclusion or prolongation of hospitalisation after inclusion for monitoring the condition under investigation

- *Special circumstances*
- 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

- *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).

9.1.2.3 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 signs the consent form
- throughout the whole follow-up period required for the trial (30 weeks)
- until 7 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 long after exposure to the medication, such as cancers or congenital abnormalities)

9.1.2.4 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.

9.1.3 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.

9.1.3.1 Analysis and declaration of serious adverse events

The sponsor assesses:

- the **seriousness** of all the adverse events reported
- the **causal relationship** between these events and each investigational medicinal product 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 **expected or unexpected nature** 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 expected/unexpected nature of a 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 investigator brochure for **"Isatuximab"**

❖ For serious adverse events that may be related to the additional medicinal product(s):

- refer to the SmPC for the brand name of **Dexamethasone; Acetaminophen (or equivalent); Diphenhydramine (or equivalent); Montelukast (or equivalent).**

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs), within the regulatory time frame, to the ANSM:

- The sponsor must send the initial report without delay upon learning of the unexpected serious adverse reaction if is fatal or life-threatening, or otherwise within 15 days from learning 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 research participants.

9.1.3.2 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.

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.

9.1.3.3 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 DSMB

The Data and Safety Monitoring Board (DSMB) will be established by the sponsor. Its primary mission is to serve as a committee for monitoring safety data. It can have other missions, such as monitoring efficacy data (especially if the protocol includes interim analyses). The DSMB is mentioned in Article L. 1123-7 of the French Public Health Code.
The sponsor is responsible for justifying the creation or absence of a supervisory committee to the Competent Authority (ANSM) and to the CPP.
A DSMB will be convened for this biomedical research and composed with:

- Dr Salim Trad, internal medicine, Ambroise Paré hospital
- Pr. Vincent Levy, hematology, Avicenne Hospital
- Pr. Bertrand Wechsler, internal medicine, 22 Rue Duret, 75016 Paris.

The DSMB will hold its preliminary meeting before the first inclusion of the first subject. All missions as well as the precise operating methods of the DSMB are described in the charter for the research's DSMB.

General information about the DSMB

The DSMB makes recommendations to the sponsor about the continuation, modification or termination of the research. The recommendations that the DSMB can make are:

- to continue the research with no modifications

- to continue the research with a modification to the protocol and/or to the monitoring of subjects
- to temporarily halt inclusions
- to permanently terminate the research in light of:
    - safety data: serious adverse reactions
    - efficacy data: proven futility or efficacy

The DSMB is appointed by the sponsor and is made up of at least 3 people with no connection to the research, including at least one clinician specialising in the pathology being studied and one specialist in the medication being studied (or a pharmacologist/pharmacovigilance specialist), and possibly a methodologist/biostatistician, particularly in the case of interim analysis.

The DSMB has a consultative role in advising the sponsor on safety issues such as tolerance and re-assessment of the benefit-risk ratio during the research.

The DSMB must hold its preliminary meeting before the first inclusions of the first subject and ideally before the protocol is submitted to the competent authority and the CPP. The committee's agenda will be as follows:

Definition of the DSMB's missions:

- Validation of the research methodology: The proposed methodology for the clinical trial will be validated by the DSMB so that it does not jeopardise the safety of subjects, in particular relating to the inclusion and randomisation methods.
- Validation of tolerance monitoring methods:
    - nature of the evaluated parameters
    - frequency of the evaluations, consultation schedule
- Validation of termination criteria:
    - criteria for terminating a subject's participation for tolerance reasons
    - criteria for the temporary or permanent termination of the research (leading to the establishment of certain recommendations ("stopping rules"))
- Modification of the protocol and recommendations:
    - In light of the interim analyses of the primary enpoint if one arm seems to be clearly in defavour of patients
    - In light of the analysis of tolerance data for the research, the DSMB can, when applicable: propose substantial modifications in order to modify certain data, in particular relating to the protocol (inclusion and non-inclusion criteria, monitoring, additional exams, etc.). Likewise, the DSMB can issue any recommendations it deems useful in order to best ensure the safety of the research subjects and to maintain a favourable benefit-risk balance throughout the research.

