Evaluation of Rituximab-based Regimen Compared to Conventional Therapeutic Strategy For Remission Induction In Patients With Newly-Diagnosed or Relapsing Eosinophilic Granulomatosis With Polyangiitis: Prospective, randomized, controlled, double-blind study

REOVAS study

BIOMEDICAL RESEARCH PROTOCOL RELATING TO A MEDICINAL PRODUCT FOR HUMAN USE

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The research will be carried out in accordance with the protocol, with current good practices and with
the legislative and regulatory provisions in force.

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The research received a favourable opinion from the CCP Ile de France III on 20/09/2016 and authorisation from the ANSM on 21/11/2016.

CONTENTS

ABREVIATIONS

AAV: ANCA-associated Vasculitis

ACR: American College of Rheumatology

ANCA: Anti-Neutrophil Cytoplasmic Antibody

ANSM: Agence Nationale de Sécurité du Médicament

BVAS: Birmingham Vasculitis Activity Score

CPP: Comité de Protection des personnes

CTCAE: Common Terminology Criteria for Adverse Events

EGPA: Eosinophilic Granulomatosis with PolyAngiïtis

ENT: Ear, nose and throat

FFS: Five Factor Score

FVSG: French Vasculitis Study Group

GPA: Granulomatosis with PolyAngiitis

HAQ: Health Assessment Questionnaire

MPA: Microscopic PolyAngiitis

MPO: Myeloperoxidase

PR3: Proteinase 3

SF-36 : Short-Form 36

VDI : Vasculitis Damage Index

1. SUMMARY

Full title	Evaluation of Rituximab-based Regimen Compared to Conventional Therapeutic Strategy For Remission Induction In Patients With Newly-Diagnosed or Relapsing Eosinophilic Granulomatosis With Polyangiitis. Prospective, randomized, controlled, double-blind study.
Acronym	REOVAS
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Sponsor	Assistance Publique – Hôpitaux de Paris (AP-HP)
Scientific justification	Systemic vasculitides are inflammatory diseases of blood vessels, among which anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are often severe with life-threatening manifestations or complications. AAV include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome). Cytotoxic drugs and glucocorticoids have been the standard of care for remission induction for nearly five decades. This regimen improved the outcome of severe AAV from death to a strong likelihood of disease control and temporary remission. However, a remission is not obtained in all patients with this combination of drugs, and most patients experience disease flares requiring repeated treatment with associated significant morbidity and mortality. In 2 prospective controlled trials, rituximab, an anti-CD20 monoclonal antibody, was shown to be non inferior to cyclophosphamide to induce remission with an acceptable safety profile in patients with systemic GPA and MPA. However, patients with EGPA were not included in these trials and rituximab has not been evaluated prospectively to induce remission in this disease which pathogenesis is complex and not only restricted to ANCA responsibility. In patients with EGPA, overall survival is good when treatment is stratified according to prognostic factors (Five Factor Score) but long-term outcome is not so good since relapses occur in more than 40% of patients, leading to high cumulative morbidity and damage. In small retrospective studies, rituximab seems promising as a remission-induction agent in patients with EGPA, independently from the ANCA status. The trial detailed here is the first prospective trial evaluating rituximab as induction-remission treatment for EGPA.

Primary objective and assessment criterion	<u>Primary objective</u> To determine the efficacy of rituximab and glucocorticoids to induce a complete remission, defined as a Birminghman Vasculitis Activity Score (BVAS) of 0 and a prednisone dose ≤7.5 mg/day at day 180, in patients with newly-diagnosed or relapsing EGPA. <u>Primary assessment criterion</u> The percentage of patients who obtained a BVAS=0 and prednisone dose ≤7.5 mg/day at day 180. *Remission will be defined as the absence of disease activity attributable to EGPA vasculitis manifestations (parenchymal lung disease, peripheral nerve involvement, skin, cardiac, renal and/or gastrointestinal signs), corresponding to BVAS=0, with a prednisone dose ≤7.5 mg/day.*
Secondary objectives and assessment criteria	<u>Secondary objectives</u> - To compare the safety profile of rituximab and conventional treatment at days 180 and 360 - To measure the corticosteroid dose at days 180 and 360 and to compare the corticosteroid sparing effect of rituximab versus conventional therapy - To compare sequelae assessed by the Vasculitis Damage Index at days 180 and 360 in both arms - To compare functional disability and quality of life at 180 days and 360 after randomization in both arms - To compare the evolution of ANCA titers and CD19+ cells in the two treatment groups, and to assess its correlation with clinical events during follow-up <u>Secondary assessment criteria</u> - The number of adverse events, expressed as adverse events according to the CTCAE toxicity grading system per patient-year at days 180 and 360 for the following adverse events combined: death (all causes), grade 2 or higher leukopenia or thrombocytopenia, grade 3 or higher infections, hemorraghic cystitis, malignancies, venous thromboembolic events, hospitalization resulting either from the disease or from a complication due to the study treatment, infusion reactions (within 24 hours of infusion) that result in the cessation of further infusions - The area under the curve for corticosteroids at days 180 and 360 in the two treatment groups - The Vasculitis Damage Index at days 180 and 360 in the two treatment groups - The HAQ and SF-36 at days 180 and 360 in the two treatment groups - Evolution of ANCA titers and CD19+ cells in the two treatment groups, and correlation with clinical events during follow-up

Experimental design	Phase III, comparative, multicenter, randomized, controlled, double-blind and superiority research, comparing rituximab-based regimen with conventional therapeutic strategy for the induction of remission in patients with EGPA. Patients with newly diagnosed or relapsing EGPA will be randomized in a 1:1 ratio to receive: - Experimental therapeutic strategy based on the use of rituximab (experimental group) - Conventional therapeutic strategy based on Five-Factor Score (FFS)-assessed disease severity (comparative group)
Population involved	Patients with a diagnosis of EGPA with newly-diagnosed disease or with a relapsing disease at the time of screening.
Inclusion criteria	- Patients with a diagnosis of EGPA independently of ANCA status, - Patient aged of 18 years or older, - Patients with newly-diagnosed disease or relapsing disease at the time of screening, with an active disease defined as a Birmingham Vasculitis Activity Score (BVAS) ≥3, - Patients within the first 21 days following initiation/increase of corticosteroids at a dose ≤ 1 mg/kg/day (pulses of methylprednisolone before oral corticosteroid therapy are authorized) - Patient able to give written informed consent prior to participation in the study. - Affiliation with a mode of social security (profit or being entitled)
Non-inclusion criteria	- Patients with GPA, MPA, or other vasculitis , defined by the ACR criteria and/or the Chapel Hill Consensus Conference, - Patients with vasculitis in remission of the disease defined as a BVAS <3, - Patients with severe cardiac failure defined as class IV in New York Heart Association - Patients with acute infections or chronic active infections (including HIV, HBV or HCV), - Patients with active cancer or recent cancer (<5 years), except basocellular carcinoma and prostatic cancer of low activity controlled by hormonal treatment, - Pregnant women and lactation. Patients with childbearing potential should have reliable contraception for the 12 months duration of the study, - Patients with EGPA who have already been treated with rituximab within the previous 12 months, - Patients with hypersensitivity to a monoclonal antibody or biologic agent, - Patients with contraindication to use rituximab, cyclophosphamide, mesna or azathioprine, - Patients with other uncontrolled diseases, including drug or alcohol abuse, severe psychiatric diseases, that could interfere with participation in the trial according to the protocol, - Patients included in other investigational therapeutic study within the previous 3 months, - Patients suspected not to be observant to the proposed treatments, - Patients who have white blood cell count ≤4,000/mm^3,

	- Patients who have platelet count ≤100,000/mm^3, - Patients who have ALT or AST level greater that 3 times the upper limit of normal that cannot be attributed to underlying EGPA disease, - Patients unable to give written informed consent prior to participation in the study.
Experimental arm	Rituximab All patients in the rituximab group will receive corticosteroids with a predefined tapering schedule similar to the conventional therapy group, in combination with 1 gram of rituximab at day 1 and day 15 as induction treatment. ***Patients with FFS=0*** will not receive neither placebo-cyclophosphamide nor maintenance therapy according to the standard of care of these patients, as recommended by the French Vasculitis Study Group. ***Patients with FFS≥1*** will receive placebo-cyclophosphamide at days 29, 50, 71, 92, 113, 134 and 155. Maintenance therapy by azathioprine will be started at day 180 according to the standard of care of these patients, as recommended by the French Vasculitis Study Group.
Control group	Conventional therapy based on FFS-assessed disease severity. All patients will receive corticosteroids with a predefined tapering schedule similar to the experimental group. ***Patients with FFS=0*** will receive placebo-rituximab at day 1 and day 15. Neither cyclophosphamide nor maintenance therapy will be administered according to the standard of care of these patients, as recommended by the French Vasculitis Study Group. ***Patients with FFS≥1*** will receive intravenous pulses of cyclophosphamide for a total of 9 pulses: 600 mg/m^2 at days 1, 15 and 29, and then 500 mg-fixed dose at days 50, 71, 92, 113, 134 and 155. Maintenance therapy by azathioprine will be started at day 180 according to the standard of care of these patients, as recommended by the French Vasculitis Study Group.
Other procedures added by the research	The two treatment groups will receive the same glucocorticoid regimen: three pulses of methylprednisolone (7.5 to 15 mg/kg each), followed by a predefined prednisone tapering schedule that will be similar in patients with FFS=0 and those with FFS≥1. Patients receiving rituximab or placebo-rituximab will receive premedication including 100 mg of methylprednisolone, paracetamol and dexchlorpheniramine. Prednisone dose will be initiated at 1 mg/kg/day (maximum dose 80 mg/day) for 3 weeks. The prednisone dose will be tapered, starting at week 3, using a predefined algorithm based on clinical and biological manifestations of EGPA activity. Prednisone dose will be tapered every week in the absence of clinical and biological manifestations of EGPA activity to the following levels: 40 mg, 35 mg, 30 mg, 25 mg, 20 mg, 17.5 mg, 15 mg, 12.5 mg and 10 mg. Prednisone dose will then be decreased of 1 mg every 3 weeks in the absence of clinical and biological manifestations of EGPA activity until discontinuation.

Risks added by the research	Risk C
Number of patients	108 patients Based on the results of previous trials from the French Vasculitis Study Group (FVSG), the proportion of patients with BVAS=0 and prednisone dose ≤7.5 mg/day at day 180 can be estimated at 60% in patients with EGPA. The primary hypothesis of the REOVAS trial is an increase of at least 25% of the proportion of patients with BVAS=0 and prednisone dose ≤7.5 mg/day at day 180, i.e. 85%. Based on this hypothesis, using a bilateral test, with a significance level of 5%, a beta level of 80%, 98 patients must be included, 49 patients in each arm. Taking into account 10% of patients lost to follow-up, 108 patients must be included, 54 in each arm.
Number of centres	National research with participation of the French Vasculitis Study Group (FVSG) network, including about fifty centers
Research period	Recruitment period : 24 months Study participation for each patient: 360 days (12 months) Total duration : 36 months
Number of inclusions expected per centre and per month	0,1 patients/month/centre in each center
Statistical analysis	Statistical analyses will be performed in the Clinical Research Unit and supervised by Dr Hendy Abdoul. Patients will be stratified with a covariate-adaptative randomization according to: - Newly diagnosed vs. relapsing EGPA - Vasculitis severity (FFS=0 vs. FFS ≥1) - ELISA ANCA status (anti-MPO or -PR3 positive vs. negative)

2. SCIENTIFIC JUSTIFICATION FOR THE RESEARCH

Hypothesis for the research

The REOVAS study aims to evaluate rituximab for induction-remission of eosinophilic granulomatosis with polyangiitis (EGPA) with the objective to obtain higher rates of complete remission at day 180 compared to conventional therapeutic strategy.

Description of knowledge relating to eosinophilic granulomatosis with polyangiitis

2.1.1 ANCA-associated vasculitides

Systemic vasculitides are inflammatory diseases of blood vessels, among which anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are the most severe diseases with life-threatening manifestations or complications.
AAV include granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome). They are classified as AAV because most patients with generalized disease have antibodies against proteinase 3 (PR3) or myeloperoxidase (MPO) ANCA. AAV affect small-to-medium-size blood vessels, with a predilection for the respiratory tract and kidneys.

2.1.2 Eosinophilic granulomatosis with polyangiitis

Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic small- and medium-sized-vessel vasculitis which is characterized by the presence of severe asthma, and blood and tissue eosinophilia.
EGPA was first described in 1951 by Jacob Churg and Lotte Strauss [1] and was initially called allergic angiitis and granulomatosis. Thus, histological findings in these very first patients included necrotizing vasculitis, eosinophilic infiltrates in tissues and granulomas. Since it is rare to identify the three lesions in the same patient, the diagnosis of EGPA mainly relies on clinical parameters.

A clinical definition of EGPA, established in 1984 by Lanham et al. [2], has allowed clinicians

to diagnose EGPA with good specificity and sensitivity without relying on histological findings. The three diagnostic criteria are asthma, blood eosinophilia exceeding 1500/mm^3, and evidence of vasculitis involving two or more organs.
Other criteria have been proposed, especially for classification purposes, notably the American College of Rheumatology criteria in which 4 out of 6 criteria should be present [3].

Table 1. American College of Rheumatology criteria for Churg-Strauss syndrome

Asthma
Eosinophilia > 10% of leukocytes
History of allergy
Pulmonary infiltrates, non fixed
Paranasal sinus abnormalities
Extravascular eosinophils

More recently, because the evidence of vasculitis is frequently lacking, expert consensus on the topic developed new diagnostic criteria, which are currently used in an international therapeutic study evaluating mepolizumab in EGPA. These criteria include a history or presence of asthma plus eosinophilia (>$1.0x10^9$/L and/or >10% of leukocytes), plus at least two the following additional features of EGPA:

- Biopsy showing histopathological evidence of eosinophilic vasculitis, or perivascular eosinophilic infiltration, or eosinophil-rich granulomatous inflammation,
- Neuropathy, mononeuropathy, multiple mononeuropathy or polyneuropathy,
- Pulmonary infiltrates, non-fixed,
- Sino-nasal abnormality,
- Cardiomyopathy (established by echocardiography or MRI),
- glomerulonephritis (haematuria, red cells casts, proteinuria),
- alveolar haemorrhage (established by bronchoalveolar lavage or CT-scan),
- palpable purpura,
- ANCA positive (MPO or PR3).

At EGPA onset, the most frequent manifestations are mononeuritis multiplex, purpura, general symptoms and eosinophilia, occurring in a previously asthmatic patient. However, some patients may develop asthma or eosinophilia simultaneously with vasculitis and sometimes although rarely, in the weeks following its onset [4]. In two recent series, a minority (less than 10%) of patients do not present asthma at disease onset [5,6]. Another feature of EGPA is its association with ANCA in around 30% of the patients [5-8]. The clinical presentation of these ANCA-positive patients differs significantly from that of ANCA-negative

patients, with more frequent mononeuritis multiplex and glomerulonephritis in the former, and more cardiomyopathy in the latter [5,7,8].
EGPA is a rare disease. Its prevalence, in the general population, ranges from 10.7 to 13 cases/million inhabitants [9], with an annual incidence of 5 new cases/million inhabitants [10], depending on their geographical location and the classification criteria applied, without clear sex predominance.

Blood hypereosinophilia and anti-MPO ANCA–positivity are the two main laboratory anomalies which can be present. Eosinophilia fluctuates but is a constant finding. An eosinophil count exceeding 10% of the total white blood cell count has been retained as one of the diagnostic criteria for EGPA [2]. Its mean value ranges from 4400 to 8190, but eosinophils may disappear rapidly after corticosteroids are started.
ANCA, predominantly perinuclear ANCA of anti-MPO specificity, are present in close to 30% of EGPA patients but some can have anti-PR3 specificity. ANCA titers do not correlate with disease-evolution characteristics. Rheumatoid factor was reported for 22 of the 41 (53.6%) published cases [2].