Definition of the DSMB's operating methods:

Meetings modalities (open session, then closed sessions) and frequency will be detailed in the DSMB charter at the latest before inclusion of the first patient,

Modalities and format expected for the transmission of SAE from the sponsor to the DSMB will be detailed in the DSMB charter at the latest before inclusion of the first patient,

The sponsor retains decision-making authority. The sponsor delivers its decision, with justification, and DSMB reports to the Competent Authority (ANSM) and when applicable to the CPP.

11 DATA MANAGEMENT

11.1 Data collection procedures

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

11.1.1.1 Right to access data and source documents

11.1.1.2 Data access

In accordance with GCPs:

- 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)

11.1.1.3 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.

The correspondence table is in the investigator's binder of the participating centre. It is the responsibility of the principal investigator. This table is accessible only to centre staff and authorised sponsor staff. It is only stored at the participating centre level by the principal investigator.

11.1.2 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.
The correspondence table between the identity of the person and the code or order number is a separate database benefiting from the same protection measures as the database containing the indirectly identifying personal health data.
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.

11.2 Data processing and storage of research documents and data

11.2.1 Identification of the data processing manager and 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 Dr Mathieu Resche-Rigon, Saint Louis hospital, Paris.

11.2.2 Data entry

e-CRF example: Non-identifying data will be entered electronically via a web browser.

11.2.3 Data processing (CNIL, the French Data Protection Authority) in France

This research falls under the "Méthodologie de référence" (MR-001) according to the provisions of Article 54, paragraph 5 of modified Law No. 78-17 of 6 January 1978 relating to information technology, data files and privacy. This change was approved in a decision made

on 5 January 2006. AP-HP, the research sponsor, has signed a commitment to comply with this “Méthodologie de reference”.

11.2.4 Archiving

Specific documents for biomedical research relating to a medication for human use will be archived by the investigator and the sponsor for a period of 15 years after the end of the research.

This indexed archival includes, in particular:

- A sealed envelope containing the original copies of all information sheets and consent forms signed for all individuals at the centre that participated in the research for the investigator
- A copy of all the information notes and consent forms signed for all subjects at the centre that participated in the research for the sponsor
- "Research" binders for the Investigator and the sponsor, including:
    - the successive versions of the protocol (identified by the version no. and date), and the appendices
    - the ANSM authorisations and CPP favourable opinions
    - letters of correspondence
    - the inclusion list or register
    - the appendices specific to the research
    - the final research report
- The data collection documents

Data will only be kept for a period strictly necessary and proportionate to the purpose of the research. It will be kept in the information systems of the controller for up to two years after the last publication of the research results.

Beyond the authorised retention period, the research data are archived on paper or computer for a period of time in accordance with the regulations in force.

11.3 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 Description of statistical methods to be used including the timetable for the planned interim analyses

This is a Phase 2 pilot prospective study of 21 patients with type I cryoglobulinemia treated by Isatuximab. Isatuximab will be perform intravenously at 10mg/kg at day 0, week (W)1, W2,

W3, and W4 then every 2 weeks for a total of 12 infusions. We used the one-sample multiple testing procedure for Phase II clinical trials Report Definitions (Fleming, T. R. 1982; Biometrics, Volume 38, pages 143-151) to calculate the sample size.

Report Definitions

P0 is the maximum response proportion of a poor drug.

P1 is the minimum response proportion of a good drug.

N is the sample size.

If the number of responses ≥ R+1, P0 is rejected.

If the number of responses ≤ R, P1 is rejected.

Alpha is the probability of rejecting that P ≤ P0 when this is true.

Beta is the probability of rejecting that P ≥ P1 when this is true.