2.1.3 Treatment and prognosis of eosinophilic granulomatosis with polyangiitis

EGPA prognosis is usually good, even though historically, before corticosteroids were available, most patients died. EGPA prognosis has been revolutionized by the use of corticosteroids and immunosuppressant(s) [11]. Whereas in 1950, the 5-year patient survival of polyarteritis nodosa (not yet separated from EGPA) was 10%, today, the overall 5-year survival of EGPA may reach 97% [12]. However, not all EGPA patients share the same prognosis, as it depends on the initial degree of disease extension and organ(s) involvement.
The original, prognostic Five-Factor Score (FFS) [13] was obtained by univariate and multivariate analyses of 342 vasculitis patients, including 82 with EGPA. The five factors (each accorded 1 point) conferring a higher risk of mortality rate were: 1) proteinuria > 1 g/24 h; 2) serum creatinine level > 140 µmol/l; 3) myocardial involvement; 4) severe gastrointestinal involvement; and 5) central nervous system involvement. The FFS helps identify which patients who, because of their higher risks of mortality, require more aggressive immunosuppressive treatment. When FFS = 0 (none of the 5 prognostic factors present), mortality at 5 years was 11.9%; when FFS = 1 (1 of the 5 factors present), mortality was 25.9% ($p < 0.005$); when FFS > 2 (3 or more of the 5 factors present), mortality was 45.95% ($p < 0.0001$ between 0 and 2, $p < 0.05$ between 1 and 2). Our group concluded that such an initial assessment of EGPA severity enables outcome and mortality to be predicted.

The FFS was then a good predictor of death and can be used to help the clinician choose the most adequate treatment (**Table 2**). In a prolonged follow-up of the EGPA patients included in the CHUSPAN trial, the overall survival was very good, reaching 89.7% at 5 years and 85.9% at 7 years, whatever the severity at baseline, validating the actual therapeutic strategy based on the FFS [11].

A revised version of the FFS 1996 was published and included patients with GPA [14]. The following factors were significantly associated with higher 5-year mortality: age >65 years, cardiac symptoms, gastrointestinal involvement, and renal insufficiency (stabilized peak creatinine ≥150 µmol/L). All were disease-specific; the presence of each was accorded +1 point. ENT symptoms, affecting patients with GPA and EGPA, were associated with a lower relative risk of death, and their absence was scored +1 point ($p < 0.001$). Only renal insufficiency was retained (not proteinuria or microscopic hematuria) as impinging on outcome.
However, in the present trial, our strategy was based on the FFS 1996 since only this version was prospectively validated in therapeutic trials, in particular in EGPA.

Along this line, in 2014, conventional therapeutic strategy in EGPA is stratified according to the FFS and is based on corticosteroids and/or immunosuppressive agents. Patients with FFS=0 are treated with corticosteroids alone for a duration ranging from 12 to 18 months. Patients with FFS≥1 are treated with corticosteroids associated with cyclophosphamide for 6 to 9 pulses then switch to maintenance with azathioprine (2 mg/kg/day) or methotrexate (10-30 mg/week). Although this regimen transformed the outcome of severe disease from death to a strong likelihood of disease control and temporary remission, not all patients have a remission with this combination of drugs, and most patients have disease flares that require repeated treatment. Long-term outcome is not so good since relapses occur in more than 40% of patients, leading to high cumulative morbidity and damage. Moreover, cumulative side effects of immunosuppressive agents as well as adverse effects of glucocorticoids are major causes of long-term disease, sequelae and death.

Table 2. The Five Factor Score (FFS), as established based on 342 patients with PAN or EGPA and further validated for patients with MPA.

Proteinuria > 1 g/24 h
Creatininemia > 140 µmol/L
Specific gastrointestinal involvement
Specific cardiomyopathy
Specific central nervous system involvement

1 point accorded for each of these 5 items when present

FFS	5 year survival rate (%)	Relative Risk
0	88.1	0.62
1	74.1*	1.35
≥ 2	54.1**	2.40

*P<0.005 and **P<0.0001 as compared to patients with FFS=0.

2.1.4 The potential role of B cells in eosinophilic granulomatosis with polyangiitis

EGPA etiology remains unknown. Its pathogenesis, based on clinical observations, has long been thought to develop through three successive phases: asthma, blood and tissue eosinophilia, and, finally, vasculitis. However, not all patients experience this clear-cut stepwise progression of their disease, and symptoms of the different phases may overlap.
Because asthma is most often the first symptom of EGPA, it has been hypothesized that the triggering pathogenic event might be an inflammatory response to inhaled antigens. Furthermore, the discovery that patients with EGPA flares often had increased levels of total serum IgE and IgE-containing immune complexes [15], initially supported the hypothesis that EGPA might be an allergy-induced, immune-complex vasculitis. Initial clinical symptoms of seemingly atopic origin, like asthma, rhinosinusitis and nasal polyposis, seemed to support an allergic etiology. However, allergy concerns barely one-third of EGPA patients [16]. Thus, different pathogenic mechanisms may account for the different EGPA subpopulations.

A closer look at possible pathophysiological EGPA subtypes found a clear clinical difference between patients with and without ANCA. Findings based on cohorts showed ANCA frequency in EGPA to be around 40%. In studies, EGPA patients with anti-MPO ANCA suffered more, albeit not exclusively, from vasculitis symptoms, such as glomerulonephritis, mononeuritis multiplex and alveolar hemorrhage, than ANCA-negative patients. The pathogenic role of anti-MPO ANCA has been demonstrated *in vitro* and *in vivo*. First, anti-MPO ANCA are able to activate neutrophils, leading to the production of reactive oxygen species and the release of lysosomal proteolytic enzymes contained in neutrophil granules, causing subsequent vascular damage [17]. Second, these antibodies might also affect the vascular endothelium itself, as they can increase vessel-wall permeability, thereby inducing vascular endothelial cell expression of numerous cytokines, such as interleukin (IL)-1, IL-6 and IL-8, and intercellular and vascular cell adhesion molecules. Finally, through experimental passive transfer of these antibodies into mice, their roles in developing vasculitis and, most consistently, glomerular nephritis were confirmed in vivo [18,19]. In those experiments, however, other EGPA features, especially blood and tissue eosinophilia, were not seen. Hence, although anti-MPO ANCA might explain the predominance of vasculitis manifestations, like glomerular nephritis, in patients who express them, they might not be implicated in others.

For ANCA-negative patients, other factors are obviously needed to induce vasculitis. Among them, eosinophils might play predominant roles.

Indeed, eosinophils are constantly present at diagnosis, and appear to be activated during flares, as suggested by their surface expression of CD25 and CD69. Eosinophil activation in EGPA requires specific cytokine stimulation. This role is partly ensured by EGPA patients' T cells, which predominantly exhibit an activated TH2 phenotype, resulting in the secretion of high levels of IL-4, IL-13 and IL-5 [20]. Those three cytokines, especially IL-5, are essential for eosinophil activation, maturation and survival. Moreover, the reported tight relationship between disease activity and IL-5 concentrations suggested prominent roles of eosinophils and, for that matter, IL-5–secreting T lymphocytes in EGPA pathogenesis. More recent studies even showed the possible cross-talk between eosinophils and TH2-type lymphocytes in EGPA, via the secretion of IL-25, a potent TH2-response enhancer, by the eosinophils themselves [21].
Active EGPA patients also exhibit a consistent increase in the production of IgG4 [22], which is the rarest IgG subclass. The switch towards IgG4 production is related to the inflammatory milieu conditioning B-cell maturation, and particularly to the presence of Th2 cytokines such as IL4, IL5 and IL13.

Autoimmune diseases can be defined as clinical syndromes caused by inappropriate activation of self-reactive B cells or T cells. Although trigger remains elusive, many fators, including genetic susceptibility and environmental factors, culminate in the breakdown of B-cell or T-cell tolerance. T cell autoreactivity has been shown to be B cell dependent in certain experimental models [23,24].
In EGPA, eosinophil activation is mainly responsible for disease manifestations, and cytokines produced by T lymphocytes, such as interleukin (IL)-4, IL-5 and IL13, are increased in active EGPA [20]. This suggests that hypereosinophilia is secondary to T cell involvement in the disease pathogenesis, and this B-cell dependency of T cell autoreactivity has been proposed to explain the therapeutic response to rituximab in human autoimmunity.

Overall, activated B cells may contribute to mechanisms of tissue injury in different ways: 1) as antigen-presenting cells, regulating the development of effector T cells by expressing costimulatory molecules, and 2) as precursors to plasma cells, giving rise to MPO ANCA pathogenic autoantibodies.

Summary of relevant pre-clinical experiments and clinical trials

Preclinical studies have shown that rituximab, an anti-CD20 monoclonal antibody, depletes B cells from the peripheral blood, lymph nodes and bonne marrow.

B cell depletion with rituximab has proved effective in hematological diseases and autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, and antineutrophil cytoplasmic antibody (ANCA) associated vasculitis.

Rituximab was shown to be non inferior to cyclophosphamide to induce remission with an acceptable safety profile in patients with systemic GPA and MPA in prospective controlled trials [25,26]. In addition, the prospective, randomized, controlled MAINRITSAN trial conducted by our group compared rituximab to azathioprine to maintain remission of GPA and MPA, and demonstrated that RTX every 6 months was superior to azathioprine to maintain remission during the 28-month follow-up [*Guillevin L, N Engl J Med, 2014, in press*]. However, patients with EGPA were not included in these trials.

There is preliminary evidence in uncontrolled studies that anti-CD20 therapy helps control EGPA. It may therefore point to a new therapeutic approach to EGPA, whatever the ANCA status.

The first two patients with refractory EGPA treated with rituximab were described in 2006 by Koukoulaki et al. [27]. In these patients, corticosteroids and cyclophosphamide were initially effective in controlling disease activity, but both patients had long histories of relapsing disease activity, despite continuous immune suppressive treatment and alternative immunotherapies. Rituximab was successful in controlling disease activity with a decrease of the BVAS and corticosteroids. B cell depletion was achieved and the eosinophil count decreased to normal levels.

Pepper et al. also reported the successful efficacy of rituximab in two EGPA patients. Rituximab resulted in a clinical, serological and biochemical improvement in both cases. In addition, serum IL-5 was elevated in these patients during the active disease period despite conventional therapy, but reduced following rituximab treatment. This effect preceded the reduction in circulating eosinophils, suggesting that rituximab mediates its beneficial actions in EGPA, at least in part, through the inhibition of T-cell IL-5 production [28].

Cartin-Ceba et al. conducted a single-center open-label pilot study using rituximab for induction of remission in EGPA patients with renal involvement [29]. Three patients were enrolled. All patients achieved the primary end point of renal remission within the first 3 months and remained in renal remission during the year following rituximab treatment. One patient experienced a nonrenal relapse (eye and joint involvement) at 6 months coinciding

with the reconstitution of CD19+ cells and eosinophilia. He was retreated with rituximab and achieved a new remission within 6 weeks. No major adverse effects were recorded. Rituximab was safe and successful in controlling renal disease activity in these three patients with EGPA.

Thiel et al. also reported a single-center cohort of patients with EGPA treated with rituximab. Nine (six ANCA-positive, three ANCA-negative) have been treated with rituximab for relapsing or refractory disease on standard immunosuppressive treatment. All patients had high disease activity before rituximab treatment. All ANCA-positive and ANCA-negative patients responded to rituximab. After a mean follow-up of 9 months, C-reactive protein concentrations normalized, eosinophils significantly decreased, and prednisone was tapered in all patients. Within the 9-month observation period, no relapse was recorded. Three patients were preemptively retreated with rituximab, and during the median follow-up time of 3 years, no relapse occurred in these patients. During the follow-up of 13 patient-years, five minor but no major infections were recorded. In this study, rituximab appeared to be an efficient and safe treatment for both ANCA-positive and ANCA-negative patients. Preemptive retreatment with rituximab, combined with standard maintenance immunosuppressants, resulted in a sustained treatment response [30].

Finally, Hot et al. showed preliminary data on thirty patients with EGPA treated with rituximab. Asthma was present in all patients, ENT involvement in 26, skin lesions in 20, and peripheral neuropathy in 19 patients. Myocardial injury was present in six patients as well as glomerulopathy. MPO ANCA were present in 13 patients. All patients were refractory to corticosteroids and immunosuppressants. The Five Factor Score (FFS) was 0 in 17 patients, and ≥1 in 13 patients. Twenty-six patients had a complete clinical response, two had a partial response, the latter two patients did not respond to treatment. Eight of the 26 patients treated in complete remission relapsed within the 18 months following initial treatment. No adverse events were observed, including no episodes of bacterial pneumonia. The authors concluded that rituximab seems to represent an alternative treatment in refractory EGPA, and that its safety profile appears satisfactory [31].

Overall, these series and recent reviews underlined that prospective studies are now needed to assess the efficacy and safety of rituximab in EGPA.

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

Data in other ANCA-associated vasculitis, in particular GPA and MPA, demonstrated the efficacy of rituximab as induction and maintenance therapy.

In patients with EGPA, overall survival is good with treatments stratified according to FFS but long-term outcome remains unsatisfactory because relapses occur in more than 40% of patients and are responsible for a high cumulative morbidity and damage.

In uncontrolled studies, anti-CD20 therapy has been shown to help controlling EGPA with a good safety profile, but no prospective studies are available neither in the induction nor in the maintenance periods. All uncontrolled series and recent reviews underlined that prospective studies are needed to assess the efficacy and safety of rituximab in EGPA.

Therefore, given the absence of any prospective trial evaluating rituximab in induction-remission of EGPA, conducting such study evaluating the efficacy and safety of rituximab seems necessary to improve the management of these patients.

Identification and description of the experimental medication or medications

Experimental medication will be the use of rituximab, an anti-CD20 monoclonal antibody that depletes B-cells in peripheral blood. Rituximab is a genetically engineered chimeric murine and human monoclonal antibody directed against the CD20 antigen. Rituximab is an IgG/kappa immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant-region sequences. It targets the CD20 antigen via the Fab domain. The Fc domain recruits immune effector functions to mediate B-cell lysis.

Description and justification of the dosage, administration method, administration design and treatment period.

Patients in the experimental arm will receive corticosteroids with a predefined tapering schedule (page 28), in combination with 1 gram of rituximab at day 1 and day 15 as induction therapy.

In the two prospective trials evaluating rituximab in AAV, the dose of 375 mg/m^2/week of rituximab for 4 consecutive weeks was used. However, in many retrospective studies, an administration schedule of 1 gram on days 1 and 15 was used without any particular adverse event or obvious inferiority. In a retrospective, standardized data collection from 65 sequential patients receiving rituximab for refractory ANCA-associated vasculitis, no difference was observed between patients who had received RTX 375 mg/m2/week for 4 consecutive weeks or 1 gram two weeks apart [32]. Overall, the FVSG recognized that both protocol could be used to treat AAV.

In the REOVAS study, rituximab will be administered intravenously at the dose of 1 gram at day 1 and day 15 after recommended intravenous premedication using 100 mg methylprednisolone, 1 gram paracetamol and 5 mg dexchlorpheniramine. This premedication protocol will be also administered in patients receiving placebo-rituximab. In addition, this regimen is mainly used for the treatment of autoimmune diseases, and is the one approved for treatment of rheumatoid arthritis.

Overall, the experimental group will receive intravenous rituximab plus placebo−cyclophosphamide.

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

Foreseeable benefits are a superior efficacy of rituximab compared to the conventional therapeutic strategy to induce remission of vasculitis, and an improved outcome with higher rates of complete remission, lower doses of corticosteroids and lower cumulative morbidity.

Foreseeable risks are those associated with toxicity of treatments.

Risks associated with rituximab

No dose-limiting averse events were observed in trials that evaluated the safety and efficacy of rituximab in participants with lymphoma and AAV such as GPA or MPA.

The most commonly observed infusion-related adverse events were chills, fever, fatigue, headache, hypotension, nausea, leucopenia, angioedema and pruritus. These adverse events respond to interrupting and then resuming the infusion at a slower rate.

Other adverse events include neutropenia, thrombocytopenia, and asthenia. Participants with preexisting cardiac conditions may have recurrences of cardiac events during rituximab infusions.

Very rare cases of progressive multifocal leukoencephalopathy and severe skin reactions (Lyell's syndrome and Stevens-Johnson syndrome), some with fatal outcome, have been reported during post-marketing use of rituximab.

Refer to the SmPC of Mabthera® for the exhausted list of adverse reactions.

Risks associated with cyclophosphamide

Adverse events resulting from the use of cyclophosphamide include nausea and vomiting, abdominal discomfort, diarrhea, skin rash, alopecia, amenorrhea, leucopenia, and impairment of fertility.