Summary Statements

The ICE study requires 21 subjects to decide whether the proportion responding, P, is less than or equal to 0,400 or greater than or equal to 0,700. If the number of responses is 13 or more, the hypothesis that P ≤ 0,400 is rejected with a target error rate of 0,050 and an actual error rate of 0,035. If the number of responses is 12 or less, the hypothesis that P ≥ 0,700 is rejected with a target error rate of 0,150 and an actual error rate of 0,148.

Statistical analysis

This is a pilot prospective Phase II clinical trial that aims at evaluating safety and efficacy of Isatuximab in type 1 cryoglobulinemia vasculitis. We hypothesize that up to 70% of the patients receiving Isatuximab will achieve a complete remission of cryoglobulinemia vasculitis at week 20 (W20). Continuous variables (cf variables described in primary and secondary objectives) will be presented with the median and IQR or with the mean ± SEM. Categorical variables will be presented with counts and proportions. Statistical comparisons will be performed by using the Mann-Whitney test for quantitative unpaired data, t-test for quantitative paired data, Kruskal-Wallis for multiple comparisons, Spearman correlation test for correlations. T-test for quantitative paired data analysis will be used to compare immunological changes between day 0 and week 12 and 20 after Isatuximab. All statistical tests will be two-tailed with a significance level of 0.05.

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 centre 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-DRC from Saint Louis hospital.

13.1.2 Scope of centre monitoring

In the case of this research, which is considered level D risk, the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the research. Thus, the sponsor and the coordinating investigator have agreed on the logistic score and impact, resulting in a research monitoring level to be implemented: High level.

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 forms

Electronic CRF:

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.

Access to clean web (e-CRF) is nominative and personalised. Authorized persons (with valid CV, GCP and FDF) are identified in a table and receive their personnel access codes by email.

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 research participants and obtaining their consent

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.

The subject (*i.e. an adult person capable of giving consent*) will be informed of the trial by the investigator during a routine consultation session of his cryoglobulinemic vasculitis. The information sheet of the protocol will be given to the subject after an oral explanation.

The person will be given a reflexion time between receiving the information and being asked to sign the consent form.

The person's free and informed written consent will be obtained by the investigator, or by a doctor representing the investigator, before the person is enrolled on the trial at the inclusion visit V0.

The information sheet and a copy of the consent form, signed and dated by the research subject and by the investigator or the doctor representing the investigator, will be sent to the individual prior to being enrolled on the trial.

In addition, the investigator will specify in the research participant's medical file the methods used for obtaining their consent as well as the methods used for providing information with a view to obtaining consent. The investigator will retain the original signed and dated consent form.

Special circumstances: Mention of the possibility for the investigator of withholding certain information relating to the diagnosis, as applicable, in accordance with paragraph 4 of Article L1122-1

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

An exclusion period of 1.5 months will apply after the subject has finished this trial.

Whilst participating in this trial, subjects may not take part in any other clinical study without first speaking to the doctor in charge of this trial.

The participants can however participate in other non-interventional studies

14.3 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

In accordance with Article L.1121-16 of the Code de la Santé Publique (French the Public Health Code), registration is required:

- for healthy persons who volunteer to participate in a study;
- for patients who participate in a study unrelated to their illness or condition;
- in certain cases at the request of the CPP (Research Ethics Committee);

State whether participants in this research will be registered. [Provide justification].

14.4 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.

14.5 Legal obligations

14.5.1 Role of the sponsor

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.

14.5.2 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.

14.5.3 Request for authorisation from 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 product for human use, within the scope of the ANSM's authority and in accordance with in force legislation and regulatory requirements.

14.5.4 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.

Choose one of the two options proposed (A or B), with the pre-drafted text and delete the option not retained. Only to be completed relative to reasons for exclusion from the MR (Reference Methodology).

- Commitment to comply with "Reference Methodology" MR-001

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" Adapt based on the *internal procedures of the entity managing the data.*

14.5.5 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.

14.5.6 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.