Serious adverse events include cardiac toxicity and cardiomyopathies, hemorrhagic cystitis, infections, leucopenia, thrombocytopenia, anaphylactoid reactions, malignancies, infertility, pneumonitis, hepatitis, and death.

Refer to the SmPC of Endoxan® for the exhausted list of adverse reactions.

Risks associated with azathioprine

Adverse events resulting from the use of azathioprine include leucopenia or infection, anemia, hepatitis, thrombocytopenia, gastrointestinal hypersensitivity reaction, nausea and vomiting, abdominal discomfort, diarrhea, and skin rash.

Serious adverse events as malignancies : skin cancer, sarcoma, in situ uterus cancer, acute myeloid leukemia, myelodysplasia.

Refer to the SmPC of Imurel® for the exhausted list of adverse reactions.

Risks associated with Mesna No side effect is usually observed at doses used in daily practice, ranging from 10 to 30 mg/kg per injection, except for local inflammatory reaction after intravenous infusion in some patients. Very rarely, skin or systemic allergic reactions may occurred.

Refer to the SmPC of Uromitexan® for the exhausted list of adverse reactions.

3. OBJECTIVES

3.1 Primary objective

The primary objective of this trial is:

- To determine the efficacy of rituximab and glucocorticoids to induce a complete remission, defined as a Birminghman Vasculitis Activity Score (BVAS) of 0 and a prednisone dose ≤7.5 mg/day at day 180, in patients with newly-diagnosed or relapsing EGPA.

3.2 Secondary objectives

The secondary objectives of this trial are the following:

- To compare the safety profile of rituximab and conventional treatment at days 180 and 360
- To measure the corticosteroid dose at days 180 and 360 and to compare the corticosteroid sparing effect of rituximab versus conventional therapy
- To compare sequelae assessed by the Vasculitis Damage at days 180 and 360 after randomization in both arms
- To compare functional disability and quality of life at days 180 and 360 in both arms.
- To compare the evolution of ANCA titers and CD19+ cells in the two treatment groups, and to assess its correlation with clinical events during follow-up

This trial will be the first prospective, randomized and controlled study evaluating efficacy and safety of rituximab to induce remission in EGPA patients. This study, if it demonstrated a benefit of rituximab compared to conventional therapeutic strategy, would improve the management of patients with EGPA.

4. PLAN FOR THE RESEARCH

Concise description of the primary and secondary assessment criteria

4.1.1 Primary assessment criterion

The primary assessment criterion of this trial is:

- The percentage of patients who obtained a BVAS=0 and prednisone dose ≤7.5 mg/day, at day 180.

Remission will be defined as the absence of disease activity attributable to EGPA vasculitis manifestations (parenchymal lung disease, peripheral nerve involvement, skin, cardiac, renal and/or gastrointestinal signs), corresponding to BVAS=0, with a prednisone dose ≤7.5 mg/day.

Based on recommendations from the EGPA Task Force that met in Paris in April 2013, ear, nose and throat (ENT) manifestations such as rhinitis or sinusitis, asthma flares and/or eosinophilia < 1000/mm^3 may not reflect vasculitis activity in the absence of other vasculitic manifestations [5,8]. Along this line, EGPA Task Force proposed that the definition of remission in EGPA not include the control of asthma and/or ENT manifestations and/or eosinophil count, and that these symptoms will be monitored separately. In addition, EULAR experts [33] recommended that the definition of remission should include a prednisone dose ≤7.5 mg/day to control systemic manifestations. In contrast, chronic rhinitis, sinusitis or asthma should be considered as chronic damage and included in the Vasculitis Damage Index (VDI) and not the BVAS.

4.1.2 Secondary assessment criteria

The secondary assessment criteria of this trial are:

- The number of adverse events, expressed as adverse events according to the CTCAE toxicity grading system per patient-year at days 180 and 360 for the following

adverse events combined: death (all causes), grade 2 or higher leukopenia or thrombocytopenia, grade 3 or higher infections, hemorrhagic cystitis, malignancies, venous thromboembolic events, hospitalization resulting either from the disease or from a complication due to the study treatment, infusion reactions (within 24 hours of infusion) that result in the cessation of further infusions

- The area under the curve for corticosteroids at days 180 and 360 in the two treatment groups
- The Vasculitis Damage Index (VDI) at days 180 and 360 in the two treatment groups
- The HAQ and SF-36 at days 180 and 360 in the two treatment groups.Evolution of ANCA titers and CD19+ cells in the two treatment groups, and correlation with clinical events during follow-up

Description of research methodology

4.1.3 Experimental plan

This is a phase III comparative, multicenter, randomized, controlled, double-blind and superiority research, comparing rituximab-based regimen with conventional therapeutic strategy for the induction of remission in patients with EGPA.

Patients with newly diagnosed or relapsing EGPA will be randomized in a 1:1 ratio to receive:

- Experimental therapeutic strategy based on the use of rituximab (experimental group)
- Conventional therapeutic strategy based on Five-Factor Score (FFS)-assessed disease severity (comparative group)

The experimental plan is summarized in **Figure 1**.
Patients will be first assessed for the presence of poor prognostic factors according to the FFS 1996. The five factors (each accorded 1 point) conferring a higher risk of mortality rate are: 1) proteinuria > 1 g/24 h; 2) serum creatinine level > 140 µmol/l; 3) myocardial involvement; 4) severe gastrointestinal involvement; and 5) central nervous system involvement.

Patients with FFS=0 will receive corticosteroids at 1 mg/kg/day (maximum 80 mg/day). They will be randomized between the experimental regimen group and the conventional therapeutic strategy group based on Five-Factor Score (FFS)-assessed disease severity.

In the experimental regimen group, all patients will receive corticosteroids with a predefined tapering schedule, in combination with 1 gram of rituximab at day 1 and day 15. No maintenance therapy will be administered according to the standard of care of these patients, as recommended by the French Vasculitis Study Group (FVSG).

In the conventional therapeutic strategy group based on FFS-assessed disease severity, all patients will receive corticosteroids with a predefined tapering schedule, in combination with placebo-rituximab at day 1 and day 15. No maintenance therapy will be administered according to the standard of care of these patients, as recommended by the FVSG. .

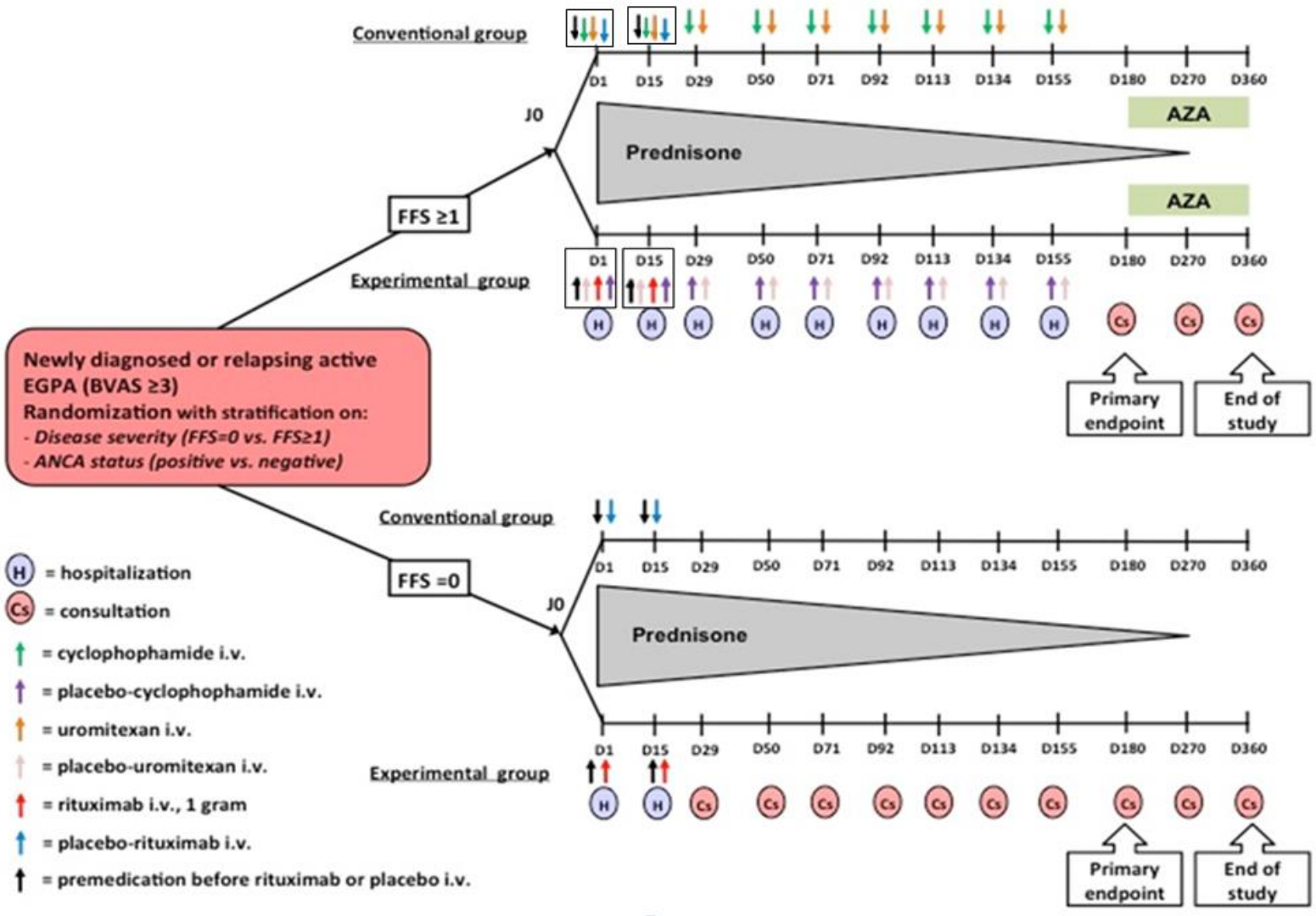
Patients with FFS≥1 will receive 3 pulses of methylprednisolone at 7,5 to 15 mg/kg then corticosteroids at 1 mg/kg/day (maximum 80 mg/day). They will be randomized between the experimental regimen group and the conventional therapeutic strategy group based on Five-Factor Score (FFS)-assessed disease severity.

In the experimental regimen group, all patients will receive corticosteroids with a predefined tapering schedule. They will receive 9 intravenous pulses including: 1 gram of rituximab at day 1 and day 15, and then placebo-cyclophosphamide and placebo-mesna at days 29, 50, 71, 92, 113, 134 and 155. Maintenance therapy by oral azathioprine (2mg/kg/day) will be started at day 180 according to the standard of care of these patients, as recommended by the FVSG.

In the conventional therapeutic strategy group based on FFS-assessed disease severity, all patients will receive corticosteroids with a predefined tapering. They will receive 9 intravenous pulses of cyclophosphamide: 600 mg/m^2 at days 1, 15 and 29, and then 500 mg-fixed dose at days 50, 71, 92, 113, 134 and 155, associated with intravenous mesna. Maintenance therapy by oral azathioprine (2 mg/kg/day) will be started at day 180 according to the standard of care of these patients as recommended by the FVSG.

Because the study will be in double-blind, premedication of rituximab will be administered in all groups of patients at day 1 and day 15.

Figure 1. Experimental plan of the REOVAS study.



All the treatment groups will receive the same glucocorticoid regimen.

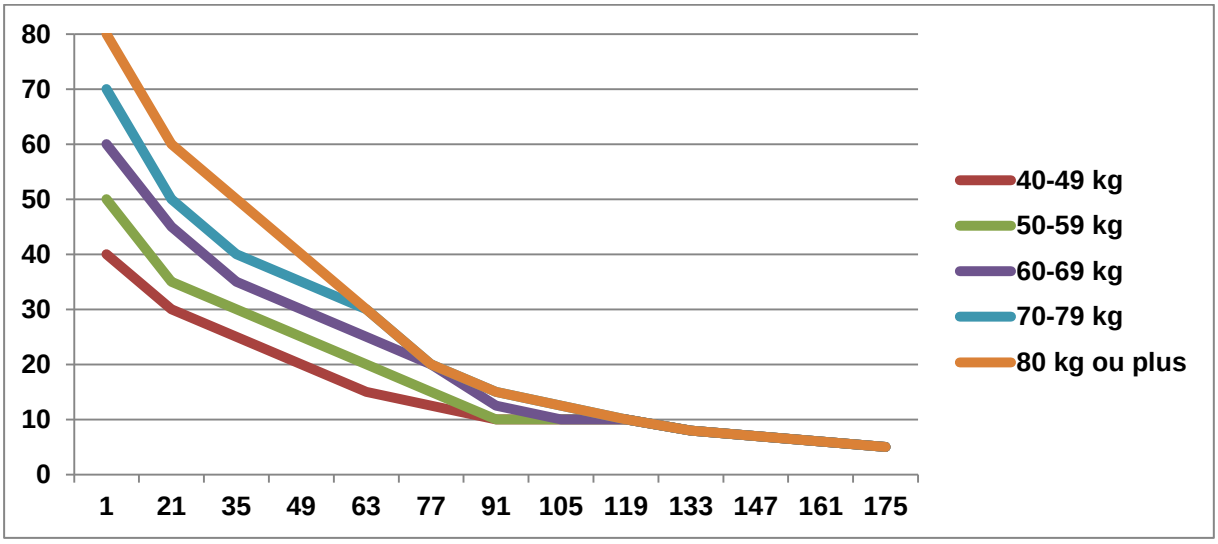
Prednisone dose will be initiated at 1 mg/kg/day (maximum dose 80 mg/day) for 3 weeks. The prednisone dose will be tapered, starting at week 3, according to clinical manifestations of EGPA.

Prednisone dose will be tapered every 2 weeks in the absence of clinical manifestations of EGPA and hypereosinophilia.

Predefined prednisone tapering schedule:

Days	40-49 kg	50-59 kg	60-69 kg	70-79 kg	≥80 kg
D1-D20	40	50	60	70	80
D21-D34	30	35	45	50	60
D35-D48	25	30	35	40	50
D49-D62	20	25	30	35	40
D63-D76	15	20	25	30	30
D77-D90	12,5	15	20	20	20
D91-D104	10	12,5	15	15	15
D105-118	10	10	12,5	12,5	12,5
D119-D132	10	10	10	10	10
D133-D146	8	8	8	8	8
D147-D160	7	7	7	7	7
D161-D174	6	6	6	6	6
D175-D195	5	5	5	5	5

Figure represents the predefined tapering of prednisone until D180.



Prednisone dose will then be decreased of 1 mg every 3 weeks in the absence of clinical and biological manifestations of EGPA activity until discontinuation.

An isolated eosinophilia or isolated increased C-reactive protein without overt clinical manifestations will not be considered as activity of the EGPA.
Instruction for corticosteroids tapering according to EGPA clinical and biological activity at clinic visit:

- Absence of activity (no vasculitis and eosinophils <1000/µL and CRP<10 mg/l): decrease prednisone dose according to schedule
- Mild asthma and/or ENT manifestations, and/or eosinophils >1000/µL and/or CRP>10 mg/l in the absence of infection: maintain current prednisone dose
- Clinical flare: prednisone dose could be increase until 20 mg/day in case of minor flare or double-blind will be stopped and optimal therapy will be chosen by the clinician in charge of the patient in case of major flare.

Clinical flares are defined as the reoccurrence or new onset of disease attributable to active EGPA. Major flare is defined as the reoccurrence or new onset of potentially organ- or life-threatening disease. Minor flare is defined as the reoccurrence or new onset of disease which is neither potentially organ-nor life-threatening disease [34].

Based on recommendations from the EGPA Task Force, ENT manifestations and/or asthma flares and/or eosinophil count may not reflect vasculitis activity. Along this line, these symptoms will be monitored separately and not included in the BVAS.

An independent Endpoint Adjudication Committee will be created to review in double-blind the classification of disease flare.

4.1.4 Number of centres participating

This multicenter research will involve the participation of the FVSG network, which includes more than 100 clinical departments involved in the management of EGPA.
As previous trials conducting by the FVSG on this topic, about 50 centers will participate in the research.

4.1.5 Identification of the subjects

For this research, the subjects will be identified as follows:

Centre No. (3 numerical positions) - Selection order No. of the person in the research (4 numerical positions) - surname initial - first name initial.
This reference is unique and will be retained for the entire research period.

4.1.6 Randomization

After screening, participants who are deemed eligible for the study will be enrolled and the randomization schedule will be designed to yield and assignment ratio of 1:1 between the two treatment groups within each stratum. The randomization will be centralized and stratified on disease severity assessed by the FFS (FFS=0 vs. FFS≥1), ANCA status (positive vs. negative ELISA), and newly diagnosed vs. relapsing disease.
Covariate adaptative randomization will be ensured by the use of an e-CRF on Cleanweb software.
No stratification on the center will be performed.

4.1.7 Blinding methods and provisions put in place to maintain blindness

This trial will be comparative, randomized, double-blind and double-dummy in order to limit performance and evaluation bias.

Neither patients, nor physicians will know the treatments allocated to their patients.

Investigators will be in blind of the CD19+ count during all study period, from day 15.
A circuit allowing the maintenance of blindness will be made after randomization in each center, between the clinical department and the laboratory measuring CD19+ cells. Measurement of CD19+ will be performed at each visit, but results will not be transmitted to the clinical department, but will be sent after anonymization to URC/CIC Paris Descartes Necker Cochin.

Patients with FFS=0 will receive oral corticosteroids associated with rituximab at day 1 and day 15 (after premedication by intravenous 100 mg methylprednisolone, 1 gram paracetamol and 5 mg dexchlorpheniramine) in the experimental group, but no placebo-cyclophosphamide according to the standard of care of these patients and recommendations

from the FVSG. In the conventional therapeutic strategy group, such patients will receive oral corticosteroids associated with placebo-rituximab at day 1 and day 15 (after the same premedication by methylprednisolone, paracetamol and dexchlorpheniramine), but no cyclophosphamide nor maintenance therapy will be administered according to the standard of care of these patients and recommendations from the FVSG.

Patients with FFS≥1 will receive corticosteroids associated with rituximab at day 1 and day 15 (after premedication by intravenous 100 mg methylprednisolone, 1 gram paracetamol and 5 mg dexchlorpheniramine) in the experimental group, but will also receive placebo-cyclophosphamide and placebo-mesna at days 29, 50, 71, 92, 113, 134 and 155. In the conventional therapeutic strategy group, such patients will receive corticosteroids associated with intravenous pulses of cyclophosphamide for a total of 9 pulses: 600 mg/m^2 at days 1, 15 and 29, and then 500 mg-fixed dose at days 50, 71, 92, 113, 134 and 155, associated with mesna.
All patients with FFS≥1 will receive maintenance therapy with oral azathioprine (2 mg/kg/day) at day 180 according to the standard of care of these patients as recommended by the French Vasculitis Study Group.

4.1.8 Procedures for breaking the blind, if applicable

Unblinding will be requested for any reason considered essential by the investigating doctor by calling upon:

- the DRCD, in a situation other than an emergency during the work day and during working hours
- the Hospital pharmacy of the center concerned,
  on weekends, bank holidays, when the DRCD is closed and when unblinding cannot be carried out at the DRCD

- the primary coordinating investigator or the scientific director will have to validate in writing the demand of the investigating doctor before breaking the blind of the trial.

5. PROCEDURE FOR THE RESEARCH

Before any inclusion or acts related to the research, the investigator will collect informed consent from the patient.

All visits will be performed by physicians involved in the management of EGPA patients, including practitioners from Internal Medicine, Nephrology, Pulmonology or Rheumatology.

Visits will take place in hospitalization or consultation according to disease severity and good clinical practices. Experimental plan summarized in **Figure 1** indicates where each visit will take place.

During the first month after randomization, visits should be performed +/- 3 days compared to reference visit, +/- 7 days from day 30 to day 155 of follow-up, and +/- 15 days from day 156 to day 360 of follow-up.

Selection visit

The selection visit will take place between 1 to 20 days before the inclusion visit.
Selection visit will include:

- Clinical examination to collect manifestations related to active EGPA and determine disease severity assessed by the FFS
- Weight and size for the calculation of the body mass index (calculated only once during the study)
- Verification of inclusion and non-inclusion criteria
- Blood tests to check for inclusion and non-inclusion criteria and to determine disease severity assessed by the FFS and ANCA status : hemogram, , serum ionogram (Na, K), renal function (serum creatinine level), C-reactive protein, liver enzymes, bilirubin, serum protein electrophoresis, CPK, LDH, calcemia, phosphoremia, glycemia, troponin, NT-pro-BNP, HIV, HBV and HCV serological tests, urine analysis, CD19+ cells, CD3+, CD4+ and CD8+ cells, ANCA using immunofluorescence and ELISA
- Imaging tests as appropriate: chest X-ray, thoracic CT-scan, echocardiogram, echocardiography, cardiac MRI
- Patient information

Subjects whose consent is sought	Who informs the subject and collects their consent	When is the subject informed	When is the subject's consent collected
Patient presenting with active EGPA	investigating doctor participating in the study	Selection visit	Inclusion visit, after a reflexion interval from 24 hours to 20 days

Inclusion and randomization visit

The randomization visit will represent day 0.

Inclusion visit will include:

- Verification of inclusion and non-inclusion criteria
- Patient information and informed consent
- Randomization by e-CRF
- Printing of experimental treatment prescription for the pharmacy
- Give to the patient the participation card in a clinical trial (see appendix 17.5)
- Pregnancy test for women of childbearing age before initiation of experimental treatment
- Serum, plasma and DNA bank before initiation of experimental treatment BVAS
- VDI
- SF36 and HAQ patient questionnaires (see Appendix 17.3 and 17.4)
- Collection book reporting prednisone tapering (see Appendix 17.6)
- Notification of associated treatments and contraceptive method for women of childbearing age
- Administration of treatments after randomization: rituximab or placebo for patients with FFS=0, and rituximab or cyclophosphamide or placebo for patients with FFS≥1

Maximal interval authorized between inclusion and randomization will be 7 days.

Maximal interval authorized between randomization and first infusion of the treatment will be 7 days.

Follow-up Visits

Follow-up visits will take place at days 15, 29, 50, 71, 92, 113, 134, 155, 180 and 270.

Patients with FFS = 0 will have the following follow-up visits: J15, J29, J92, J180, J270 and J360.

Patients with FFS ≥1 will have the following follow-up visits: J15, J29, J50, J71, J92, J113, J134, J155, J180, J270 and J360.

Follow-up visits will include:

- Clinical examination to collect manifestations related to active EGPA or remission
- Biological tests
- Imaging tests as appropriate
- Notification of associated treatments
- Notification of adverse events
- Administration of treatments
- Filling of the e-CRF

Follow-up assessment will include:

- Biological tests: hemogram, serum ionogram, renal function, C-reactive protein, liver enzymes, bilirubin, serum protein electrophoresis, CPK, LDH, calcemia, phosphoremia, glycemia, urine analysis, , CD3+, CD4+and CD8+ cells, and as appropriate troponin and NT-pro-BNP
- CD19+ cells : results must not be sent to the investigator, but be sent by the laboratory, after anonymization, to the URC/CIC, in envelope T supplied
- ANCA using immunofluorescence and ELISA
- Serum and plasma bank (only at days 29, 92, and 180)
- BVAS
- VDI
- Imaging tests as appropriate: chest X-ray, thoracic CT-scan, echocardiogram, echocardiography, cardiac MRI
- SF36 and HAQ patient questionnaires (only at day 180)
- Collection book reporting prednisone tapering (only at days 92, 180 and 270)

After month 3, dates of each visit will be planned by the protocol, with a margin of +/- 15 days for each visit.

End of research visit

End of research visit will take place at day 360 and will include:

- Clinical examination to collect manifestations related to active EGPA or remission
- Biological tests
- Imaging tests
- Notification of associated treatments
- Notification of adverse events
- Administration of treatments
- Filling of the e-CRF

End of research assessment will include:

- Biological tests: hemogram, serum ionogram, renal function, C-reactive protein, liver enzymes, bilirubin, serum protein electrophoresis, CPK, LDH, calcemia, phosphoremia, glycemia, urine analysis, CD3+, CD4+ and CD8+ cells, and as appropriate troponin and NT-pro-BNP
- CD19+ cells : results must not be sent to the investigator, but be sent by the laboratory, after anonymization, to the URC/CIC, in envelope T supplied
- ANCA using immunofluorescence and ELISA
- Serum and plasma bank
- BVAS
- VDI
- Imaging tests as appropriate: chest X-ray, thoracic CT-scan, echocardiogram, echocardiography, cardiac MRI
- SF36 and HAQ patient questionnaires

Return of the last collection book reporting prednisone tapering

Expected length of participation and description of the chronology and duration of the research.

The duration of participation for each patient will be 360 days, whereas the duration of recruitment will be 24 months. Overall, the total duration of the study will be 36 months.
The maximum duration between selection and inclusion will be 21 days. Patients will be randomized during the inclusion visit, and blindness will be effective from the inclusion visit to the end of the research.
Patients will receive treatments for the all duration of the study.

At the month 9 visit of the REOVAS trial, patients could receive information about the MAINRITSEG trial, in which they could participate if they want to. Inclusion visit in the MAINRITSEG trial may coincide with the last visit of REOVAS trial (month 12 evaluation).

Maximum period between selection and inclusion	21 days
Inclusion period	24 months
The included subjects' length of participation, of which:	
• Treatment period:	180 days
• Follow-up period:	180 days
Total research period:	36 months

Beyond the visit at month 12, the study will be ended. However, the patients will be followed in on a quarterly or biannual basis, according to the clinical state, until the 5th year after inclusion (post-hoc follow-up recommended by the FVSG), then according to a rhythm freely chosen by the doctor until the tenth year in charge of the patient.

A data analysis in 5 years is also planned to study the possible profit of this treatment on the long term
The economic impact of the treatments used in the REOVAS study will be analysed.
The information collected during hospitalizations and consultations will be analysed.

Table or diagram summarising the chronology of the research

The chronology of the research is summarized in **Figure 1**.

Actions	D-21 to D0 (Selection visit)	D0 (Inclusion visit)	D1, D15, D29 +/- 3 days (Treatment administration and/or follow-up visits)	D50, D71, D92, D113, D134, D155 +/- 7 days (Treatment administration and/or follow-up visits)	D180, D270 +/- 15 days (follow-up visits)	Day 360 +/- 15 days (End of research)
Informed consent		X				
Randomization		X				
History	X					
Clinical examination	X	X	X	X	X	X
Medical procedures (ECG)	X	X	X			
BVAS, VDI		X	X	X	X	X
Biological tests (biochemistry, haematology, urine analysis, ANCA)	X	X *	X	X	X	X
CD19 result in open	X	X *				
CD19 result blind			X	X	X	X
Imaging tests (chest X-ray, thoracic CT-scan, echocardiography, cardiac MRI)	X					
HAQ and SF36 questionnaires		X			X (only at day 180)	X
Biological collection		X	X Only at day J29	X Only at day 92	X Only a day 180	X
Dispensation of treatments			X	X		
Compliance		X	X	X	X	X
Collection book of prednisone tapering		x		X (only at day 92)	X	
Adverse events			X	X	X	X

**The biological tests must be redone in the inclusion, if that of the selection dates more than 3 days (3 open days).*

- Distinction between care and research

TABLE: Distinction between procedures associated with "care" and procedures added because of the "research"

Procedures and treatments carried out as part of the research	**Procedures and treatments associated with <u>care</u>**	**Procedures and treatments added because of <u>the research</u>**
Treatments	3 pulses of methylprednisolone (7.5 to 15 mg/kg each), followed by a predefined prednisone tapering schedule that will be similar in patients with FFS=0 and those with FFS≥1 (corticosteroids), Azathioprine	Rituximab, and premedication of rituximab (paracetamol, methylprednisolone and dexchlorpheniramine) according to baseline FFS and randomization Cyclophosphamide, Mesna, according to baseline FFS
Consultations	Consultations or hospitalizations every 3 weeks then every 3 months	One-day hospitalization at day 15 only in patients with FFS=0
Blood samples	At inclusion, then every 3 weeks, then every 3 months: Hemogram, renal function, liver tests, calcemia, phosphoremia, glycemia, troponin, NT-pro-BNP, proteinuria, hematuria, ANCA At inclusion only: HIV, HBV and HCV serology	At inclusion only : DNA samples (14 ml of blood) At inclusion and 29, 92, 180 and 360 : Serum and plasma samples (7 ml of blood for each samples)
Imaging as appropriate	Chest X-ray Thoracic CT-scan Echocardiography Electrocardiogram Cardiac MRI according to clinical presentation	None
Questionnaires	None	SF36 and HAQ patient questionnaires (at days 0, 180 and 360) Collection book reporting prednisone tapering (at days 0, 92, 180 and 270)

Biological Collection

The samples (serum bank, plasma bank and DNA bank) taken as part of the research will be included in a biological collection.
The collections will be stored at the "Neutrophils et vascultis" laboratory (Hôpital Cochin, 27 rue du Faubourg Saint-Jacques, 75014 Paris) under the supervision of Prof. Luc Mouthon for an illimited duration.

Serum bank: 7 ml of blood will be taken and centrifuged, with serum extraction that will be aliquoted into 2 ml cryotubes and stored at -80°C by the investigator center. Transportation and delivery of serum banks will be conducted in dry ice to the coordinator at the Cochin hospital center, at the end of follow-up of patients in the center.

Plasma bank: 7 ml of blood will be taken and centrifuged, with plasma extraction that will be aliquoted into 2 ml cryotubes and stored at -80°C by the investigator center. Transportation and delivery of serum banks will be conducted in dry ice to the coordinator at the Cochin hospital center, at the end of follow-up of patients in the center.

DNA bank: 14 ml of blood will be taken at baseline only, stored at room temperature and immediately transported at room temperature to the coordinator at the Cochin hospital center.
A second blood sample for DNA extraction would be proposed to the patient in case of technical failure during DNA extraction of DNA with the first sample.

The samples will be used with the explicit agreement of the subject on the consent form for further analyses not included in the protocol but that could be beneficial for the scientific knowledge and the management of the disease.
The collection will be declared to the ANSM in the context of biomedical research.

At the end of the research, the samples will be preserved for an illimited duration. The collection will be declared to the minister responsible for research and to the director of the regional health authority with local jurisdiction (Article L. 1243-3 of the CSP (French Public Health Code).

If the patient gave its informed consent for the conservation without time limitation and the reuse of its samples for subsequent genetic studies in the field of vasculitis, in France or abroad, he won’t be prompted again to give a new consent for the realization of each of these future genetic studies

Type of sample	Quantity	Storage location	Collection supervisor	Purpose of the collection	Storage period	Outcome (destruction, etc.)
DNA	14 ml at inclusion	Cochin Hospital	Prof. Luc Mouthon	Scientific knowledge	Illimited	Storage
Serum	7 ml at inclusion and days 29, 92, 180 and 360	Cochin Hospital	Prof. Luc Mouthon	Scientific knowledge	Illimited	Storage
Plasma	7 ml at inclusion and days 29, 92, 180 and 360	Cochin Hospital	Prof. Luc Mouthon	Scientific knowledge	Illimited	Storage

Termination rules

5.1 Criteria and methods for prematurely terminating the research treatment

5.1.1 Different situations

- Temporary termination of treatment, the investigator must document the reason for stopping and restarting the treatment in the subject's source file and the case report form (CRF)
- Premature termination of treatment, but the subject is still included in the research, until the end of the subject's participation, the investigator must document the reason
- Premature termination of treatment and end of participation in the research.

The investigator must:

- Document the reason(s)
- Collect the assessment criteria when participation in the research ends, if the subject agrees

5.1.1.1 Criteria and methods for the premature termination of the research

- Any subject can withdraw from participating in the research at any time and for any reason.
- The investigator can temporarily or permanently end a subject's participation in the research for any reason that affects the subject's safety or which would be in the subject's best interests.

If a subject is lost to follow-up, the investigator will make every effort to contact the subject to at least know if the subject is alive or dead

If a subject leaves the research prematurely, data relating to the subject can be used unless an objection was recorded when the subject signed the consent form.

If consent is withdrawn, no data about the subject may be used unless the subject states in writing that he/she does not object. In practice, the subject is excluded from the research.

The case report form must list the various reasons for the premature termination of treatment:

- Ineffective
- Adverse reaction
- Other medical problem
- Subject's personal reasons
- Explicit withdrawal of consent

The case report form must list the various reasons for ending participation in the research:

- ☐ Other medical problem
- ☐ Subject's personal reasons
- ☐ Explicit withdrawal of consent

Follow-up of the subjects after the premature termination of treatment

Ending a subject's participation does not affect the normal management of the subject's illness in any way.
If there are serious adverse events, the investigator must notify the sponsor and monitor the subject following the premature termination of treatment. If treatment is stopped prematurely due to a serious adverse event, a serious adverse event notification form will be sent by fax to the sponsor. The serious adverse event will be monitored until it is resolved.
In this research, a data and safety monitoring board (DSMB) will be created, this committee will validate the monitoring methods.

Methods for replacing subjects, if applicable
No replacing subject is planned in this study.

Terminating part or all of the research

AP-HP as sponsor or the Competent Authority (ANSM) can prematurely terminate all or part of the research, temporarily or permanently, upon the recommendation of a data and safety monitoring board in the following situations:

- first of all, if suspected unexpected serious adverse reactions (SUSARs) are seen in an arm being treated or if there is a discrepancy in the serious adverse reactions between the 2 arms being treated, and which require a reassessment of the benefit-risk ratio for the research.
- likewise, unexpected facts, new information about the product, in light of which the objectives of the research or of the clinical programme are unlikely to be achieved, can lead AP-HP as sponsor or the Competent Authority (ANSM) to prematurely halt the research AP-HP as sponsor reserves the right to permanently suspend inclusions at any time if it appears that the inclusion objectives are not met.

If the research is terminated prematurely, the decision and justification will be given by the sponsor, AP-HP, to the Competent Authority (ANSM) and to the CPP within 15 days, along with recommendations from the Data and Safety Monitoring Board.

6. ELIGIBILITY CRITERIA

6.1 Inclusion criteria

Will be included in the trial patients with the following criteria:

- Patients with a diagnosis of EGPA independently of ANCA status,
- Patient aged of 18 years or older,
- Patients with newly-diagnosed disease or relapsing disease at the time of screening, with an active disease defined as a Birmingham Vasculitis Activity Score (BVAS) ≥3,
- Patients within the first 21 days following initiation/increase of corticosteroids at a dose ≤ 1 mg/kg/day (pulses of methylprednisolone before oral corticosteroid therapy are authorized)
- Patient able to give written informed consent prior to participation in the study.
- Affiliation with a mode of social security (profit or being entitled)

Diagnosis of EGPA will be based on one of the three following classification criteria:

- Lanham diagnostic criteria including:
  - Asthma,
  - Blood eosinophilia exceeding 1500/mm^3,
  - And evidence of vasculitis involving two or more organs.

- American College of Rheumatology criteria requiring in a patient with an evidence of vasculitis the presence of 4 out of the 6 following criteria:

Asthma
Eosinophilia > 10% of leukocytes
History of allergy
Pulmonary infiltrates, non fixed
Paranasal sinus abnormalities
Extravascular eosinophils

- Finally, because an evidence of vasculitis is frequently lacking, diagnosis of EGPA may be based on the history or presence of asthma plus eosinophilia (>$1.0x10^9$/L and/or >10% of leukocytes), plus at least two the following additional features of EGPA:
  - Biopsy showing histopathological evidence of eosinophilic vasculitis, or perivascular eosinophilic infiltration, or eosinophil-rich granulomatous inflammation,
  - Neuropathy, mononeuropathy, multiple mononeuropathy or polyneuropathy,
  - Pulmonary infiltrates, non-fixed,
  - Sino-nasal abnormality,
  - Cardiomyopathy (established by echocardiography or MRI),
  - glomerulonephritis (haematuria, red cells casts, proteinuria),
  - alveolar haemorrhage (established by bronchoalveolar lavage or CT-scan),
  - palpable purpura,
  - ANCA positive (MPO or PR3).

6.2 Non-inclusion criteria

Will not be included in the trial patients with one of the following criteria:

- Patients with GPA, MPA, or other vasculitides, defined by the ACR criteria and/or the Chapel Hill Consensus Conference,
- Patients with vasculitis in remission of the disease defined as a BVAS <3,
- Patients with severe cardiac failure defined as class IV in New York Heart Association
- Patients with acute infections or chronic active infections (including HIV, HBV or HCV),
- Patients with active cancer or recent cancer (<5 years), except basocellular carcinoma and prostatic cancer of low activity controlled by hormonal treatment,
- Pregnant women and lactation. Patients with childbearing potential should have reliable contraception for the 12 months duration of the study,
- Patients with EGPA who have already been treated with rituximab within the previous 12 months,
- Patients with hypersensitivity to a monoclonal antibody or biologic agent,
- Patients with contraindication to use rituximab, cyclophosphamide, mesna or azathioprine,
- Patients with other uncontrolled diseases, including drug or alcohol abuse, severe psychiatric diseases, that could interfere with participation in the trial according to the protocol,
- Patients included in other investigational therapeutic study within the previous 3 months,
- Patients suspected not to be observant to the proposed treatments,
- Patients who have white blood cell count ≤4,000/mm^3,
- Patients who have platelet count ≤100,000/mm^3,
- Patients who have ALT or AST level greater that 3 times the upper limit of normal that cannot be attributed to underlying EGPA disease,
- Patients unable to give written informed consent prior to participation in the study.

The appearance of a non-inclusion criteria during follow-up will lead to an interruption of the experimental medication but not to a termination of the study. However, it is important to note that the experimental medication will be administered only at days 1 and 15. Patients with a non-inclusion criteria appearing after day 15 will be then followed in the protocol until the end of the study.

6.3 Recruitment methods

Patients will be included in the trial via the participation of the FVSG network. This French network includes physicians and medical departments involved in the management of patients with ANCA-associated vasculitis, in particular EGPA.
Each of the previous trials conducted by the FVSG network have included all patients planned by the protocol and have been published in high ranked journals.

For the REOVAS study, we plan to include 108 patients with EGPA.
Based on the results of previous trials from the FVSG, the proportion of patients with BVAS=0 and prednisone dose ≤7.5 mg/day at day 180 can be estimated at 60% in patients with EGPA.
The primary hypothesis of the REOVAS trial is an increase of at least 25% of the proportion of patients with BVAS=0 and prednisone dose ≤7.5 mg/day at day 180, i.e. 85%.
Based on this hypothesis, using a bilateral test, with a significance level of 5% and a beta level of 80%, 98 patients must be included, 49 patients in each arm. Taking into account 10% of patients lost to follow-up, 108 patients must be included, 54 in each arm.

This objective is achievable in 2 years, by including main centers participating for many years in trials of the FVSG, in addition to networks of national scientific societies (French National Society of Internal Medicine, French Society of Rheumatology, French Society of Nephrology, French Society of Pulmonology).

Management and quality control of patient data will be made jointly by the Clinical Research Unit Cochin-Necker and investigators.

	Number of subjects
Total number of subjects chosen	*108*
Number of centres	*50*
Inclusion period (months)	*24*
Number of subjects/centre	*2,5*
Number of subjects/centre/month	***0,1***

7. TREATMENT ADMINISTERED TO RESEARCH PARTICIPANTS

7.1 Description of the experimental medications :

Experimental medications depend on the disease severity (patient's FFS status). Each strata has 2 arms : an experimental group versus a conventional group.

Patients will receive the same intravenous premedication protocol before rituximab or placebo-rituximab injections, with 100 mg of methylprednisolone, 1 gram of paracetamol and 5 mg of dexchlorpheniramine, at day 1 and day 15.

7.1.1 Experimental groups :

Whatever their FFS status, all patients in the experimental regimen groups will receive corticosteroids with a predefined tapering schedule similar to the conventional therapy group, in combination with 1 gram of rituximab at day 1 and day 15 as induction therapy.

In the experimental arms of both strata :

- ***Patients with FFS≥1*** will receive at J 1 and J15 : 1 gram of rituximab at day 1 and day 15 and a placebo-cyclophosphamide in combination with a placebo-uromitexan (at H0 and H4).
- At days 1 and 15 ,29, 50, 71, 92, 113, 134 and 155 a placebo-cyclophosphamide in combination with a placebo-uromitexan (at H0 and H4).
- Maintenance therapy by azathioprine (2 mg/kg/day) will be started at day 180 according to the standard of care of these patients, as recommended by the FVSG.

- ***Patients with FFS=0*** will receive 1 gram of rituximab at day 1 and day 15 not receive placebo-cyclophosphamide nor maintenance therapy according to the standard of care of these patients, as recommended by the FVSG.

7.1.2 Description of conventional groups

Whatever their FFS status, all patients of conventional groups will receive corticosteroids with a predefined tapering schedule similar to the experimental group, in combination with placebo of rituximab at day 1 and day 15 and the same premedication than the experimental group.

In the conventional arms :

- ***Patients with FFS≥1*** will receive intravenous pulses of cyclophosphamide for a total of 9 pulses: 600 mg/m^2 at days 1, 15 and 29, and then 500 mg-fixed dose at days 50, 71, 92, 113, 134 and 155, in combination with mesna at H0 and H4 (200mg/m^2 until D29, and 200mg from D50 to D155). Maintenance therapy by azathioprine will be started at day 180 according to the standard of care of these patients as recommended by the FVSG.

- ***Patients with FFS=0*** will receive placebo-rituximab at day 1 and day 15. Neither cyclophosphamide nor maintenance therapy will be administered according to the standard of care of these patients, as recommended by the FVSG.

7.2 Non-experimental medications :

7.2.1 Corticosteroids

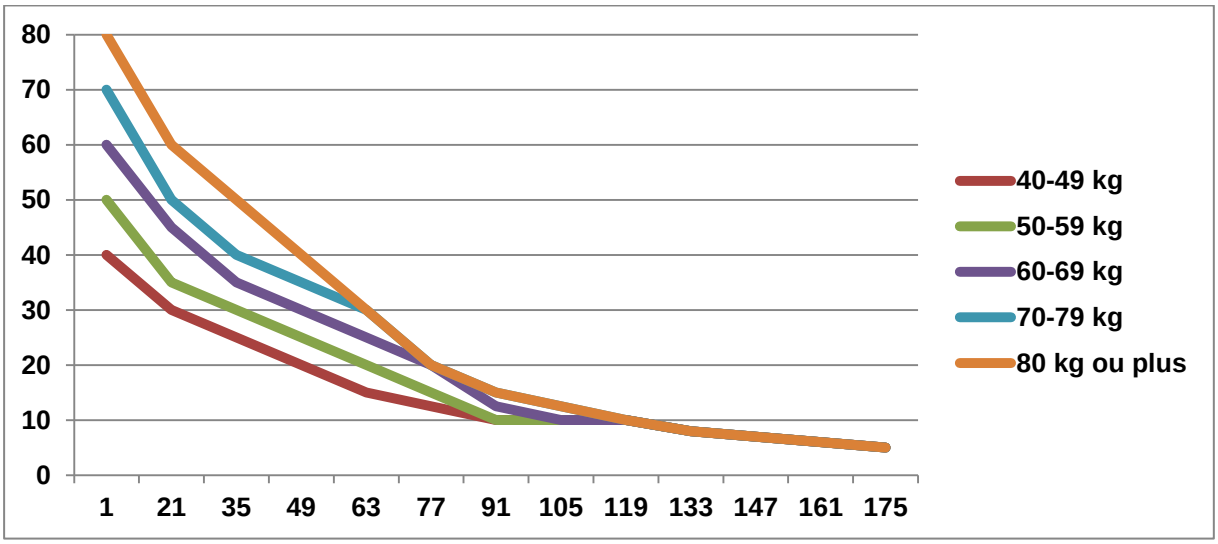
The two treatment groups (experimental and conventional) will receive the same glucocorticoid regimen.
Three pulses of methylprednisolone (15 mg/kg each) will be performed in patients with FFS≥1, followed by a predefined prednisone tapering schedule.

Prednisone dose will be initiated at 1 mg/kg/day (maximum dose 80 mg/day) for 3 weeks. The prednisone dose will be tapered, starting at week 3, according to clinical manifestations of EGPA. Prednisone dose will be tapered every 2 weeks in the absence of clinical manifestations of EGPA and hypereosinophilia.

Predefined prednisone tapering schedule:

Days	40-49 kg	50-59 kg	60-69 kg	70-79 kg	≥80 kg
D1-D20	40	50	60	70	80
D21-D34	30	35	45	50	60
D35-D48	25	30	35	40	50
D49-D62	20	25	30	35	40
D63-D76	15	20	25	30	30
D77-D90	12,5	15	20	20	20
D91-D104	10	10	12,5	15	15
D105-118	10	10	10	12,5	12,5
D119-D132	10	10	10	10	10
D133-D146	8	8	8	8	8
D147-D160	7	7	7	7	7
D161-D174	6	6	6	6	6
D175-D195	5	5	5	5	5

Figure represents the predefined tapering of prednisone until D180.



Prednisone dose will then be decreased of 1 mg every 3 weeks in the absence of clinical and biological manifestations of EGPA activity until discontinuation.

An isolated eosinophilia or isolated increased C-reactive protein without overt clinical manifestations will not be considered as activity of the EGPA.

Instruction for corticosteroids tapering according to EGPA clinical and biological activity at clinic visit:

- Absence of activity (no vasculitis and eosinophils <1000/µL and CRP<10 mg/l): decrease prednisone dose according to schedule
- Mild asthma and/or ENT manifestations, and/or eosinophils >1000/µL and/or CRP>10 mg/l in the absence of infection: maintain current prednisone dose
- Clinical flare: prednisone dose could be increase until 20 mg/day or double-blind will be stopped and optimal therapy will be chosen by the clinician in charge of the patient according to the severity of the clinical flare.

7.2.2: Azathioprine

Patients with FFS≥1 : all patients (two treatment groups : experimental and conventional) will receive maintenance therapy by azathioprine (2 mg/kg/day) will be started at day 180 according to the standard of care of these patients, as recommended by the FVSG.

7.3 Description of the traceability elements that accompany the experimental medications

The Clinical Trial Department of AGEPS will be responsible for labelling and supply of active experimental drugs to all centers.

7.3.1. Origins and storage conditions :

Only MABTHERA 500 mg (Roche) will be used for this study.

MABTHERA **Rituximab 500 mg / 50 mL** for intravenous use after dilution, concentrate for solution for infusion of 1 vial containing 10 mg/mL rituximab.
Storage : in a refrigerator (+2 °C – +8 °C). Keep the container in the outer carton in order to protect from light.

Cyclophosphamide 500 mg: Powder for Solution for Injection or Infusion.
Storage : Do not store above +25°C.

Mesna : ampoules 400 mg in 4 ml for IV injection.
Storage : protected from light, below +30°C.

All commercial boxes will be labelled for clinical trials by the DEC of AGEPS with respect to GMP.

Placebo and solvents : Nacl 0.9% IV bags, 100, 250 and 500ml. They will be supplied by the hospital pharmacies.

7.3.2. Supply

Due to the cost, the number of centers, the infrequency of the illness, shipments will be made after the inclusion in order to limit losses.

Supply: the supply order will be send by the eCRF.
The shipment will be adapted to the patient's disease severity and its randomisation group. It will contain all injections of the patients.

The hospital pharmacist will confirm receipt in writing of all batches of study medication sent and maintain an accurate accounting of them

Hospital storage
Drugs must be stored by the pharmacy in accordance with instructions and kept separate from normal hospital drugs.

7.3.3 Preparation

The hospital pharmacy will be in charge of preparation and blindness.
Infusion bags will be prepared by the hospital pharmacy with respect to patient's group and disease status.
The preparation will be made in accordance to SMPC of each commercial drugs.and will be recorded on the " Reovas manufacturing form" (model supplied by the sponsor).
Each bag will be labelled with all mandatory mentions and its shelf life. For storage conditions and duration after reconstitution please see the SMPC of each drug and "Reovas manufacturing form".
Infusion bags should be stored between 2 and 8°C until administration.

7.3.4 Dispensing

Pharmacies will dispense to care givers, the experimental medication on the basis of a specific prescription and with respect to local procedures.

7.3.5 Administration and follow up

Cf information in "Reovas nurse track file "of each strata (FFS=0 or FF>1)

It is important to check the medicinal product labels to ensure that the appropriate preparation is being given to the patient, as prescribed according to the randomization group and FFS.

MabThera / placebo should be administered under the close supervision of an experienced healthcare professional, and in an environment where full resuscitation facilities are immediately available, after premedication. The prepared MabThera/placebo solution should be administered as an intravenous infusion through a dedicated line.
All patients receiving rituximab or placebo-rituximab will be monitored for 4 hours after infusion of the experimental medication, as recommended in clinical daily practice, for measurements of blood pressure, oxygen, temperature every 30 minutes during the infusion, and if necessary after the end of the infusion.
Cyclophosphamide/placebo: Prior, during and immediately after the administration, adequate amounts of fluid should be ingested or infused to force diuresis in order to reduce the risk of urinary tract toxicity. Therefore, Cyclophosphamide should be administered in the morning.

Uromitexan (Mesna)/placebo : should be given with and after cyclophosphamide/placebo infusion (H0, H4 with respect to the prescription) for the prevention of urothelial toxicity.

Cyclophosphamide and uromitexan are prepared in the same infusion solution or in 2 different solutions, according to the habits of the pharmacy.

After administration, waste material should be disposed of in accordance with local requirements.

7.3.6 Accountability and destruction

Unused experimental medications must be accounted by the CRA in open, during and/or at the end of the study. After completion, study drug medication (unused) might be destroyed by each hospital pharmacy according to local procedures.

7.3.7 Methods for monitoring compliance with the treatment

Rituximab, cyclophosphamide, placebo-rituximab and placebo-cyclophosphamide will be administered intravenously and will be easily monitored for compliance on “Reovas nurse file”.
For corticosteroids, a collection book reporting prednisone tapering will be completed by the patients and transmitted to the investigators at each visit, as well as a copy of prescribed medications.

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

Authorized treatments will include:

- Cortisteroid-induced osteoporosis prophylaxis with calcium and vitamin D supplementation, and bisphosphonates as appropriate
- *Pneumocystis jiroveci* prophylaxis, with cotrimoxazole or pentaminidine aerosol is highly recommended, according to the FVSG recommendations for all patients included in the protocol.
- Vaccines for influenza virus and *Streptococcus pneumoniae*
- Proton pump inhibitors
- Hypokaliemia propylaxis with potassium supplementation.

In addition, all patients with FFS≥1 will receive maintenance therapy with azathioprine (2 mg/kg/day) that will be started at day 180 for a duration of at least 12 months, according to the standard of care of these patients, as recommended by the French Vasculitis Study Group.

Prohibited treatments will include:

- Any other immunosuppressive or immunomodulatory agent administered for the control of vasculitis or any other inflammatory disorders, except for azathioprine as maintenance therapy that patients with FFS≥1 will receive after day 180 after randomization.
- Allopurinol in association with azathioprine.
- Phenytoin in association with cyclophosphamide.

8. ASSESSMENT OF EFFICACY

8.1 Description of parameters for assessing efficacy

Clinical and biological examination will be performed at each visit to collect manifestations related to active EGPA or remission and to determine BVAS. Prednisone dosage will be also collected.

Remission will be defined as the absence of disease activity attributable to EGPA vasculitis manifestations (parenchymal lung disease, peripheral nerve involvement, skin, cardiac, renal and/or gastrointestinal signs), corresponding to BVAS=0, with a prednisone dose ≤7.5 mg/day.
Clinical flares attributable to vasculitis activity will be defined as the reoccurrence or new onset of disease attributable to active EGPA. Major flare will be defined as the reoccurrence or new onset of potentially organ- or life-threatening disease. Minor flare will be defined as the reoccurrence or new onset of disease which is neither potentially organ-nor life-threatening disease [34].
Based on recommendations from the EGPA Task Force, eosinophil-count increases, without any other clinical EGPA manifestations; isolated asthma, sinusitis or rhinitis exacerbations, with or without concomitant eosinophil-count rise; or mild clinical EGPA manifestations that only required corticosteroid-dose increase of less than twice the previous one, or <10 mg/day without immunosuppressants prescription, will be recorded but not considered as failures, or recurrent EGPA manifestations or relapse *per se*, and will be registered as therapeutic adjustment(s) and analyzed separately.
An independent Endpoint Adjudication Committee will be created to review in double-blind the classification of disease flare.

For secondary endpoints, adverse event rate will be assessed, expressed as adverse events according to the CTCAE toxicity grading system per participant-year.
The severity of every adverse event will be estimated by the investigator, who follows the patient by using the classification CTCAE. .

The duration of complete remission, defined as the total accrued duration in weeks with BVAS=0 and prednisone dose ≤7.5 mg/day over the 360 days study period, will be also assessed using the same parameters as previously described.
The area under the curve for corticosteroids in the two treatment groups will be analyzed.
Finally, damage, functional disability and quality of life will be assessed using Vasculitis Damage Index, HAQ and SF-36 questionnaires during follow-up, respectively.

8.2. Anticipated methods and timetable for measuring, collecting and analysing the parameters for assessing efficacy

An independent Endpoint Adjudication Committee will be created to review in double-blind the classification of disease relapse.
Relapse is defined as re-occurrence or new onset of disease attributable to active vasculitis.

Minor relapse is defined as the re-occurrence or new onset of disease which is neither potentially organ- nor life-threatening.
Major relapse is defined as the re-occurrence or new onset of potentially organ- or life-threatening disease.

The deaths will be also review in double-blind by the committee. It will be necessary for these cases to have the CD19, hemogram, the rate of gammaglobulines +/-the weight dosage of the IgG, and at least for the toxic shocks the CD4 and CD8. The committee will estimate the link with the pathology and the experimental medications.

9. SAFETY ASSESSMENT - RISKS AND RESTRICTIONS ADDED BY THE RESEARCH

9.1. Definitions

According to Article R1123-39 of the French Public Health Code and the guideline on good pharmacovigilance practices (EMA, 2012):

- **Adverse event**

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

- **Adverse drug reaction**

  Any response to a medicinal product which is noxious and unintended.

- **Serious adverse event**

  Any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

- **Unexpected adverse reaction**

  An adverse reaction, the nature, severity or outcome of which is not consistent with the applicable product information: the summary of product characteristics (SmPC) for an authorised product or the investigator's brochure for an unauthorised investigational product.

<u>According to the notice to sponsors of clinical trials for medications (ANSM)</u>:

- **New safety issue**

Any new information regarding safety:
- that could significantly alter the assessment of the benefit-risk ratio for the experimental medication, or for the trial
- or which could lead to the possibility of altering the administration of the experimental medication or altering the conduct of the trial

9.2. The investigator's roles

9.2.1. Regulatory obligations of the investigator (Art R1123-54 of the French Public Health Code)

The investigator must notify the sponsor, **<u>immediately on the day when the sponsor becomes aware</u>**, of all the serious adverse events, except those that are listed in the protocol (see. Section 9.2.3.1) as not requiring immediate notification.

These serious adverse events are recorded in the "serious adverse event" section of the case report form and the investigator must immediately notify the sponsor's Vigilance division (see 9.2.3.2.).

9.2.2. The investigator’s other roles

The investigator must document the serious adverse event as thoroughly as possible and provide the medical diagnosis, if possible.

The investigator will assess the severity of the adverse events by using an adverse events rating scale, attached to the protocol, Common Terminology Criteria for Averse Events (v4.0) [National Cancer Institute].

The investigator will assess the causal relationship between the serious adverse events and the experimental medication**.**

9.2.3. Specific features of the protocol

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

9.2.3.1. Serious adverse events that do not require the investigator to immediately notify the sponsor

These serious adverse events are only recorded in the "adverse event" section of the case report form.

- **<u>Normal and natural evolution of the pathology</u>:**

The normal and natural evolution of the disease will include consultations to assess activity and safety of the treatments administered.

This normal and natural evolution may also include clinical or biological manifestations related to disease relapse with no aggravation of the disease since baseline, including:

- Dyspnea, asthma, cough
- Sino-nasal abnormalities

- Arthralgia or arthritis, myalgia
- Skin manifestations
- Other manifestations related to active EGPA

- **Special circumstances**

Special circumstances that will not require to immediately notify the sponsor include:
- Hospitalization related to previous disease
- Hospitalization for medical treatment or surgery planned before the research
- Hospitalization for social or administrative reasons
- Hospitalization in the Emergency Unit for less than 12 hours
- Hospitalization planned per protocol (ex : one-day hospitalization at day 15 in patients with FFS=0)

- **Adverse events likely to be associated with the treatments prescribed as part of the patient's care during the monitoring of the research**

9.2.3.2. Serious adverse events that require the investigator to immediately notify the sponsor

The investigator must report all adverse events that meet one of the seriousness criteria below, except for events listed in section 9.3.3.1 as not requiring immediate notification to the sponsor :
1- Death
2- Life threatening situation
3- Requiring hospitalisation or prolonging hospitalisation
4- Persistent or significant disability or incapacity
5- Congenital abnormality or birth defect
6- Or any other adverse event considered "medically significant"

9.2.3.3. Other events that require the investigator to immediately notify the sponsor

- In utero exposure

The sponsor must be notified immediately about any pregnancy during which the foetus (from the pre-embryonic stage up to birth) could have been exposed at a given time to an experimental medication, even if the pregnancy is not associated with an adverse event.

- Exposure while breastfeeding

Exposure while breastfeeding occurs if an infant or child could have been exposed to a medication via the breast milk of a mother being treated with an experimental medication.
Even if such exposure is not associated with an adverse event, the investigator must always notify the sponsor about exposure while breastfeeding as soon as the investigator becomes aware.

9.3.4. Procedures and deadlines for notifying the sponsor

Notification of an SAE must initially be provided in a written report using the special form for reporting SAE (see Appendix 17.1). The report must be signed by the investigator.

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

This initial notification must be followed by one or more detailed follow-up report(s), in writing and signed, within a maximum of 8 days in the case of a fatal or life-threatening event and within 15 days for all other cases.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results of additional exams, etc.). These documents must be made anonymous. In addition, the documents must include the following: research acronym, number and initials of the subject, nature and date of the serious adverse event.

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 subject has left the trial.

The initial notification, the SAE follow-up reports and all other documents must be sent to the sponsor via fax only to the Vigilance Division of the DRCD, fax No. **01 44 84 17 99**.

For studies using e-CRF:
- the investigator completes the SAE notification form in the e-CRF, validates, prints and signs the form before sending it *via* fax.
- if it is not possible to connect to the e-CRF, the investigator will complete, sign and send the SAE notification form**.** As soon as the connection is restored, the SAE notification form in the e-CRF must be duly completed.

The investigator must comply with all requests from the sponsor for additional information.
For all questions relating to the notification of an adverse event, the Vigilance Division of the DRCD can be contacted via email: vigilance.drcd@drc.aphp.fr

***In utero* exposure**

The investigator completes the "form for monitoring a pregnancy that developed during a biomedical research" and sends it by fax to the Vigilance Division at **01 44 84 17 99**.

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 SAE.
If the exposure involves the father, the investigator must obtain the mother's permission before collecting information about the pregnancy.

The initial pregnancy notification, the SAE follow-up reports and all other documents must be sent to the sponsor via fax only to the Vigilance Division - of the DRCD, fax No. **01 44 84 17 99**.

9.3.5. Period for notifying the sponsor

The investigator must report all SAE that occur in research subjects:
- after the date on which the consent was signed
- throughout the period during which the participant is monitored, as determined by the research

- with no time limit, if the SAE is likely to be due to the experimental medication or to the research procedures (for example, serious reactions that could appear long after exposure to the medication, such as cancers or congenital abnormalities)

9.3.6 The sponsor's role

The sponsor, represented by its Vigilance Division, continuously assesses the safety of each experimental medication throughout the research.

9.3.6.1. Analysis and declaration of serious adverse events

The sponsor assesses:

- the seriousness of all adverse events reported
- the causal relationship of these events with each experimental medication and/or specific medical procedures/exams added by the research and with other possible treatments
- the expected or unexpected nature of these adverse reactions

The reference safety informations used for the expectedness of serious adverse reactions are

- For SAE related to the investigational drug rituximab : refer to SmPC of Mabthera®
- For SAE related to the investigational drug cyclophosphamide : refer to SmPC of Endoxan®
- For SAE related to the investigational drug mesna : refer to SmPC of Uromitexan
- For SAE related to the non investigational drug but considered as research procedures :
    - For SAE related to the premedication (paracetamol, dexchlorpheniramine, methylprednisolone): refer to SmPC of Perfalgan®, Polaramine®, Solumedrol®.
    - For SAE related to prednisone : refer to SmPC of Cortancyl®
    - For SAE related to the pulses methylprednisolone: refer to SmPC of Solumedrol®.
    - For SAE related to azathioprine : refer to SmPC of Imurel®

All serious adverse events which the investigator and/or the sponsor believe could reasonably have a causal relationship with the experimental medication are considered as suspected adverse reactions.

All suspected unexpected serious adverse reactions (SUSAR) are declared by the sponsor, within the legal time frame, to the Agence Nationale de Sécurité des Médicaments (ANSM, French Health Products Safety Agency) and to the relevant Comité de Protection des Personnes (CPP, ethical committee).

- The initial declaration must be made no later than 7 calendar days after the date on which the serious adverse event occurs in the case of death or of a life-threatening diagnosis.

- The initial declaration must be made no later than 15 calendar days after the date on which the serious adverse event occurs in the case of other serious situations.

- The follow-up declaration must be made no later than 8 days after the 7- or 15-day deadline (depending on the seriousness).

Any suspected unexpected serious adverse reaction must also be declared electronically in the Eudravigilance European database for adverse events due to medications, established by the European Medicines Agency (EMA).
The sponsor must notify all relevant investigators about any data that could adversely affect the safety of the research subjects.

9.3.6.2.1. Analysis and declaration of other safety data

This relates to any safety data or new fact that could significantly alter the assessment of the benefit-risk ratio for the experimental medication, or for the research, or which could lead to the possibility of altering the administration of the experimental medication or altering the conduct of the research.

New facts must be declared to the competent authorities within 15 calendar days of the sponsor becoming aware. Additional relevant information must be sent within an additional 8 days after the 15 day deadline.

9.3.6.2.2. Annual safety report

Once a year for the duration of the clinical trial, the sponsor must draw up an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:
- an analysis of the safety of the research subjects,

- a description of the patients included in the trial (demographic characteristics, etc.)
- a line listing of suspected serious adverse reactions that occurred during the period covered by the report,
- a cumulative summary tabulation of serious adverse events that have occurred since the start of the research.

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

9.3.7 Data Safety Monitoring Board

A 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. 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.

<u>General information about the DSMB</u>
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 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:

- meeting types (open session, then closed sessions) and schedule
- desired methods and format of SAE notification from the sponsor to the DSMB

The DSMB appoints its chairman at the first meeting.

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

10. DATA MANAGEMENT

10.1 Data collection methods

Data will be collected in each center by the investigator or by a clinical research technician, supervised by the investigator. Most data will be collected on the e-CRF, except patient questionnaires (HAQ and SF36) which will be collected on forms and secondly input in an electronic database.

10.2 Identification of data collected directly in the CRFs and that will be considered as source data

No data will be directly collected in the CRF.

Data collected in the CRF and the medical record of the patient will include:

- Age
- Weight
- Clinical examination to collect manifestations related to active EGPA or remission
- BVAS
- VDI
- Biological tests: hemogram, serum ionogram, renal function, C-reactive protein, liver enzymes, bilirubin, serum protein electrophoresis, CPK, LDH, calcemia, phosphoremia, glycemia, urine analysis, CD19+ cells at D0 only, CD3+, CD4+ and CD8+ cells.
- ANCA using immunofluorescence and ELISA
- prednisone tapering

10.3 Right to access source data and documents

Access to data

In accordance with GCPs:
- the sponsor is responsible for obtaining the permission of all parties involved in the research to guarantee direct access to all locations where the research will be carried out, to the source data, to the source documents and the reports, with the goal of quality control and audit by the sponsor
- the investigators will make available to those in charge of monitoring, quality control and audit relating to the biomedical research the documents and personal data strictly necessary for these controls, in accordance with the legislative and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

Source documents

Source documents are defined as any original document or object that can prove the existence or accuracy of a piece of information or a fact recorded during the research. These documents will be kept for 15 years by the investigator or by the hospital in the case of a hospital medical file.

Data confidentiality

Those responsible for biomedical research quality control (Article L.1121-3 of the French Public Health Code) will take all necessary precautions to ensure the confidentiality of information about the experimental medications, the research, the research subjects and in particular the identity of the subjects and the results obtained.
These individuals, as well as the investigators themselves, are subject to professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the Penal Code).
During or after the biomedical research, the data collected about the research subjects and sent to the sponsor by the investigators (or any other specialised parties) will be made non-identifying.
Under no circumstances should the names and addresses of the subjects involved be shown.

The sponsor will ensure that each research subject has given permission in writing for access to personal information about him or her which is strictly necessary for the quality control of the research.

10.4 Data processing and storage of documents and data

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

Data will be stocked in an e-CFR, on a web server owned by the sponsor. The data management will be performed in the clinical research unit Paris Descartes Cochin/Necker and supervised by Pr Treluyer.

Data entry

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

Data processing 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 référence".

Archival

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.

10.5 Ownership of the data

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

11. STATISTICAL ASPECTS

11.1 Statistical aspects

Statistical analyses will be performed in the Clinical Research Unit Paris Descartes Cochin/Necker, and supervised by Dr Hendy Abdoul.
Analysis will be performed using SAS Statistical Software 9.2. All tests will be bilateral with p=5%.
No interim analyse is planned.
All statistical methods used will be described in the statistical analysis plan before data analyses.

Data description

The results will be expressed as mean +/- SD for continuous variables and as percentage with 95% confidence interval for categorical variables.

Primary endpoint analysis

Primary endpoint analysis will be analysed in intention to treat population.

The primary endpoint is defined as the percentage of patients who obtained a BVAS=0 and prednisone dose ≤7.5 mg/day, 180 days after randomization. Remission will be defined as the absence of disease activity attributable to EGPA vasculitis manifestations (parenchymal lung disease, peripheral nerve involvement, skin, cardiac, renal and/or gastrointestinal signs), corresponding to BVAS=0, with a prednisone dose ≤7.5 mg/day.

Every attempt will be done to obtain complete data for patients at 180 days (contact with investigators or general practitioner).

In addition, the Independent Endpoint Adjudication Committee will blindly review parameters of efficacy (classification of disease relapse). In case of lost to follow-up patients or missing data, the independent Endpoint Adjudication Committee will categorize patients as failure or success according to last observation data. If no imputation is possible, primary endpoint will be considered as failure.
Chi Square test will be used to compare primary endpoint (percentage of remission with a BVAS= o and prednisone dose ≤7.5 mg/day) in each arm. Multivariate logistic regression models will be used to analyse primary endpoint taking in account stratification criteria (FFS score,ANCA status and Newly diagnosed vs. relapsing EGPA). Other potential confounding factors may be explored as age (>ou<=65 years old) and kidney failure.

Sensitivity analysis will be performed to analyse primary endpoint following different hypotheses on population selected for analyses as exclusion of lost to follow up patients.

Secondary endpoint analyses

Analyses of secondary endpoints will be done in intention to treat and per protocol populations (particularly for safety data).

The following criteria will be:
The number of adverse events, expressed as adverse events according to the CTCAE toxicity grading system per patient-year at days 180 and 360 for the following adverse events combined: death (all causes), grade 2 or higher leukopenia or thrombocytopenia, grade 3 or higher infections, hemorrhagic cystitis, malignancies, venous thromboembolic events, hospitalization resulting either from the disease or from a complication due to the study treatment, infusion reactions (within 24 hours of infusion) that result in the cessation of further infusions
The area under the curve for corticosteroids at days 180 and 360 in the two treatment groups
The Vasculitis Damage Index (VDI) at days 180 and 360 in the two treatment groups. The HAQ and SF-36 scores at days 180 and 360 in the two treatment groups.
ANCA titers and CD19+ cells in the two treatment groups, and correlation with clinical events during follow-up
For severe adverse events that include treatment toxicity and relapse-related symptoms, analysis will be performed at the end of the study to classified these events in the right group.

Comparisons of two means will be analyzed using Student's t-test or wilcoxon signed rank test, when appropriate. Associations between categorical data will be analyzed using the Chi square or Fisher's exact test, when appropriate. Associations between two continuous measurements will be analyzed using Pearson correlation coefficient or Spearman correlation coefficient, when appropriate.

11.2 Calculation hypotheses for the number of subjects required and the result

Based on the results of previous trials from the French Vasculitis Study Group (FVSG), the proportion of patients with BVAS=0 and prednisone dose ≤7.5 mg/day at day 180 can be estimated at 60% in patients with EGPA.
The primary hypothesis of the REOVAS trial is an increase of at least 25% of the proportion of patients with BVAS=0 and prednisone dose ≤7.5 mg/day at day 180, i.e. 85%.
Based on this hypothesis, using a bilateral test, with a significance level of 5%, a beta level of 80%, 98 patients must be included, 49 patients in each arm. Taking into account 10% of patients lost to follow-up, 108 patients must be included, 54 in each arm.

11.3 Management of modifications made to the analysis plan for the initial strategy

A detailed analysis plan will be written and validated by the investigator and the biostatistician before database frozen. This plan will be validated by the scientific committee and any modification will be submitted and validated by this committee.

12. QUALITY CONTROL AND ASSURANCE

Each biomedical research project managed by AP-HP is ranked from A to D according to the projected risk incurred by research subjects using the classification of biomedical research sponsored by AP-HP.

12.1 General organisation

The sponsor must be responsible for the safety and respect of those subjects who have agreed to participate in the research. The sponsor must implement a quality assurance system to best monitor the conduct of the research in the investigation centres.

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

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

12.2 Quality control

A blind Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the proper conduct of the research, for collecting and documenting, recording and reporting the data generated in writing, in accordance with the Standard Operating Procedures applied within the DRCD and in accordance with the French Good Clinical Practices as well as with the legislative and regulatory provisions in force.

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

- written consent
- compliance with the research 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.

12.3 Case Report Form

All information required according to 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. Each missing data item must be coded.
This digital case report form will be implemented in each of the centres thanks to a web-based data collection medium. Investigators will be given a document offering guidance in using this tool.
When the investigators complete the case report 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. Thus, the investigator must validate any changes to the values in the case report form. These modifications will be subject to an audit trail. A justification can be added when applicable, as a comment. A certificate authenticated (signed and dated) by the investigator, will be requested at the end of the research in each center. The investigator must archive a copy of the authenticated document that was delivered to the sponsor.

12.4 Management of non-compliances

Any events that occur as a result of non-compliance, by the investigator or any other individual involved in conducting the research, with the protocol, with the standard operating procedures, with the good clinical practices or with the legislative and regulatory provisions in force must be noted in a declaration of non-compliance addressed to the sponsor. As a first step, major or critical non-compliances will be reviewed and processed by the DRCD's medical coordinator in order to implement the necessary corrective or preventive actions. Next, the non-compliances will be sent to the Quality - Risk Management Division of the DRCD for verification and analysis. These verifications could result in the investigator in charge of the research location in question being asked for information or could lead to compliance or audit visits.

12.5 Audits/inspections

The investigators agree to accept 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. Medical secrecy cannot be invoked in opposition to these audits and inspections.

An audit can be carried out at any time by individuals appointed by the sponsor and who are not associated with the research directors. The objective of the audit is to ensure the quality of the research, the validity of the results and compliance with the legislation and regulations in force.

The individuals who lead and monitor the research agree to comply with the sponsor's requirements and with the competent authority regarding research audits or inspections.

The audit may be applicable to all stages of the research, from the development of the protocol to the publication of the results and the organisation of the data used or produced as part of the research.

12.6 Primary investigator's commitment to assume responsibility

Before starting the research, each investigator will give the sponsor’s representative a copy of his/her personal curriculum vitæ, signed and dated, with his/her number in the RPPS (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals).

Each investigator will undertake to comply with the legislation and to carry out the research according to French GCP, adhering to the Declaration of Helsinki terms in force.

The primary investigator at each participating centre will sign a responsibility commitment (standard DRCD document) which will be sent to the sponsor's representative.

The investigators and their employees will sign a delegation of duties form specifying each person's role.

13. ETHICAL AND LEGAL CONSIDERATIONS

13.1 Methods for obtaining information and consent from research participants

In accordance with Article L1122-1-1 of the French Public Health Code, no biomedical research can be carried out on a person without free and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of said Code.

The subject will be granted a reflection period from one day to twenty days.
The free and informed consent, in writing, of the subject is obtained by the investigator, or by a doctor representing the investigator, before the inclusion of the subject in the research.

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, are given to the individual prior to his or her participation in the research.

In addition, the investigator will specify in the research participant's medical file the methods used for obtaining his or her consent as well as the methods used for providing information with the goal of obtaining their consent. The investigator will retain the original signed and dated copy of the subject's consent form.

13.2 Subject prohibited from participating in another research or an exclusion period anticipated after the research : Not applicable.

13.3 Legal obligations

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

13.4 Request for an opinion from the Comité de Protection des Personnes (CPP, ethical review board)

AP-HP, as sponsor, obtains for this biomedical research relating to a medication for human use and prior to starting the research, the favourable opinion of the appropriate CPP, within

the scope of its authority and in accordance with the legislative and regulatory provisions in force.
Of the many clinical variables that will be recorded, ethnicity will be noted because it may impact the efficacy of the experimental medication, as previously reported in lupus patients treated with rituximab, but also the analysis of genetic studies.

13.5 Request for authorisation to ANSM

AP-HP, as sponsor, obtains for this biomedical research relating to a medication for human use and prior to starting the research, authorisation from the ANSM, within the scope of its authority and in accordance with the legislative and regulatory provisions in force.

AP-HP, the research sponsor, has signed a commitment to comply with this "Méthodologie de reference".

14. FUNDING AND INSURANCE

14.1 Funding source

The present study will be submitted for funding to the PHRC 2014.

14.2 Insurance

For the duration of the research, the Sponsor will take out an insurance policy covering the sponsor's own civil liability as well as the civil liability of all the doctors involved in carrying out the research. The sponsor will also provide full compensation for all harmful consequences of the research for the research subjects and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any agent. The act of a third party or the voluntary withdrawal of the person who initially consented to participate in the research cannot be invoked against said compensation.

Assistance Publique - Hôpitaux de Paris (AP-HP) has taken out insurance from HDI-GERLING through BIOMEDIC-INSURE for the full research period, covering its own civil

liability and that of any agent (doctor or research staff), in accordance with Article L.1121-10 of the French Public Health Code.

15. PUBLICATION RULES

15.1 Mention of the AP-HP manager (DRCD) in the acknowledgements of the text

-"The sponsor was Assistance Publique – Hôpitaux de Paris (Département de la Recherche Clinique et du Développement, Clinical Research and Development Department)"

“The authors thank URC-CIC Paris Descartes Necker/Cochin for implementation, monitoring and data management of the study and DEC-AGEPS”

15.2 Mention of the financier in the acknowledgements of the text

-“ The research was funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC 2014 (Ministère de la Santé)”

This research will be registered on the website http://clinicaltrials.gov/.

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17. ADDENDA

17.1 Form for reporting Serious Adverse Events version 3 du 27/09/2017

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) Département de la Recherche Clinique et du Développement (DRCD)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS **Formulaire de notification d'un Evènement Indésirable Grave (EIG) survenant au cours d'une Recherche Biomédicale portant sur un Médicament ou produit assimilé**	**PARTIE RESERVEE AU PROMOTEUR** REFERENCE VIGILANCE : Référence GED : REC-DTYP-0192

Dès la prise de connaissance de l'EIG par l'investigateur, ce formulaire doit être dûment complété (3 pages), signé et retourné **sans délai** au secteur Vigilance du DRCD-Siège par **télécopie** au +33 (0)1 44 84 17 99

Notification initiale ☐ Suivi d'EIG ☐ N° du suivi |__|__|

1. Identification de la recherche	
Acronyme : REOVAS	Date de notification : __/__/2010 (jj mm aaaa)
Code de la Recherche : P140915	Date de prise de connaissance de l'EIG par l'investigateur : __/__/2010 (jj mm aaaa)
Risque : C	

Titre complet de la Recherche Biomédicale :
Comparaison d'un traitement par rituximab à la stratégie thérapeutique conventionnelle pour l'induction de la rémission au cours de la granulomatose éosinophilique avec polyangéite (syndrome de Churg-Strauss). Etude prospective, multicentrique, en double-aveugle, contrôlée, randomisée contre la stratégie thérapeutique conventionnelle

2. Identification du centre investigateur	
Nom de l'établissement :	Investigateur (nom/prénom) : .....
Ville et code postal :	
Service :	Tél : ..... Fax : .....

3. Identification et antécédents de la personne se prêtant à la recherche	
Référence de la personne : ___ - _____ - __ - __ (n° centre – n° d'inclusion – initiale nom – initiale prénom)	Antécédents médicaux-chirurgicaux/familiaux pertinents pour l'évaluation du cas (joindre un CRH anonymisé le cas échéant) : .....
Sexe : ☐ M ☐ F Poids : ___ kg Taille : ___ cm Surface corporelle : ___ m²	Date de naissance : __/__/____ (mm aaaa) Age : ___ ans
Date de signature du consentement : __/__/2010 (jj mm aaaa)	
Date de randomisation : __/__/2010 (jj mm aaaa)	Score FFS : ☐ FFS = 0 ☐ FFS ≥ 1
Patient : ☐ En rechute ☐ Nouvellement diagnostiqué	Présence d'ANCA à l'inclusion : ☐ Oui ☐ Non
Vaccination contre le pneumocoque : ☐ Oui ☐ Non	Vaccination contre la grippe : ☐ Oui ☐ Non

4. Médicament(s) expérimental(aux) (ME) avant la survenue de l'EIG
(barrer l'encadré si traitement non débuté)

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie[1]	Posologie (préciser l'unité ex : mg/j)	Date de début (jj/mm/aaaa)	En cours[1]	Date de fin (jj/mm/aaaa)
Rituximab ou placebo J1	.....	.....	|_|_| |_|_| |2|0|_|_|	☐	|_|_| |_|_| |2|0|_|_|
Rituximab ou placebo J15	.....	.....	|_|_| |_|_| |2|0|_|_|	☐	|_|_| |_|_| |2|0|_|_|
Cyclophosphamide ou placebo (pour FFS ≥ 1 ou ☐ NA) Préciser nombre de cures administrées : |_|_|	.....	.....	|_|_| |_|_| |2|0|_|_|	☐	|_|_| |_|_| |2|0|_|_|
Mesna ou placebo (pour FFS ≥ 1 ou ☐ NA)	.....	.....	|_|_| |_|_| |2|0|_|_|	☐	|_|_| |_|_| |2|0|_|_|

5. Médicament(s) non expérimental(aux) (ME) considérés comme procédures de la recherche avant la survenue de l'EIG
(barrer l'encadré si traitement non débuté)

Bolus de méthylprednisolone (pour FFS ≥ 1 ou ☐ NA)	.....	.....	|_|_| |_|_| |2|0|_|_|	☐	Nombre de pulse : .....
Prednisone (1ère dose administrée) J1	.....	.....	|_|_| |_|_| |2|0|_|_|	☐	|_|_| |_|_| |2|0|_|_|
Prednisone (dernière dose administrée : J |_|_|)	.....	.....	|_|_| |_|_| |2|0|_|_|	☐	|_|_| |_|_| |2|0|_|_|
Prémédication : Méthylprednisolone ☐ NA	.....	.....	|_|_| |_|_| |2|0|_|_|	☐	|_|_| |_|_| |2|0|_|_|
Prémédication : Paracétamol ☐ NA	.....	.....	|_|_| |_|_| |2|0|_|_|	☐	|_|_| |_|_| |2|0|_|_|
Prémédication : Dexchlorphéniramine ☐ NA	.....	.....	|_|_| |_|_| |2|0|_|_|	☐	|_|_| |_|_| |2|0|_|_|
Azathioprine ☐ NA	.....	.....	|_|_| |_|_| |2|0|_|_|	☐	|_|_| |_|_| |2|0|_|_|

6. Médicament(s) concomitant(s) au moment de l'EIG, à l'exclusion de ceux utilisés pour traiter l'événement indésirable
(compléter le tableau ci-après et si nécessaire l'annexe relative aux médicaments concomitants ou barrer l'encadré si non applicable)
⇨ Annexe jointe au présent formulaire : ☐ Oui ☐ Non

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie[1]	Posologie (préciser l'unité ex : mg/j)	Dates d'administration (du jj/mm/aa au jj/mm/aa)	En cours [2]	Indication	*Action prise* *0 : poursuite sans modification de la posologie* *1 : arrêt* *2 : diminution de la posologie* *3 : augmentation de la posologie* *4 : ne sais pas*	*Causalité de l'EIG* *0 : non lié au médicament* *1 : lié au médicament* *2 : ne sais pas*
			du |_|_| |_|_| |_|_| au |_|_| |_|_| |_|_|	☐			
			du |_|_| |_|_| |_|_| au |_|_| |_|_| |_|_|	☐			

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser) (2) En cours au moment de la survenue de l'EIG

Acronyme : REOVAS

Référence de la personne se prêtant à la recherche : |__|__|__|- |__|__|__|__|__| - |__| - |__|
centre - n° d'inclusion - initiale nom - initiale prénom

PARTIE RESERVEE AU PROMOTEUR
REFERENCE VIGILANCE :
Référence GED : REC-DTYP-0192

7. Evènement indésirable grave [EIG]

Diagnostic : ☐ Définitif ☐ Provisoire

.....

Organe(s) concerné(s) :

.....

Date de survenue des premiers symptômes : |__|__| |__|__| |2|0|__|__|

Préciser lesquels :

.....

Date d'apparition de l'EIG :
|__|__| |__|__| |2|0|__|__|
jj mm aaaa

Heure de survenue : |__|__| hh |__|__| min
☐ *donnée manquante*

Délai entre la date de la dernière administration du ME/produit assimilé ou la date de procédure/acte ajouté par la recherche et la date de survenue de l'EIG :
|__|__| / |__|__| |__|__|
jj hh min

Critères de gravité :

☐ Nécessite ou prolonge l'hospitalisation :

ou |__|__| |__|__| |2|0|__|__|

au |__|__| |__|__| |2|0|__|__| ☐ *en cours*

☐ Décès
☐ Mise en jeu du pronostic vital
☐ Incapacité ou handicap important ou durable
☐ Anomalie ou malformation congénitale
☐ Autre(s) critère(s) médicalement significatif(s), préciser :

.....

L'évènement a-t-il conduit à :
☐ aucune mesure prise concernant le ME
☐ diminution de la posologie du ME ☐ augmentation de la posologie du ME
☐ arrêt définitif du ME
☐ arrêt transitoire du ME, date de reprise : |__|__| |__|__| |2|0|__|__|
☐ ne sais pas

Récidive de l'EIG après ré-administration : ○ Non ○ Oui Date : |__|__| |__|__| |2|0|__|__|
○ Non applicable

Des mesures symptomatiques ont-elles été prises ?
☐ Non ☐ Oui Date : |__|__| |__|__| |2|0|__|__| Préciser : .....

L'évènement a-t-il conduit à une levée d'insu ?
☐ Non ☐ Oui Date : |__|__| |__|__| |2|0|__|__| Préciser le résultat : .....

Degré de sévérité selon l'échelle CTCAE :
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

L'évènement fait-il suite à :

- une erreur médicamenteuse ?	☐ Non	☐ Oui	Date : |__|__| |__|__| |2|0|__|__|
- un surdosage ?	☐ Non	☐ Oui	Date : |__|__| |__|__| |2|0|__|__|
- un mésusage ?	☐ Non	☐ Oui	Date : |__|__| |__|__| |2|0|__|__|
- autre (préciser) :	☐ Non	☐ Oui	Date : |__|__| |__|__| |2|0|__|__|

Evolution de l'événement

☐ **Décès**
○ sans relation avec l'EIG
○ en relation avec l'EIG
Date : |__|__| |__|__| |2|0|__|__|
jj mm aaaa

☐ **Sujet non encore rétabli**, préciser :
○ Etat stable ○ Amélioration ○ Aggravation

☐ **Résolu :**
○ sans séquelles
○ avec séquelles, préciser lesquelles :
Date : |__|__| |__|__| |2|0|__|__|
jj mm aaaa
|__|__| |__|__|
hh min

☐ **Evolution inconnue**

Acronyme : REOVAS

Référence de la personne se prêtant à la recherche : |_|_|_|_|- |_|_|_|_|_|_|_| - |_|_| - |_|_|
(Centre - n° d'inclusion - Initiale nom - Initiale prénom)

PARTIE RESERVEE AU PROMOTEUR
REFERENCE VIGILANCE :
Référence GED : REC-DTYP-0192

8. Autre(s) étiologie(s) envisagée(s)

☐ Non ☐ Oui Si oui, préciser : .....

9. Examen(s) complémentaire(s) réalisé(s)

☐ Non ☐ Oui Si oui, préciser date, nature et résultats : (joindre les bilans anonymisés, par exemple : CD19, hémogramme, taux d'Immunoglobulines, taux de CD4, CD8 ..)

.....

10. Selon l'investigateur, l'événement indésirable grave est (plusieurs cases possibles)

Lié à la recherche biomédicale :

☐ **Oui :**

☐ **au(x) médicament(s)/produit(s) assimilé(s) de la recherche : le(s)quel(s) ?**

Rituximab/placebo ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable ☐ non lié
Cyclophosphamide/placebo ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable ☐ non lié
Mesna/placebo ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable ☐ non lié

☐ **à la (aux) procédure(s)/acte(s) de la recherche biomédicale : la/le(s)quel(les) ?**

Méthylprednisolone (bolus) ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable ☐ non lié
Prednisone ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable ☐ non lié
Azathioprine ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable ☐ non lié
Méthylprednisolone ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable ☐ non lié
Dexchlorpheniramine ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable ☐ non lié
Paracétamol ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable ☐ non lié

☐ **Non :** ☐ **à la progression de la maladie faisant l'objet de la recherche : granulomatose éosinophilique avec polyangéite**
☐ **à un (ou plusieurs) médicament(s) concomitant(s) administré(s), le(s)quel(s) :** .....
☐ **à une maladie intercurrente, laquelle :** .....
☐ **autre, préciser :** .....

Notificateur	Investigateur	Tampon du service :
Nom et fonction : Signature	Nom : Signature	

17.2 : Birmingham Vasculitis Activity Score (BVAS) version 3

Ne cocher que les manifestations témoignant d'une maladie active (les séquelles présentes depuis plus de 3 mois sont appréciées par le VDI). 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 sont ceux pour une maladie active récemment / maladie faiblement active, « grumbling » (case du bas cochée). Ne faire que la somme d'une seule des colonnes.

	Oui
1. Signes généraux	**|__| (maximum 3 / 2)**
Myalgies	☐ 1 / 1
Arthralgies ou arthrites	☐ 1 / 1
Fièvre ≥ 38°C	☐ 2 / 2
Amaigrissement ≥ 2 kg	☐ 2 / 2
2. Signes cutanés	**|__| (maximum 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	**|__| (maximum 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	**|__| (maximum 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	**|__| (maximum 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

	Oui
6. Signes cardiaques	**|__| (maximum 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. Manifestations digestives	**|__| (maximum 9 / 4)**
Péritonite	☐ 9 / 3
Diarrhée sanglante	☐ 9 / 3
Douleur abdominale (angor digestif)	☐ 2 / 6
8. Signes rénaux	**|__| (maximum 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	**|__| (maximum 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 ☐

Préciser :……
……
……
……..

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

17.3 Questionnaire patient HAQ

REOVAS Page 1 / 4	Code d'identification Patient __ __ __ / __ __ __ __ / __ __	Visite : __ __ Date : __ __/__ __ /__ __

Questionnaire HAQ d'évaluation des capacités fonctionnelles

Ce questionnaire est destiné à connaître les répercussions de votre maladie sur vos capacités à effectuer les activités de la vie quotidienne. Répondez à toutes les questions et n'hésitez pas à ajouter vos commentaires au bas de ce questionnaire.

• Pendant les huit derniers jours, avez-vous été capable de :
(Entourez la réponse choisie)

	Sans AUCUNE difficulté	Avec QUELQUE de difficulté	Avec BEAUCOUP de difficulté	Incapable de le faire
S'habiller et se préparer				
• Vous habiller, y compris nouer vos lacets et boutonner vos vêtements	0	1	2	3
• Vous laver les cheveux	0	1	2	3
Se lever				
• Vous lever d'une chaise	0	1	2	3
• Vous mettre au lit et vous lever du lit	0	1	2	3
Manger				
• Couper votre viande avec un couteau	0	1	2	3
• Porter à votre bouche une tasse ou un verre bien plein	0	1	2	3
• Ouvrir une brique de lait ou de jus de fruit	0	1	2	3
Marcher				
• Marcher en terrain plat à l'extérieur	0	1	2	3
• Monter 5 marches	0	1	2	3

• Cochez chacun des appareils dont vous vous servez régulièrement pour effectuer ces activités :

|__| Canne |__| Déambulateur

|__| Béquilles |__| Chaise spécialement adaptée

|__| Chaise roulante

|__| Accessoire pour s'habiller (crochet à bon ou à fermeture-éclair, chausse-pied à long manche…)

|__| Autre(s) (préciser) : _____

• Cochez chacun des items pour lesquels vous avez habituellement besoin de l'aide d'une autre personne :

|__| S'habiller et se préparer |__| Manger

|__| Se lever |__| Marcher

• Au cours des huit derniers jours, quelle réponse décrit le mieux vos capacités :
(Entourez la réponse choisie)

	Sans AUCUNE difficulté	Avec QUELQUE difficulté	Avec BEAUCOUP de difficulté	Incapable de le faire
Hygiène				
• Vous lavez et vous sécher entièrement	0	1	2	3
• Prendre un bain	0	1	2	3
• Vous asseoir et vous relever des toilettes	0	1	2	3
Attraper				
• Prendre un objet pesant 2,5 kg situé au dessus de votre tête	0	1	2	3
• Vous baisser pour ramasser un vêtement par terre	0	1	2	3
Préhension				
• Ouvrir une porte de voiture	0	1	2	3
• Dévisser le couvercle d'un pot déjà ouvert une fois	0	1	2	3
• Ouvrir ou fermer un robinet	0	1	2	3
Autres activités				
• Faire vos courses	0	1	2	3
• Monter et descendre de voiture	0	1	2	3
• Faire des travaux ménagers tels que passer l'aspirateur ou faire du petit jardinage	0	1	2	3

• Cochez chacun des appareils ou accessoires dont vous vous servez régulièrement pour effectuer ces activités :

|__| Siège de W-C surélevé

|__| Poignée ou barre de baignoire

|__| Siège de baignoire

|__| Ouvre pots (pour les pots déjà ouverts)

|__| Instrument à long manche pour attraper les objets

|__| Instrument à long manche dans la salle de bain

Autre(s) (préciser) :_____

• Cochez chacun des items pour lesquels vous avez habituellement besoin de l'aide d'une autre personne :

|__| Hygiène

|__| Saisir et ouvrir des objets

|__| Atteindre et attraper

|__| Courses et tâches ménagères

17.4 Questionnaire patient SF36

REOVAS Page 3 / 4	Code d'identification Patient __ __ __ / __ __ __ __ / __ __	Visite : __ __ Date : __ __/__ __ /__ __

Questionnaire de santé SF36

Version JUILLET 2009

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

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

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

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
À peu près pareil	3
Plutôt moins bon	4
Beaucoup moins bon	5

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 souhaitées ?	1	2
c. Avez-vous dû 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 gêné(e) dans votre vie sociale et vos relations avec les autres, votre famille, vos amis, 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

10. Au cours de ces 4 dernières semaines. y a-t-il eu des moments où votre état de santé, physique ou émotionnel, vous a gêné(e) dans votre vie 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

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3. Voici une liste d'activités que vous pouvez avoir à faire dans votre vie de tous les jours. Pour chacune d'entre elles indiquez si vous êtes limité(e) en raison de votre état de santé actuel. *(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 les courses	1	2	3
d. Monter plusieurs étages par l'escalier	1	2	3
e. Monter un étage par l'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

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)*

	En permanence	Très souvent	Souvent	Quelque 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	6
h. vous vous êtes senti(e) heureux (se)?	1	2	3	4	5	6
i. vous vous êtes senti(e) fatigué(e)?	1	2	3	4	5	6

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)*

	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

Veuillez vérifier que vous avez bien fourni une réponse pour chacune des questions. Merci de votre collaboration.

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17.5 Patient card

CARTE PATIENT

Merci de garder cette carte en permanence avec vous

Nom :…….…… Prénom : …….

Code d'identification patient : ___ ___ ___ / ___ ___ ___ ___ / ___ ___

Je participe à la recherche biomédicale REOVAS dont le promoteur est l'AP-HP.

☐ **Si FFS = 0**

Je reçois du rituximab/placebo IV, à la dose de 1g, à J1 et J15.

☐ **Si FFS ≥ 1**

Je reçois du cyclophosphamide/placebo IV, à H0, à la dose de 600mg/m² à J1, J15 et J29 (plafonnée à 2m²)
puis à 500mg dose fixe à J50, J71, J92, J113, J134, et J155
associé à du mesna/placebo IV, à la dose de 200mg/m² à H0 et H4, à J1, J15 et J29
puis à 200mg dose fixe à J50, J71, J92, J113, J134, et J155.
Je reçois aussi du rituximab/placebo IV, à la dose de 1g, à J1 et J15.

Date de début de traitement : ___ ___ /___ ___ /___ ___ ___ ___

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CARTE PATIENT

Je suis suivi(e) par le Dr……

A l'Hôpital ……..……..

☎……...

Version n°2.0 du 20/06/2016

17. 6 Collection book for patient reporting prednisone tapering

Etude REOVAS	Code d'identification patient |___|___|___| / |___|___|___|___| / |___|-|___|	CARNET n° 1 / 4 De l'inclusion à la visite à 3 mois

Etude REOVAS

Comparaison d'un traitement par rituximab à la stratégie thérapeutique conventionnelle pour l'induction de la rémission au cours de la granulomatose éosinophilique avec polyangéite (syndrome de Churg-Strauss).
Etude prospective, multicentrique, en double-aveugle, contrôlée, randomisée contre la stratégie thérapeutique conventionnelle

CARNET N°1 POUR LE SUIVI DE L'OBSERVANCE DES CORTICOIDES

DU |___|___| / |___|___| / |___|___| **au** |___|___| / |___|___| / |___|___|

Etude REOVAS	Code d'identification patient |___|___|___| / |___|___|___|___| / |___|-|___|	CARNET n° 1 / 4 De l'inclusion à la visite à 3 mois

Nous vous remercions de bien vouloir remplir ce carnet à partir du 1er jour de traitement dans l'étude et pendant vos 12 mois de participation, et de le rapporter à votre médecin lors de chaque consultation.

**N'OUBLIEZ PAS DE DEMANDER TOUS LES 3 MOIS A VOTRE MEDECIN,
LE CARNET POUR LES 3 MOIS SUIVANTS.**

Aide au remplissage :

Notez le jour de la semaine qui correspond à l'administration de votre 1ère cure (lundi, mardi, … ou dimanche)

La semaine 1 commence ce jour-là et se termine le dimanche qui suit.

A partir du lundi d'après, vous êtes à la semaine 2 (une ligne par semaine).

Ce carnet vous permet de noter tous les changements de doses dans les corticoïdes que vous prenez avec les dates correspondantes à ces changements.

Il vous sera demandé par votre médecin et sera revu avec lui lors de chaque consultation.

Tous les 3 mois vous aurez un nouveau carnet.

Etude REOVAS	Code d'identification patient |___|___|___| / |___|___|___|___|___| / |___|-|___|	CARNET n° 1 / 4 De l'inclusion à la visite à 3 mois

Date du début de votre traitement : 1ère cure __ __ /__ __ /__ __ __ __	CORTICOIDES : Dose en mg/jour |___|___|, |___|	Noter dans cette colonne tous les changements dans les doses de corticoïdes que vous prenez avec les dates correspondantes		Les doses de corticoïdes prescrites ont-elles été respectées ? Oui ❒ Non ❒ Si non (traitement non pris ou partiellement pris), indiquez-en le motif ci-dessous :
A quel jour de la semaine cela correspond : _____	= Semaine 1			
Semaine 2 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |___|___|, |___| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____
Semaine 3 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |___|___|, |___| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____
Semaine 4 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |___|___|, |___| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____

17.7 Summary of product characteristics (SmPC)

Rituximab : http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000165/WC500025821.pdf (dernière version du 02/08/2016)

Cyclophosphamide : http://base-donnees-publique.medicaments.gouv.fr/affichageDoc.php?specid=68564413&typedoc=R (dernière version du 21/08/2015)

Uromitexan : http://base-donnees-publique.medicaments.gouv.fr/affichageDoc.php?specid=69566673&typedoc=R (dernière version du 04/07/2016)