14.5.7 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 *state the period based on the type of data (the storage time will depend on the type of research)* 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

14.6 Compensation for participants

Travelling costs might be reimbursed for the visits (D0 to W48) with a maximum amount of 150 € per visit, for patients residing more than 300 km away from the recruiting site.

15 FUNDING AND INSURANCE

15.1 Funding sources

Sanofi will provide Isatuximab and 350000 euros for the research.

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 RULES

The author(s) of any publication relating to this study must include the AP-HP among their affiliations and must 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 of the sponsor and funders).

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

- If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is unimportant
- However, if the study is funded in the context of an internal AP-HP call for tender, 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 (Délégation à la Recherche Clinique et à l’Innovation)”

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

- “The study was funded by a grant from Sanofi Genzyme (ISS)”

This study has been registered on the website http://clinicaltrials.gov/ under number: NCT05114109

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18 LIST OF ADDENDA

18.1 List of investigators

N° centres	service	Service	First name Surname	Telephone/E-mail/Fax	Ville
001	AP-HP - Pitie Salpetrière hospital	Internal medicine	David Saadoun	David.saadoun@aphp.fr	75013 PARIS
002	AP-HP - Saint Louis hospital	Hematology	Bertrand Arnulf	Bertrand.arnulf@aphp.fr	75010 PARIS
003	AP-HP - Saint Antoine hospital	Internal medicine	Arsene Mekinian	Arsene.mekinian@aphp.fr	75012 PARIS
004	AP-HP – Necker hospital	Hematology	Olivier Hermine	ohermine@gmail.com	75015 PARIS
005	AP-HP - HEGP Paris	Nephrology	Alexandre Karras	alexandre.karras@aphp.fr	75015 PARIS
006	AP-HP - Tenon hospital	Nephrology	Jean Jacques Boffa	jean-jacques.boffa@aphp.fr	75020 PARIS
007	AP-HP - CHU H Mondor creteil	Internal medicine	Nicolas Limal	Nicolas.limal@aphp.fr	94000 CRETEIL
008	AP-HP - CHU Bicêtre	Internal medicine	Nicolas Noel	Nicolas.noel@aphp.fr	94270 KREMLIN BICETRE
009	CH Avignon	Nephrology	David VERHELST	DVerhelst@ch-avignon.fr	Avignon
010	CHU Bordeaux GH Sud - Hôpital Haut Lévêque	Internal medicine	Estibaliz Lazaro	estibaliz.lazaro@chu-bordeaux.fr	Bordeaux
011	CHU Dijon	Internal medicine	Bonnotte Bernard	bernard.bonnotte@chu-dijon.fr	Dijon
012	CHU Poitiers	Nephrology	Vincent Javaugue	Vincent.JAVAUGUE@chu-poitiers.fr	Poitiers
013	CHU Bordeaux – Hôpital Saint-André	Internal medicine	Fabrice Bonnet	Fabrice.bonnet@chu-bordeaux.fr	Bordeaux
014	CHU Rouen	Internal medicine	Mathilde Leclercq	mat3leclercq@gmail.com	Rouen
015	CHU Estaign	Rhumatology	Marc Ruivard	mruivard@chu-clermontferrand.fr	Clermont-Ferrand
016	CHU Toulouse	Nephrology and clinical Immunology	Stanislas Faguer	stanislas.faguer@inserm.fr	Toulouse
017	CH Valenciennes	Nephrology	Thomas Quemeneur	quemeneur-t@ch-valenciennes.fr	Valenciennes

18.2 Questionnaire or scale

Annexe 1 : SF36

Questionnaire de santé SF-36

1. **Dans l'ensemble, pensez-vous que votre santé est** : (entourez la bonne réponse)

Excellente	1
Très bonne	2
Bonne	3
Médiocre	4
Mauvaise	5

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

Bien meilleur que l'an dernier	1
Plutôt meilleur	2
A peu près pareil	3
Plutôt moins bon	4
Beaucoup moins bon	5

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 limit(é) en raison de votre état de santé actuel.** (Entourez la réponse de 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	1	2	3
b. Efforts physiques modérés tels que déplacer une table, passer l'aspirateur, jouer aux boules	1	2	3
c. Soulever et porter des courses	1	2	3
d. Monter plusieurs étages par l'escalier	1	2	3
e. Monter un étage par escalier	1	2	3
f. se pencher en avant, se mettre à genoux, s'accroupir	1	2	3
g. Marcher plus d'un km à pied	1	2	3
h. Marcher plusieurs centaines de mètres	1	2	3
i. Marcher une centaine de mètres	1	2	3
j. Prendre un bain, une douche ou s'habiller	1	2	3

4. **Au cours de ces 4 dernières semaines, et en raison de votre état physique**
(Entourez la réponse de votre choix, une par ligne)

	Oui	Non
a. Avez-vous réduit le temps passé à votre travail ou à vos activités habituelles	1	2
b. Avez-vous accompli moins de choses que vous auriez souhaité ?	1	2
c. Avez-vous du arrêter de faire certaines choses ?	1	2
d. Avez-vous eu des difficultés à faire votre travail ou toute autre activité ? (par exemple, cela vous a demandé un effort supplémentaire)	1	2

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

	Oui	Non
a. Avez-vous réduit le temps passé à votre travail ou à vos activités habituelles	1	2
b. Avez-vous accompli moins de choses que vous auriez souhaité ?	1	2
c Avez-vous eu des difficultés à faire ce que vous aviez à faire avec autant de soin et d'attention que d'habitude ?	1	2

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

Pas du tout	1
Un petit peu	2
Moyennement	3
Beaucoup	4
Enormément	5

7. **Au cours de ces 4 dernières semaines, quelle a été l'intensité de vos douleurs (physiques) ?** (Entourez la réponse de votre choix)

Nulle	1
Très faible	2
Faible	3
Moyenne	4
Grande	5
Très grande	6

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 ?** (Entourez la réponse de votre choix)

Pas du tout	1
Un petit peu	2
Moyennement	3
Beaucoup	4
Enormément	5

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 :**
(Entourez la réponse de votre choix, une par ligne)

Liste d'activités	En permanence	Très souvent	Souvent	Quelques fois	Rarement	Jamais
a. vous vous êtes senti(e) dynamique ?	1	2	3	4	5	6
b. vous vous êtes senti(e) très nerveux(se) ?	1	2	3	4	5	6
c. Vous vous êtes senti(e) si découragé(e) que rien ne pouvait vous remonter le moral	1	2	3	4	5	6
d. vous vous êtes senti(e) calme et détendu(e) ?	1	2	3	4	5	6
e. vous vous êtes senti(e) débordant(e) d'énergie?	1	2	3	4	5	6
f. vous vous êtes senti(e) triste et abattu(e) ?	1	2	3	4	5	6
g. vous vous êtes senti(e) épuisé(e) ?	1	2	3	4	5	
h. vous vous êtes senti(e) heureux(e)	1	2	3	4	5	6
i. vous vous êtes senti(e) fatigué(e) ?	1	2	3	4	5	6

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

En permanence	1
Une bonne partie du temps	2
De temps en temps	3
Rarement	4
Jamais	5

11. **Indiquez pour chacune des phrases suivantes dans quelle mesure elles sont vraies ou fausses dans votre cas :**
(Entourez la réponse de votre choix, une par ligne)

Liste d'activités	Totalement vrai	Plutôt vrai	Je ne sais pas	Plutôt fausse	Totalement fausse
a. je tombe malade plus facilement que les autres	1	2	3	4	5
b. je me porte aussi bien que n'importe qui	1	2	3	4	5
c. je m'attends à ce que ma santé se dégrade	1	2	3	4	5
d. je suis en excellent santé	1	2	3	4	5

→ **Score (0 à 100) : l__l__l__l**

Annexe 2 : BVAS

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)	◘ 6 / 2 ◘
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)

18.3 Common Terminology Criteria for Adverse Events [National Cancer Institute]

Document available at

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf