MAINtenance of remission with **RIT**uximab versus azathioprine for patients with newly-diagnosed or relapsing **E**osinophilic **G**ranulomatosis with polyangiitis. A prospective, randomized, controlled, double-blind study: the MAINRITSEG trial.

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Title: **MAIN**tenance of remission with **RIT**uximab versus azathioprine for patients with newly-diagnosed or relapsing **E**osinophilic **G**ranulomatosis with polyangiitis. A prospective, randomized, controlled, double-blind study: the MAINRITSEG trial.

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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 24/03/2017 and authorisation from the ANSM on 18/11/2016.

CONTENTS

18.6. Sino-Nasal Outcome Test-22 Questionnaire
18.7. Patient’s card
18.8. Logbook for the adhesion to the treatment
18.9. Link for the SmPC for the “Azathioprine 25mg“speciality
18.10. Form for reporting Serious Adverse Events
18.11. Form for monitoring a pregnancy that developed during a biomedical research
18.12. Abacuses for azathioprine/placebo
18.13. Link for the SmPC for the Mabthera
18.14. Information letter for patients included in the REOVAS study

ABREVIATIONS

AAV: ANCA-associated Vasculitis
ACQ: Asthma Control Questionnaire
ACR: American College of Rheumatology
ANCA: Anti-Neutrophil Cytoplasmic Antibody
ANSM: Agence Nationale de Sécurité du Médicament
BVAS: Birmingham Vasculitis Activity Score
CPP: French Ethics Committee (Comité de Protection des Personnes)
CS: corticosteroids
CYC: Cyclophosphamide
EGPA: Eosinophilic Granulomatosis with PolyAngiitis
ENT: Ear, Nose and Throat
FFS: Five Factor Score
FVSG: French Vasculitis Study Group
GPA: Granulomatosis with PolyAngiitis
HAQ: Health Assessment Questionnaire
IL: interleukin
MAINRITSAN: MAINtenance of remission using RITuximab in Systemic ANca associated vasculitides
MPA: Microscopic PolyAngiitis
MPO: Myeloperoxidase
PR3: Proteinase 3
RTX: rituximab
SNOT-22: Sino-Nasal Outcome Test-22
ST2: growth STimulation expressed gene 2
TARC: Thymus and Activation Regulated Chemokine
TSLP: Thymic Stromal Lymphopoietin
ULN: Upper Limit of Normal
VDI: Vasculitis Damage Index

1. SUMMARY

Full title	**MAIN**tenance of remission with **RIT**uximab versus azathioprine for patients with newly-diagnosed or relapsing **E**osinophilic **G**ranulomatosis with polyangiitis. A prospective, randomized, controlled, double-blind study.
Acronym	MAINRITSEG
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Scientific justification	Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss). EGPA has distinct features: asthma, rhino-sinusal involvement, hypereosinophilia, eosinophilic tissue infiltration and necrotizing granulomatosis vasculitis. Conventional immunosuppressive therapy and corticosteroids have been the standard of care for remission induction and maintenance for four decades. This regimen has transformed the disease outcome from death to a strong likelihood of disease control and temporary remission. However, most patients have recurrent relapses that lead to damage and require repeated treatment. Cumulative side effects of immunosuppressants and corticosteroids remain major causes of long-term morbidity, damage and death. Rituximab, an anti-CD20 monoclonal antibody, has been shown to be as effective as cyclophosphamide to induce GPA and MPA remission, with an acceptable safety profile, leading to its registration by the FDA and EMA as remission-induction therapy in these patients. In addition, in the MAINRITSAN trial (PHRC-2008), our group has demonstrated that 500 mg rituximab given every 6 months for 18 months was significantly more effective than azathioprine standard of care to maintain remission in GPA and MPA, with a similar profile of tolerance. EGPA patients were excluded from these trials. Long-term studies have shown that only 29% of EGPA patients achieved long-term remission and that relapses occurred in more than 40% of them, leading to high cumulative morbidity and damage. Moreover, most patients cannot be weaned off corticosteroids due to asthma and rhino-sinusal manifestations, even after vasculitis remission. However, recent retrospective series indicated that rituximab may also be an effective remission induction and maintenance agent in refractory or relapsing EGPA. REOVAS (PHRC-2013), the first randomized controlled trial with rituximab as induction therapy in EGPA, has started within our network.
Primary objective and assessment criterion	Primary objective To investigate, after achievement of remission, the efficacy of

	rituximab compared with azathioprine maintenance therapy on duration of remission, defined as accrued duration in weeks where BVAS=0 and prednisone dose ≤7.5 mg/day, in patients with relapsing or newly-diagnosed EPGA receiving standard of care therapy including corticosteroid therapy reduction/withdrawal. <u>Primary assessment criterion</u> The total duration of remission over the 28 month study period, i.e., the accrued number of weeks where a patient remains in remission with BVAS=0 and prednisone dose ≤7.5 mg/day.
Secondary objectives and assessment criteria	<u>Secondary objectives</u> To investigate rituximab versus azathioprine maintenance therapy on: - proportion of patients remaining in remission with a BVAS=0 and prednisone dose ≤7.5 mg/day at month 28 - number and severity of vasculitis relapses and asthma/rhino-sinusal exacerbations - variation of the obstructive pulmonary disease - time to vasculitis relapses - time to significant asthma/rhino-sinusal exacerbations - corticosteroid sparing effect - safety, survival, damage, and quality of life. <u>Secondary assessment criteria</u> - proportion of patients remaining in remission with a BVAS=0 and prednisone dose ≤7.5 mg/day over the 28 month study period - proportion of patients remaining in remission with a BVAS=0 over the 28 month study period - proportion of patients with at least one vasculitis relapse (major, minor, either) over the 28 month study period - proportion of patients with at least one clinically significant asthma/rhino-sinusal exacerbation defined as a worsening of asthma/rhino-sinusal disease leading to the doubling (or more) of the existing maintenance dose of corticosteroids for 3 or more days or hospital admission or an emergency department visit over the 28 month study period - time to first vasculitis relapse - time to first significant asthma/rhinosinusal exacerbation variation of the obstructive pulmonary disease assessed by change of FEV_1 at pulmonary function tests after use of a bronchodilator over the 28 month study period - prednisone dose at months 6, 12, 18, 24 and 28, and area under the curve over the 28 month study period mean blood eosinophilia during the trial - proportion of patients over the 28 month study period with adverse events, serious adverse events and selected severe adverse events including grade 3 or 4 adverse effects (Common Terminology Criteria for Adverse Events), necessitating hospitalization, all cause deaths, cancers or infusion reactions (within 24hours of infusion) that contraindicated further infusions, number and causes of deaths over the 28 month study period, rhino-sinusal exacerbation assessed by the Sino-Nasal Outcome Test-22 questionnaire (SNOT-S22) over the 28 month study period - the damage (VDI), disability (HAQ) and quality of life (SF36) scores over the 28 month study period - asthma exacerbation assessed by the Asthma Control Questionnaire (ACQ) over the 28 month study period - damage assessed by the mean variation of the Vasculitis Damage Index (VDI) during the 28 months after randomization

	- quality of life assessed by the mean variation of the SF-36 over the 28 month study period - disability assessed by the mean variation of the Health Assessment Questionnaire (HAQ) over the 28 month study period - the number of days of hospitalization over the 28 month study period.
Experimental design Randomization	Phase III, comparative, multicenter, randomized, double-blind, double-dummy and superiority trial, comparing pre-emptive low-dose rituximab-based regimen with azathioprine standard therapy, for the remission maintenance in newly-diagnosed or relapsing EGPA. Patients will be randomized, with competitive recruitment, in a 1:1 ratio to receive (Figure 1). - Standard regimen: maintenance oral azathioprine (2 mg/kg/day) for 24 months. This control group will receive conventional therapy plus 4 infusions of placebo-rituximab (every 6 months for 18 months) - Experimental regimen: pre-emptive 500-mg fixed-dose of rituximab every 6 months for 18 months (4 infusions). This group will receive intravenous rituximab plus orally placebo-azathioprine for 24 months.
Population involved	Patients with newly diagnosed or relapsing EGPA, after achievement of remission. Patients included in the REOVAS study will be eligible. The REOVAS last visit (month 12 evaluation) may coincide with the selection visit of the MAINRITSEG trial.
Inclusion criteria	- Patients with a diagnosis of EGPA according to Lanham and/or ACR 1990 criteria and/or Revised Chapel Hill Nomenclature and/or MIRRA study inclusion criteria - 18 years of age or more - with newly-diagnosed EGPA or after a vasculitis flare and remission achieved within the past year - independently of ANCA status - within 30-360 days following achievement of vasculitis remission (corresponding to a Birmingham Vasculitis Activity Score (BVAS)=0) achieved with an induction regimen including the one used in the REOVAS trial: either CS alone or in association with CYC (total dose ranging from 4.5-10 g) or RTX (2 x 1g (D1, D15) or 4 weekly 375 mg/m^2). - with a stable prednisone dose for 30 days or no more prednisone - after oral immunosuppressive drug cessation if started at remission. - Patients included in the REOVAS trial and achieving remission can be included at month 12 visit if they fulfil the other criteria - Patients 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 vasculitides - patients with vasculitis not in remission defined as a BVAS >0 - acute or chronic active infections (including HIV, HBV or HCV) - active or recent cancer (<5 years), except basocellular carcinoma and low activity prostatic cancer controlled by hormonal treatment - severe heart failure (New York Heart Association Class IV) or

	severe, uncontrolled cardiac disease - pregnant women and lactation - patients with childbearing potential will have reliable contraception for all the duration of the study and another 12 months after - patients who had already been treated with rituximab before the last relapse/flare - patients who have been treated with rituximab with a different induction regimen than 2 x 1g (D1, D14) or 4 weekly 375 mg/m^2 infusions - hypersensitivity to a monoclonal antibody or biologics - contraindication to rituximab or azathioprine - other uncontrolled diseases, including drug or alcohol abuse, severe psychiatric diseases, that could interfere with participation - patients included in other investigational therapeutic study within the previous 3 months except in the REOVAS trial, after which patients achieving remission can be included if they fulfil the other criteria - patients suspected not to be observant to the proposed treatments - white blood cell count ≤4,000/mm^3 - platelet count ≤100,000/mm^3 - ALT or AST level >3 times the upper limit of normal that cannot be attributed to underlying EGPA disease - patients not able to stop allopurinol and febuxostat which may enhance azathioprine toxicity - patients unable to give written informed consent prior to participation in the study.
Experimental arm	All patients will receive: - pre-emptive 500-mg fixed-dose of IV rituximab every 6 months (total duration of 18 months = 4 infusions) - plus orally placebo-azathioprine for 24 months.

Control group	The control group will receive: - standard maintenance oral azathioprine therapy (2 mg/kg/day) for 24 months - plus 4 placebo−rituximab infusions given every 6 months for 18 months -
Other procedures added by the research	Patients receiving rituximab or placebo-rituximab infusion will receive premedication including 100 mg of methyl-prednisolone, paracetamol and dexchlorpheniramine. In accordance with standard of care, in the absence of clinical manifestations, to obtain total prednisone therapy duration after disease onset/flare of approximately 12 months, both groups will receive the same predefined prednisone tapering regimen of 1 mg/day/month, until discontinuation. For example: - D0-D27: 7 mg/day - D28-D55: 6 mg/day - D56-D83: 5 mg/day - D84-D111: 4 mg/day - D112-D139: 3 mg/day - D140-D167: 2 mg/day - D168-D195: 1 mg/day - After D196 (6.5 months): discontinuation of prednisone. Corticosteroids dose according to EGPA activity: - No activity: decrease prednisone according to schedule

	- Mild asthma and/or ENT manifestations: maintain current steroids dose - Clinical flare: optimal therapy chosen according to severity by the physician in charge of the patient.
Risks added by the research	Risk C
Number of patients	98 patients, 49 patients in each arm In absence of hypothesis on total duration of remission and based on the results of our previous trials in EGPA, whatever the Five Factor Score, the proportion of patients experiencing vasculitis relapse or asthma-rhino-sinusal exacerbation despite maintenance therapy is expected to be 35% at 28 months. Thus, a total of 35% of patients are expected to have an uncontrolled disease at 28 months in the azathioprine control group.The primary hypothesis of the trial is a decrease of at least 66% of the rate of uncontrolled disease at 28 months, i.e. 12%. With this hypothesis, including patients lost to follow-up, using a bilateral test, 98 patients are required to have 80% power to detect a 66% reduction in the relative risk with a two-sided alpha level of 5%.
Number of centers	50 centers of the French Vasculitis Study Group network
Research period	Recruitment period: 24 months Study participation for each patient: 28 months Total duration of the trial: 52 months
Inclusions (Nb) expected per center and per month	1.96 patients per center (0.98 per year per center) among the French Vasculitis Study Group network.
Statistical analysis	Statistical analyses will be performed in the Department of Epidemiology, Paris Descartes University, INSERM U 738 (Pr Philippe Ravaud). Patients will be stratified with a covariate-adaptative randomization according to: - Newly diagnosed vs. relapsing EGPA - Vasculitis severity (FFS=0 vs. FFS ≥1) of the last flare - ELISA ANCA status (anti-MPO or -PR3 positive vs. negative) at the last vasculitis flare - Induction therapy (corticosteroids + cyclophosphamide vs. corticosteroids + rituximab vs. corticosteroids alone). A random-effects Cox proportional hazards will be used to compare total duration of remission over the 28 month study period with a random effect at center levels.

2. SCIENTIFIC JUSTIFICATION for the research

2.1. Hypothesis for the research

The MAINRITSEG study aims to evaluate rituximab compared with azathioprine conventional strategy for remission maintenance inpatients with eosinophilic granulomatosis with polyangiitis (EGPA) with the objective to obtain longer total duration of remission with prednisone dose ≤7.5 mg/day over the 28 month study period.

2.2. Description of knowledge relating to the hypothesis for the research

2.2.1 ANCA-associated vasculitides

Systemic vasculitides are inflammatory diseases of blood vessels, among which anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are among the most severe 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-sized blood vessels, with a predilection for the respiratory tract and kidneys.

2.2.2. Clinical manifestations of 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 have to be present in a patient with evidence of vasculitis (Table 1) [3].

Table 1. American College of Rheumatology classification criteria for Churg-Strauss syndrome [3]

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

Extravascular eosinophils

Revised Chapel Hill nomenclature

EGPA is defined as eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. Nasal polyps are common.

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 40% of the patients [5-8]. The clinical presentation of the 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 eosinophilia usually disappears rapidly after corticosteroids are started.

ANCA, predominantly perinuclear ANCA of anti-MPO specificity, are present in close to 40% of EGPA patients but few can haveinfrequentlyanti-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].

2.2.3. 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 other immunosuppressant(s) [11]. Whereas in 1950, the 5-year patient survival of polyarteritis nodosa (not yet separated from EGPA) was 10%, today, the overall 8-year survival of EGPA is up to 92% [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, are: *1*) proteinuria >1 g/24h; *2*) serum creatinine level >140 µmol/l; *3*) myocardial involvement; *4*) severe gastrointestinal involvement; *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 46.0% ($p < 0.0001$ 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 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 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 has been 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 haematuria) as impinging on outcome.

Along this line, in 2015, 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, most patients still have disease flares that require repeated treatment.

When EGPA patients without poor prognosis factor (FFS=0) have been treated with AZA in association with corticosteroids as induction therapy, the results of the CHUSPAN 2 trial remain comparable, with a still high percentage of patients having an uncontrolled disease and requiring long-term immunosuppressive drugs [15].

Analyses of long-term trials in patients with EGPA, conducted by the French Vasculitis Study Group, have also shown that the probability of uncontrolled disease without maintenance therapy was similar in patients whatever the FFS score at inclusion and remains to be improved [11]:
In EGPA patients with FFS=0 who had initially received only corticosteroid therapy without maintenance treatment in the CHUSPAN BP trial [11,16], at month 28, vasculitis flares (EULAR definition) have occurred in 28.4% and asthma/rhino-sinusal exacerbation/eosinophilia leading to an increase in corticosteroid dose or other immunosuppressant use in 30.2% patients, giving a total of 58% patients with uncontrolled disease at month 28.
In EGPA patients with FFS ≥1,who had received initially corticosteroid therapy and were randomized to receive 6 or 12 pulses of cyclophosphamide without maintenance therapy in the CHUSPAN MP trial [11,12], vasculitis flares have occurred at month28 in 29.7% and asthma/rhino-sinusal exacerbation/eosinophilia leading to an increase in corticosteroid dose or other immunosuppressant use in 30.5% patients, giving also a total of 60% patients with uncontrolled disease at month 28.
ANCA-positivity, cutaneous manifestations and a low eosinophil count at the time of EGPA diagnosis were predictive of vasculitis relapse [5].
It has to be stressed that none of these patients had received a maintenance regimen which was not given routinely at that time. These data suggested that, as with other AAV, EGPA patients would also benefit from maintenance therapy to avoid relapses and allow corticosteroid tapering but no study has yet evaluated immunosuppressant use for EGPA maintenance therapy.

The prospective, multicenter, randomized, WEGENT trial, conducted by the French Vasculitis Study Group, evaluated the safety and efficacy of azathioprine versus methotrexate, combined with prednisone, as maintenance therapy for severe GPA or MPA, after complete remission had been achieved with glucocorticoids and pulse intravenous cyclophosphamide [17]. Trial results demonstrated that azathioprine was as effective as MTX at maintaining GPA or MPA remission at short- and long-term analysis [18]. Thus, either agent has emerged as standard care for AAV-remission maintenance.

The optimal duration of maintenance therapy remains unknown. According to the BSR and BHPR guideline, maintenance therapy is recommended for at least 24 months following successful disease remission for AAV patients [19].

In conclusion, the current therapeutic strategy in EGPA has led to good remission and survival rates. But without maintenance therapy, relapses remain a matter of concern and uncontrolled disease is observed in nearly one half of the patients at month 28, leading to high cumulative morbidity and damage. Cumulative side effects of immunosuppressive agents as well as adverse effects of glucocorticoids remain major causes of long-term disease and sequelae in these patients. Thus, it remains unmet needs to improve the long-term outcome and to evaluate maintenance regimen in controlled studies of EGPA patients.

Table 2. The Five Factor Score (FFS), as established based on 342 patients with PAN or EGPA [13].

Proteinuria > 1 g/24 h **Creatinemia >140 µmol/L** **Specific gastrointestinal involvement** **Specific cardiomyopathy** **Specific central nervous system involvement**	**FFS**	**5 year survival rate (%)**	**Relative risk**
	0	88.1	0.62
	1	74.1*	1.35
	≥ 2	54.1**	2.40

1 point accorded for each of these 5 items when present

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

2.3. Justification of the research

2.3.1. Description of knowledge relating to the hypothesis for the research

The 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 [20], 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 [21]. 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 [7,8]. 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 haemorrhage, 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 [22]. 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 [23,24]. 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 [25]. 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 [26].

Active EGPA patients also exhibit a consistent increase in the production of IgG4 [27], 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 IL-4, IL-5 and IL-13.

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 factors, including genetic susceptibility and environmental factors culminate in the breakdown of B-cell or T-cell tolerance. T cell auto-reactivity has been shown to be B cell dependent in certain experimental models [28,29].

In EGPA, eosinophil activation is mainly responsible for disease manifestations, and cytokines produced by T lymphocytes, such as IL-4, IL-5 and IL-13, are increased in active EGPA [25]. This suggests that hypereosinophilia may be 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.

2.3.2. 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 bone marrow.

B cell depletion with rituximab has proved effective in hematological diseases and autoimmune diseases, including rheumatoid arthritis and ANCA-associated vasculitis GPA and MPA.

Data in ANCA-associated vasculitis, in particular GPA and MPA, support the efficacy of rituximab as induction and maintenance therapy.
Rituximab has been 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 [30,31]. In addition, the prospective, randomized, controlled MAINRITSAN trial conducted by our group compared rituximab with azathioprine to maintain remission of severe GPA and MPA, and demonstrated that RTX every 6 months was superior to azathioprine to maintain remission during the 28-month follow-up [32]. 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. [33]. 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 (Birmingham Vasculitis Activity Score) and corticosteroid dose. B cell depletion was achieved and the eosinophil count decreased to normal levels.

Pepper et al. also reported the efficacy of rituximab in two EGPA patients[34]. 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.

Cartin-Ceba et al. conducted a single-center open-label pilot study using rituximab for induction of remission in EGPA patients with renal involvement [35]. 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 non-renal 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 [36]. Nine patients (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 pre-emptively 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. Pre-emptive retreatment with rituximab, combined with standard maintenance immunosuppressants, resulted in a sustained treatment response.

Novikov et al. described their experience of off-label use of rituximab in a case series of 6 patients, of whom 5 had relapsing EGPA [37]. Complete remission was achieved in 4 patients at 6 months with an acceptable safety profile. Rituximab appeared to be an efficient and safe treatment for both ANCA-positive and ANCA-negative patients.

The largest series to date has reported 41 EGPA patients, who received rituximab as single or repeated courses in four expert vasculitis centers, mostly for refractory or relapsing disease [38]. Patients with positive ANCA testing were significantly more likely to achieve remission at 12 months: 80% (12/15) who were ANCA-positive versus 36% (8/21) who were ANCA-negative. Prednisone doses decreased in all patients by 6 and 12 months. 22 patients received maintenance preemptive rituximab retreatment and had favorable outcome. Adverse events included 15 infections of which 6 were severe. Despite the refractory and relapsing nature of EGPA in many patients included in this study, the authors concluded that treatment of EGPA with rituximab resulted in high rates of improvement and reduced requirement of prednisolone and that rituximab role as maintenance treatment needs to be addressed in future studies.

In summary, uncontrolled studies have shown that anti-CD20 therapy can help controlling EGPA with a good safety profile, but no prospective controlled studies are available neither in the induction nor in the maintenance periods. All uncontrolled

series and recent reviews [39] underlined that prospective studies are now needed to assess the efficacy and safety of rituximab in EGPA. Therefore, given the absence of any prospective trial evaluating i/ maintenance therapy and ii/ rituximab therapy in remission maintenance of EGPA, conducting a study evaluating the efficacy and safety of rituximab seems necessary to improve the management of these patients.

EGPA is a rare disease, and this is the first prospective controlled maintenance study with use of rituximab in this disease. The study could be crucial in providing information on rituximab use; and immunogenicity data would be important from safety point of view, also considering it being used as maintenance therapy.

The first randomized controlled trial with rituximab as induction therapy in patients with EGPA will be implemented by the French Vasculitis Study Group network and started to recruit since December 2017 (PHRC-2014, REOVAS). We anticipate that approximately 80 EGPA patients included in this trial will achieve remission in 2017-2018 and could be available to participate in the MAINRITSEG trial.

3. OBJECTIVES

3.1. Primary objective

The primary objective of this trial is to investigate, after achievement of remission, the efficacy of rituximab compared with azathioprine maintenance therapy on duration of remission, defined as accrued duration in weeks where BVAS=0 and prednisone dose ≤7.5 mg/day, in patients with relapsing or newly-diagnosed EPGA, receiving standard of care therapy including corticosteroid therapy reduction/withdrawal (Figure 1) .

3.2. Secondary objectives

The secondary objectives of this trial are to investigate the efficacy of rituximab compared with azathioprine maintenance therapy on:

- proportion of patients remaining in remission with BVAS=0 and prednisone dose ≤7.5 mg/day at month 28,
- number and severity of vasculitis relapses,
- number and severity of asthma/rhino-sinusal exacerbations,
- variation of the obstructive pulmonary disease
- time to vasculitis relapses
- time to significant asthma/rhino-sinusal exacerbations,
- corticosteroid sparing effect,
- survival,
- safety,
- damage,
- quality of life.

This trial will be the first prospective randomized controlled study:

- **evaluating maintenance therapy in EGPA patients,**
- **and investigating efficacy and safety of rituximab to maintain remission.**

This study, if it demonstrated a benefit of rituximab compared to conventional therapeutic strategy, would improve the management of patients with EGPA.

3.3. Objective of the associated ancillary research.

As emphasized in the rationale of the MAINRITSEG trial, relapses are common in EGPA but discriminating disease activity from worsening of underlying asthma and sinusitis is challenging. The identification of serum biomarkers supporting the diagnosis of disease flares in EGPA would be thus extremely helpful in daily clinical practice.

Serum bank that will be collected during the MAINRITSEG trial will give us the opportunity to evaluate biomarkers of disease activity.
Since EGPA is characterized by asthma and increased eosinophilia, the assessment of the kinetic of eosinophil-related chemokines and TH2-related cytokines to predict disease activity could be crucial.
Of the many chemokines and cytokines that could be relevant, we will measure TSLP, IL-25, IL-33, TARC, soluble ST2, periostin, eostaxin-3, IL-4, IL-5, IL-9, IL-13, IL-17A, interferon-gamma and IgG4 levels.

We thus plan to measure these chemokines and cytokines in the serum of patients in a blind manner regarding disease activity and correlate these results with disease activity.

We expect to identify relevant serum biomarkers that will help to identify active patients and adapt treatments.

4. PLAN FOR THE RESEARCH

4.1. Concise description of the primary and secondary assessment criteria

4.1.1. Primary assessment criterion

The primary assessment criterion of this trial is the total duration of remission over the 28 month study period, i.e., the accrued number of weeks where a patient remains in remission with BVAS=0 and prednisone dose ≤7.5 mg/day (Figure 1).

The vasculitis activity will be assessed by the mean BVAS version 3 (18.3) [46]. EULAR experts [43] recommended that the definition of VAA remission should include a prednisone dose ≤7.5 mg/day to control systemic manifestations. 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.

Similarly, vasculitis relapse will be defined as new onset of disease activity attributable to vasculitis. A major relapse will be defined as the new onset of potentially organ- or life-threatening disease activity that cannot be treated with an increase of glucocorticoids alone and requires further escalation of treatment [43]. All other relapses will be classified as minor.

Ear, nose and throat (ENT) manifestations and/or asthma flares may not necessarily reflect vasculitis activity [5,8,44]. Along this line, the EGPA Task Force concluded that these symptoms be monitored separately and proposed that the definition of remission in EGPA not include the control of asthma and/or ENT manifestations [44]. Thus, an increase in the eosinophil count without any other clinical EGPA exacerbation; or isolated asthma, sinusitis, or rhinitis exacerbations, with/without a concomitant increase in eosinophil count, will not be considered recurrent vasculitis manifestations.

4.1.2. Secondary assessment criteria

The secondary assessment criteria of this trial are in the two treatment groups:

- proportion of patients remaining in remission with a BVAS=0 and prednisone dose ≤7.5 mg/day over the 28 month study period.
- proportion of patients remaining in remission with a BVAS=0 over the 28 month study period.
- proportion of patients with at least one vasculitis relapse (major, minor, either) over the 28 month study period.
- proportion of patients with at least one clinically significant asthma/rhino-sinusal exacerbation defined as a worsening of asthma/rhino-sinusal disease leading to the

doubling (or more) of the existing maintenance dose of corticosteroids for 3 or more days or hospital admission or an emergency department visit over the 28 month study period [45].

- time to first vasculitis relapse.
- time to first significant asthma/rhino-sinusal exacerbation.
- prednisone dose at months 6, 12, 18, 24 and 28, and a under the curve over the 28 month study period.
- mean blood eosinophilia during the trial, proportion of patients with adverse events or serious adverse events over the 28 month study period. proportion of patients over the 28 month study period with selected severe adverse events including grade 3 or 4 adverse effects (Common Terminology Criteria for Adverse Events), necessitating hospitalization, all cause deaths, cancers or infusion reactions (within 24 hours of infusion) that contraindicated further infusions.
- number and causes of deaths over the 28 month study period.
- rhino-sinusal exacerbation assessed by the Sino-Nasal Outcome Test-22 questionnaire (SNOT-S22) over the 28 month study period (18.8) [47,48].
- variation of the obstructive pulmonary disease assessed by change of the forced expiratory volume in one second (FEV_1) after use of bronchodilator at pulmonary function tests over the 28 month study period, asthma exacerbation assessed by the Asthma Control Questionnaire (ACQ) over the 28 month study period (18.7) [49], damage assessed by the mean variation of the Vasculitis Damage Index (VDI) during the 28 months after randomization (18.4) [50].
- quality of life assessed by the mean variation of the SF-36 over the 28 month study period (18.5),
- disability assessed by the mean variation of the Health Assessment Questionnaire (HAQ) over the 28 month study period (18.6).
- the number of days of hospitalization over the 28 month study period.

4.2. Description of research methodology

4.2.1. Experimental plan

This is a phase III comparative, multicenter, randomized, controlled, double-blind and double-dummy superiority trial, comparing pre-emptive low-dose rituximab-based regimen with azathioprine conventional therapy for the remission maintenance in EGPA patients. The experimental plan is summarized (Figure 1) (page 34).

4.2.2. Number of centers participating

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

4.2.3. Randomization

After achievement of remission and screening, patients with newly diagnosed or relapsing EGPA will be randomized in a 1:1 ratio to receive:

- Standard regimen: maintenance oral azathioprine therapy (2 mg/kg/day) for 24 months. This control group will receive conventional therapy plus 4 infusions of placebo−rituximab (every 6 months for 18 months).

- Experimental regimen: all patients will receive pre-emptive 500-mg fixed-dose of rituximab every 6 months for a total duration of 18 months (4 infusions). The rituximab group will receive intravenous rituximab plus oral placebo-azathioprine for 24 months.

To assure that the randomization does balance patients' prognostic factors such as the vasculitis severity, relapsing disease, or MPO-ANCA positivity that may influence the outcomes, a covariate-adaptive randomization method will be used, which refers to a randomized treatment allocation scheme that depends on covariates or prognostic factors but is conditionally independent of the outcomes, given the covariates used in randomization.

4.2.4. Stratification

The patients will be centralized and stratified at randomization according to parameters observed at the last flare:

- Newly diagnosed vs. relapsing EGPA
- Vasculitis severity (FFS=0 vs. FFS ≥1) at the last flare

- ELISA ANCA status (anti-MPO or anti-PR3 positive vs. negative) at the last vasculitis flare
- Induction therapy (corticosteroids in association with cyclophosphamide vs. corticosteroids in association with rituximab vs. corticosteroids alone)

The randomization will be generated by computer program. Allocation will be ensured by the use of an e-CRF on Cleanweb software. No stratification on the center will be performed.

The predefined prednisone tapering schedule and instruction for corticosteroids dose according to EGPA clinical activity at clinic visit are depicted page 54 .

4.2.5. 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.

Therefore, neither patients, nor physicians will know the treatments allocated to their patients. Sites will be provided a set of blinded medication kits.
The CD19 results will be blinded for the investigators with a standardized procedure set up at the initiation of the research in the centers.

4.2.6. Procedures for breaking the blind, if applicable

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

- the DRCI in a situation other than an emergency during the work day and during working hours,
- the poison center of Fernand Widal Hospital, in the case of an emergency (see emergency situations requiring unblinding), on weekends, bank holidays, when the DRCI is closed and when unblinding cannot be carried out at the DRCI.

The primary investigator of the trial will validate the requirement for breaking the blind in the situations other than emergencies.

4.2.7. Adjudication Committee

An independent Endpoint Adjudication Committee will review in double-blind the classification of disease flare and validate the reason for the corticosteroids increase with

particular attention given on distinction between vasculitis flare and asthma/rhino-sinusal exacerbation.

4.2.8. Identification of the subjects

The subjects will be identified as follows:
Center No. (3 numerical positions) - Inclusion 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.

5. PROCEDURE FOR THE RESEARCH

Before any procedure 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.

After randomization, visits should be performed +/- 15 days until month 28 of follow-up.

5.1. Selection visit

The selection visit will take place between 1 to 30 days before the inclusion visit.
Selection visit may coincide with the last visit of REOVAS (month 12 evaluation) and will include:

- Clinical evaluation to determine disease activity,
- Assessment of severity of the last flare with FFS,
- ANCA status at the last flare,
- Verification of inclusion and non-inclusion criteria,
- Patient information,
- Blood tests
    - for inclusion and non-inclusion criteria, including:
    - hemogram, potassium results and renal function, MDRD clearance, C-reactive protein, fibrinogen, AST, ALT, albumin & gamma-globulin assessed by serum protein electrophoresis, IgG, IgA, IgM, CPK, LDH, calcemia, phosphoremia, glycemia, troponin, NT-pro-BNP, HIV, HBV and HCV serological tests, urine analysis, CD4+ and CD8+ cells, CD19+ cells blinded,
    - ANCA using immunofluorescence and ELISA,
- Imaging tests as appropriate: chest X-ray, thoracic CT-scan, electrocardiogram, echocardiography, cardiac MRI,

All patients who are already taking oral concomitant commercial immunosuppressive drug will have to stop it before inclusion visit.

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 EGPA after achievement of remission	Investigators participating in the study At month 9 evaluation of the REOVAS trial, the patient will receive the information about the MAINRITSEG trial. The information and the consent form could be given to the patient for this trial at the M9 visit of REOVAS, so that the patient will have reflexion time before being included at the next visit M12 REOVAS.	Selection visit	Inclusion visit, after a reflexion interval from 24 hours to 30 days.

5.2. Inclusion visit

The inclusion visit will represent day 0.
Inclusion visit may coincide with the last visit of REOVAS (month 12 evaluation)

Inclusion visit will include:

- Checking of inclusion and non-inclusion criteria,
- Signature of patient inform consent (by the patient and the clinical investigator)
- Clinical examination to collect manifestations related to EGPA and determine disease activity,
- Biological tests only if the selection biological tests date more than 15 days : hemogram, serum ionogram, renal function, C-reactive protein, fibrinogen, liver enzymes,
- Urinary or Blood pregnancy test,
- CD19+ cells blinded,
- Imaging tests as appropriate : chest X-ray, thoracic CT-scan, echocardiogram, echocardiography, cardiac MRI
- Serum, plasma, (except for patients included in the REOVAS M12 visit)

- DNA bank (except for patients included in the REOVAS study. Patients from REOVAS for whom DNA extraction failed will be sampled again)
- Serum for ancillary research,
- Pulmonary function test,
- BVAS (see Appendix 18.1),
- VDI (see Appendix 18.2),
- SF36 and HAQ patient questionnaires (see Appendix 18.3 and 18.4).
- Asthma control patient questionnaire = ACQ (see Appendix 18.5),
- Sino-nasal outcome test-22 patient questionnaire = SNOT-22 (see Appendix 18.6)
- Notification of associated treatments,
- Randomization by e-CRF,
- Administration of treatments after randomization:
    - rituximab infusion and oral placebo-azathioprine in the experimental arm
    - placebo-rituximab infusion and oral azathioprine arm in the conventional arm.
- Patient's card (see Appendix 18.7)
- Logbook for the adhesion to the treatment (see Appendix 18.8)

Maximal interval authorized between randomization and first infusion of the treatment will be 1 day.

5.3. Follow-up Visits

Follow-up visits will take place at month 1, month 3, month 6, month 9, month 12, month 15, month 18, month 21, month 24 and month 28.
Dates of each visit will be planned by the protocol, with a margin of+/- 15 days for each visit.

Follow-up visits will include:

- Clinical examination to collect manifestations related to EGPA activity or remission, and asthma/rhino-sinusal exacerbation
- 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, potassium results and renal function, MDRD clearance, C-reactive protein, fibrinogen, liver enzymes (AST, ALT), albumin & gamma-globulin assessed by serum protein electrophoresis, IgG, IgA, IgM, CPK, LDH, calcemia, phosphoremia, glycemia, urine analysis, CD4+ and CD8+ cells, and as appropriate troponin and NT-pro-BNP
- CD19+ cells blinded : 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 every 6 months
- Serum and plasma bank every 6 months
- Serum for ancillary research at months 6, 12, 18 and 24 and before each relapse (minor and major)
- BVAS
- VDI
- Imaging tests as appropriate: chest X-ray, thoracic CT-scan, echocardiogram, echocardiography, cardiac MRI, pulmonary function test (M12 only),
- Asthma control and sino-nasal outcome test-22 patient questionnaires at months 6, 12, 18 and 24

- SF36 and HAQ patient questionnaires at months 6, 12, 18 and 24
- Logbook for the adhesion to the treatment at months 3, 6, 9, 12, 15, 18, 21 and 24

5.4. End of research visit

End of research visit will take place at month 28 +/- 15 days and will include:

- Clinical examination to collect manifestations related to EGPA activity or remission, and asthma/rhino-sinusal exacerbation
- Biological tests
- Imaging tests as appropriate
- Notification of associated treatments
- Notification of adverse events
- Filling of the e-CRF

End of research assessment will include:

- Biological tests: hemogram, TP/TCA, serum ionogram, renal function, C-reactive protein, fibrinogen, liver enzymes, serum protein electrophoresis, IgG, IgA, IgM, CPK, LDH, calcemia, phosphoremia, glycemia, urine analysis, CD4+ and CD8+ cells, and as appropriate troponin and NT-pro-BNP
- CD19+ cells blinded : 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
- Serum for ancillary research
- BVAS
- VDI
- Pulmonary function test
- Imaging tests as appropriate : chest X-ray, thoracic CT-scan, echocardiogram, echocardiography, cardiac MRI
- Asthma control and sino-nasal outcome test-22 patient questionnaires
- SF36 and HAQ patient questionnaires

5.5. Relapse visit(s)

Relapse visit will include:

- The immediately notification of the relapse of the GEPA, to the sponsor, as a SAE, is the relapse answer to one of the seriousness criteria listed in a section 10.4.2
- Clinical examination to collect manifestations related to EGPA activity
- Biological tests
    - hemogram, TP/TCA, serum ionogram, renal function, C-reactive protein, fibrinogen, liver enzymes, serum protein electrophoresis, IgG, IgA, IgM, CPK, LDH, calcemia, phosphoremia, glycemia, urine analysis, CD4+ and CD8+ cells, and as appropriate troponin and NT-pro-BNP
    - CD19+ cells blinded : 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 for ancillary research before treatments
- Imaging tests as appropriate
- Notification of associated treatments
- Notification of adverse events
- Filling of the e-CRF
- BVAS
- Pulmonary function test
- Asthma control and sino-nasal outcome test-22 patient questionnairesSF36 and HAQ patient questionnaires

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

The duration of participation for each patient will be 28 months, whereas the duration of recruitment will be 24 months. Overall, the total duration of the study will be 52 months.
The maximum duration between selection and inclusion will be 30 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 a total duration of 24 months of the study.

Maximum period between selection and inclusion	30 days
Inclusion period	24 months
The included subjects' length of participation, of which:	
• Treatment period:	24 months
• Total follow-up period:	28 months
Total research period:	52 months

A data analysis at 5 and 10 years post-inclusion is also planned to evaluate the long-term ratio of profit/toxicity of this strategy and factors associated with long-term relapses.

5.7. Table 3. Summary of the chronology of the research

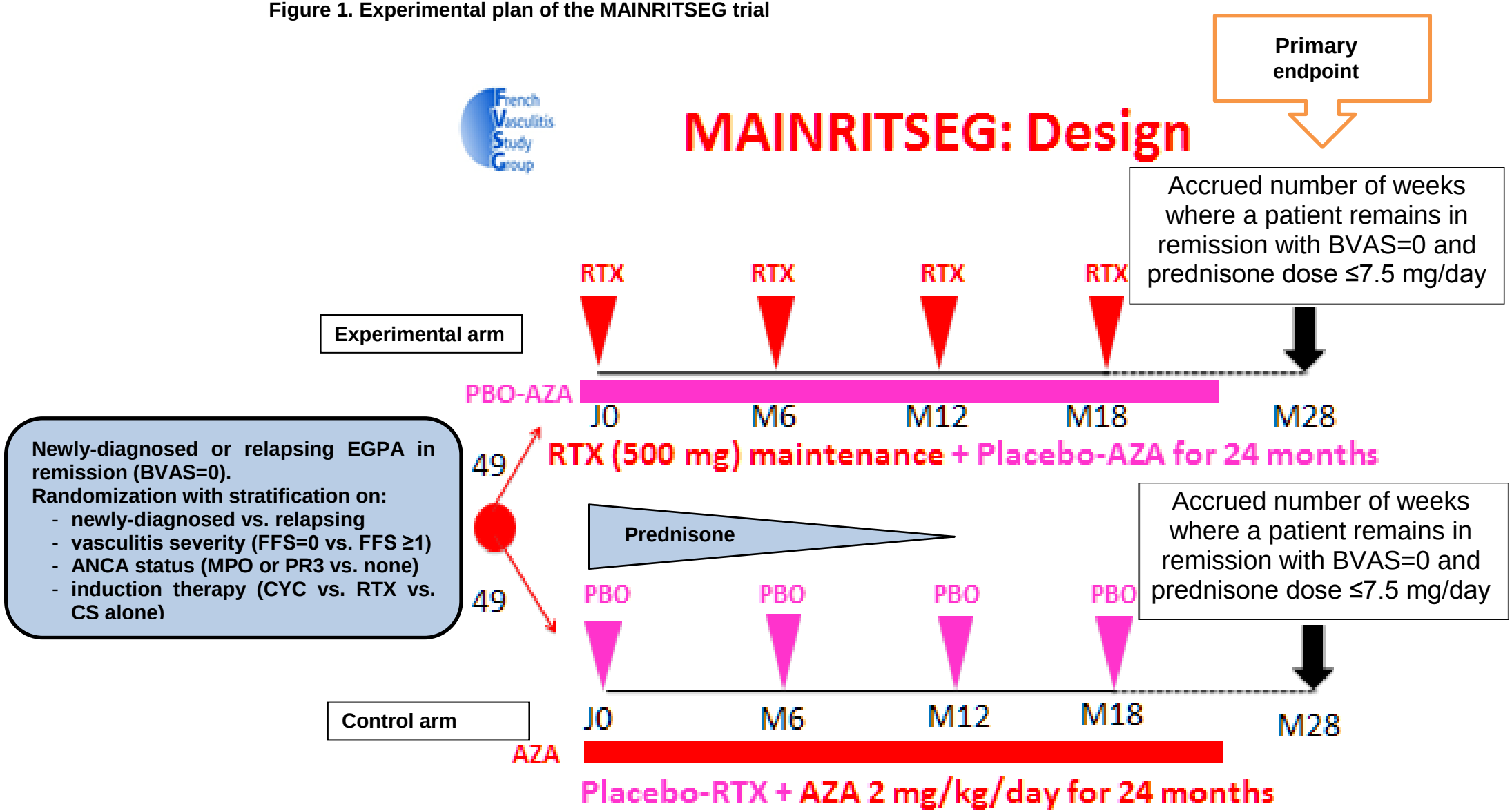
Actions	D-30 (Selection) to D0 (Visit 1)	D0 (Inclusion) (Visit 2)	Month 1, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, Month 21, Month 24+/- 15 days (Treatment administration and/or follow-up visits)	Month 28 +/- 15 days (End of research)
Informed consent		X		
Randomization		X		
History	X			
Clinical examination	X	X	X	X
Medical procedures (EKG)		X		X
Biological tests (biochemistry, haematology, urine analysis, ANCA)	X	X * If > 15 days	X	X
Urinary or Blood pregnancy test		X		
CD19 result blind	X	X If > 15 days	X	X
BVAS		X	X	X
VDI		X	X	X
Imaging tests as appropriate (chest X-ray, thoracic CT-scan, echocardiography, cardiac MRI)	X			X
Pulmonary function test		X	X (M12 only)	X
ACQ and SNOT-22 patient questionnaires		X	X (M6, M12, M18, M24 and M28)	X
HAQ and SF36 patient questionnaires		X	X (M6, M12, M18, M24 and M28)	X

Biological collection : DNA sample		X		
Biological collection : serum and plasma samples		X	X every 6 months	X
Serum for ancillary research		X	X every 6 months	X
Logbook for the adhesion to the treatment		X	X (except at month 1)	X
Dispensation of treatments		X	X	
Compliance		X	X	X
Adverse events (AE and SAE)			X	X

***The biological tests must be redone at inclusion, only if that of the selection dates more than 15 days.**

The design of the research is summarized next page in Figure 1.

Figure 1. Experimental plan of the MAINRITSEG trial



5.8. 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	Corticosteroids	rituximab or placebo-rituximab and premedication of rituximab (paracetamol+ methylprednisolone + dexchlorpheniramine) and placebo-azathioprine or azathioprine, according to randomization
Consultations	Consultations or hospitalizations every 3 to 6 months according to severity	
Blood samples	At selection only : HIV, HBV and HCV serology At inclusion only : Urinary or Blood Pregnancy test At selection, then every 3 months Hemogram, potassium and renal function, MDRD clearance, C-reactive protein, CRP, fibrinogen, liver tests (AST, ALT), calcemia, phosphoremia, glycemia, serum protein electrophoresis (albumin & gamma-globulin), IgG, IgA, IgM, CPK, LDH, troponin, NT-pro-BNP, urine analysis (proteinuria, hematuria), CD4+ and CD8+ cells, ANCA using	At inclusion only : DNA samples (14 ml of blood) At inclusion and month 6, month 12, month 18, month 24 and month 28: Serum and plasma samples (7 ml of blood for each samples) + serum for ancillary research (7ml) At selection, inclusion and month 1, month 3, month 6, month 9, month 12, month 15, month 18, month 21, month 24+/- 15 days and month 28 : CD19+ cells blinded

	immunofluorescence and ELISA	
Imaging as appropriate	Chest X-ray, pulmonary function test, Thoracic CT-scan, Echocardiography, Electrocardiogram, Cardiac MRI according to clinical presentation	None
Patient questionnaries		Asthma control and sino-nasal outcome test-22 patient questionnaires : at months 0, 6, 12, 18, 24 and 28 SF36 and HAQ patient questionnaires : at months 0, 6, 12, 18, 24 and 28 Logbook for the adhesion to the treatment at inclusion and new logbook at months 3, 6, 9, 12, 15, 18, 21 and 24

5.9. Serum for ancillary research

At inclusion, M6, M12, M18, M24 and M28 and in case of relapse (minor and major) before treatment : 7ml blood will be taken in a dry tube, and quickly centrifuged then aliquoted into 2ml cryotubes and stored at -80°C by the investigator center.
Transportation and delivery of serum for the ancillary research will be conducted in dry ice to the coordinator at the Cochin hospital center, in the "Neutrophile et vascularites" laboratory at the end of follow-up of patients in the center.

At the end of the research, the samples that will not be utilised for the ancillary research, will be preserved for an unlimited duration in a biological collection.

5.10. 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 "Neutrophile et vascularites" laboratory (Bâtiment Gustave Roussy, 6ème étage, Hôpital Cochin, 27 rue du Faubourg Saint-Jacques, 75014 Paris) under the supervision of Prof. Luc Mouthon for an unlimited duration.

Serum bank: 7ml of blood will be taken in a dry tube 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 in a EDTA tube 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 in ACD tubes at baseline only, stored at room temperature and immediately transported at room temperature to the coordinator at the Cochin hospital.
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.
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.

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 unlimited 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).

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	unlimited	Storage
Serum	7 ml at inclusion and M6, M12, M18, M24 and M28	Cochin Hospital	Prof. Luc Mouthon	Scientific knowledge	unlimited	Storage
Serum for ancillary research	7 ml at inclusion and M6, M12, M18, M24 and M28 and in case of relapse (minor and major) before treatment	Cochin Hospital	Prof. Luc Mouthon	Ancillary research	unlimited	Storage
Plasma	7 ml at inclusion and M6, M12, M18, M24 and M28	Cochin Hospital	Prof. Luc Mouthon	Scientific knowledge	unlimited	Storage

5.9. Termination rules

5.9.1. Criteria and methods for prematurely terminating of the research treatment

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.
The investigator must:

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

The case report form must list the various reasons for the premature termination of treatment and/or ending participation in the research:

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

5.9.2. 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.

5.9.3. Methods for replacing subjects, if applicable

No replacing subject is planned in this study.

5.9.4. 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, if unexpected facts, new information about the product, in light of which the objectives of the research are unlikely to be achieved.
- 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

The patients included in the REOVAS study will be eligible. The REOVAS last visit (month 12 evaluation) may coincide with the selection visit of the MAINRITSEG trial.

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

- patient aged of 18 years or older,
- patients with a diagnosis of EGPA,
- patients with newly-diagnosed disease or after a vasculitis flare and remission achieved within the past year
- independently of ANCA status,
- within 30-360 days following achievement of vasculitis remission (corresponding to a Birmingham Vasculitis Activity Score (BVAS) = 0) with an induction regimen including the one used in the REOVAS trial:
    - either corticosteroids alone (for patients with FFS=0 of the control group),
    - or in association with RTX 2 x 1g (D1, D15) or 4 weekly 375 mg/m^2 infusions,
    - or in association with CYC induction regimen ranging from 4.5-10 g total dose.
- with a stable prednisone dose for 30 days or no more prednisone,
- after oral immunosuppressive drug cessation if it has been started at remission,
- patient able to give written informed consent prior to participation in the study.
- patients included in the REOVAS trial and achieving remission can be included at month 12 visit if they fulfil the other criteria
- Affiliation with a mode of social security (profit or being entitled).

Diagnosis of EGPA will be based on one of the four 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 classification criteria** requiring the presence of 4 out of the 6 following criteria in a patient with an evidence of vasculitis:

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

Extravascular eosinophils

- **Revised Chapel Hill nomenclature**

EGPA is defined as eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. Nasal polyps are common.

- **MIRRA study inclusion criteria**

Subjects who have been diagnosed with EGPA for at least 6 months based on **the history** or **presence of**: asthma **plus** eosinophilia (>1.0x10^9/L and/or >10% of leucocytes) plus at least two of the following additional features of EGPA:

- a biopsy showing histopathological evidence of eosinophilic vasculitis, or
- perivascular eosinophilic infiltration, or eosinophil-rich granulomatous
- inflammation;
- neuropathy, mono or poly (motor deficit or nerve conduction abnormality);
- pulmonary infiltrates, non-fixed;
- sino-nasal abnormality;
- cardiomyopathy (established by echocardiography or MRI);
- glomerulonephritis (haematuria, red cell casts, proteinuria);
- alveolar haemorrhage (by bronchoalveolar lavage);
- palpable purpura;
- ANCA positive (MPO or PR3).

6.2. Non-inclusion criteria

Patients with one of the following criteria will not be included in the trial:

- Patients with GPA, MPA, or other vasculitides, defined by the ACR criteria and/or the Chapel Hill Consensus Conference,
- Patients with vasculitis not in remission of the disease defined as a BVAS >0,
- Patients with severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease,
- 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 all duration of the study and another 12 months after,
- Patients who had already been treated with rituximab before the last relapse/flare
- Patients who have been treated with rituximab with a different induction regimen than 2 x 1g (D1, D15 or 4 weekly 375 mg/m^2 infusions,
- Patients with hypersensitivity to a monoclonal antibody or biologic agent,
- Patients with contraindication to use rituximab 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 except in the REOVAS trial, after which patients achieving remission can be included if they fulfil the other criteria
- 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 than 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.
- Patients not able to stop allopurinol or febuxostat which may enhance azathioprine toxicity.

6.3. Recruitment methods

Patients will be included in the trial via the participation of the French Vasculitis Study Group network with competitive recruitment. 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.

The rituximab maintenance trial in MPA and GPA patients (MAINRITSAN, PHRC-2008), conducted by our network, has changed their standard of care and results have been published in the *New Journal of Medicine* [32].

The REOVAS induction trial in EGPA (PHRC-2014) started in our network. The primary endpoint is the proportion of patients achieving remission at 6 months. We thus expect to have nearly 80 EGPA patients during the next 2 years achieving remission and available to participate in the MAINRITSEG maintenance trial. We also planned to recruit additional EGPA patients after remission achieved with an induction regimen treatment similar to the one used in the REOVAS trial.

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, and French Society of Pulmonology).

	Number of subjects
Total number of subjects chosen	*98*
Number of centers	*50*
Inclusion period (months)	*24*
Number of subjects/center	*1.96*
Number of subjects/center/year	*0.98*
Number of subjects/center/month	*0.08*

7. TREATMENT ADMINISTERED TO RESEARCH PARTICIPANTS

7.1. Description of the experimental medication or medications

7.1.1. Description of the experimental group

Patients in the experimental arm will receive corticosteroids, in combination with fixed-dose of 500 mg of rituximab therapy at inclusion, month 6, month12 and month 18, as maintenance therapy (4 injections for 18 months), in association with placebo-azathioprine for 24 months. We now consider this low-dose rituximab pre-emptive regimen in GPA and MPA patients as the standard of maintenance care after the results of the MAINRITSAN trial which have shown that this regimen was both more effective than standard of care AZA maintenance therapy and well tolerated [32].

Rituximab is 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.

7.1.2 Description of conventional group

All patients in the conventional regimen group will receive maintenance azathioprine therapy (2 mg/kg/day orally) for 24 months, as recommended by the BSR and BHPR guideline [19].

The conventional therapy group will receive conventional azathioprine therapy plus placebo−rituximab every 6 months for 18 months (4 infusions).

Daily dosage will be from 50 to 200 mg, rounded off in 25 mg inferiors and adjusted according to the age of the participants (18-59 years; 60-74 years and ≥ 75 years old; see abacuses (see appendix 18.12).

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

Foreseeable benefits area superior efficacy of rituximab compared with the conventional maintenance therapeutic strategy to improve outcome of EGPA by maintaining remission and decreasing asthma/rhino-sinusal exacerbations, and to lower doses of corticosteroids and cumulative morbidity.

Foreseeable risks are those associated with toxicity of treatments

7.1.4. . 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.

In patients with EGPA, other safety issues included worsening of asthma which has been reported in few patients. In one report [38], severe infusion reactions were observed in two cases and required admission to hospital and treatment with intravenous corticosteroids (one required intubation due to worsening of asthma). Whether these two patients had received premedication is not mentioned in the article. Another study [40] has reported severe bronchospasm during the first 15 minutes of rituximab infusions in two EGPA patients. In these two cases, premedication had included intravenous dexchlorpheniramine (5 mg) and paracetamol (1 g), without IV corticosteroids. In the two patients, infusion was stopped and their breathing returned to baseline after two salbutamol inhalations; in one patient, 1h later, a slower rituximab infusion was resumed, without any incident. In another article [37], one patient developed severe bronchospasm during two infusions that necessitated high dose intravenous glucocorticoid administration. The following infusions of rituximab after intensified premedication with 500 to 1000 mg prednisolone were not associated with side effects.

It is known that approximately 80% of severe rituximab infusion reactions occurred in association with the first infusion in patients with rheumatoid arthritis. The DANCER trial has also shown that intravenous corticosteroid premedication reduced the frequency and intensity of first infusion-associated events [41].

In the MAINRITSEG trial, in addition to a close monitoring of patients during the rituximab infusions and particularly during the first infusions, 100 mg intravenous methylprednisolone will be administered in 30 minutes associated with intravenous dexchlorpheniramine (5 mg) and paracetamol (1 g), prior to each infusion. This premedication is recommended in rheumatoid arthritis to reduce the incidence and severity of rituximab infusion reactions. It has also been used successfully in AAV patients in the MAINRITSAN trial, in association with the rituximab infusions.

Pneumocystis jiroveci pneumonia prophylaxis is also highly recommended for patients with GPA and MPA during treatment and for at least 6 months following the last rituximab infusion [42,44]. Prophylactic co-trimoxazole (400 mg/80 mg) (i.e. one single strength tablet [480 mg total] daily or one double strength tablet [960 mg total] thrice weekly), with the dose being adjusted to renal function, will be given to all patients for the entire duration of the MAINRITSEG trial. In the case of allergy to co-trimoxazole, monthly aerosolized pentamidine or atovaquone can be used.

7.1.5. 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.

The starting dose of azathioprine may be reduced to 1.5 mg/kg/day in patients >60 years old and to 1 mg/kg/day in patients >75 years old.

Full blood counts and aminotransferases will be performed every two weeks for the first month of azathioprine therapy and then every two months for the first year of therapy and every three months thereafter.

Patients with a WBC count $<4x10^9$/L should have their azathioprine temporarily held and have their WBC count checked weekly. Once the WBC count is $>4x10^9$/L, azathioprine should be restarted at a dose of at least 25 mg/day less than the previous dose with continued weekly monitoring for at least one month.

Patients with a declining WBC count but no overt leucopenia (i.e. WBC count $<6x10^9$ and at least $2x10^9$/L lower than previous) should have their WBC count rechecked within 1 week and have their oral azathioprine reduced by at least 25 mg/day if the WBC count continues to fall.

In patients with intolerance or side effects requiring azathioprine withdrawal during the trial, physicians will be encouraged to give methotrexate orally until month 28 (progressively titrated up to 0.3 mg/kg/week within one month) if non contra indicated and adapted to the creatinine level.

7.2. Description of the non-experimental treatment (medications required for carrying out the research)

Patients in both arms will receive:

- corticosteroids with the same predefined tapering schedule,
- and premedication protocol using 100 mg methylprednisolone, paracetamol and dexchlorpheniramine administered at inclusion and every 6 months for 18 months.

- **Corticosteroids**

During the treatment period, in accordance with standard of care, corticosteroid dose will be tapered. In the absence of EGPA clinical manifestations, prednisone dose will be tapered in order to obtain prednisone therapy for an average total duration after disease onset / flare of approximately 12 months. Both groups will receive the same prednisone regimen with a predefined tapering schedule of 1 mg/day every 4 weeks until discontinuation.

For example, a patient randomized while being on 7 mg/day of prednisone will receive:

- D0-D27: 7 mg/day
- D28-D55: 6 mg/day
- D56-D83: 5 mg/day
- D84-D111: 4 mg/day
- D112-D139: 3 mg/day
- D140-D167: 2 mg/day
- D168-D195: 1 mg/day
- After D196 (6.5 months): discontinuation of prednisone.

An isolated elevated eosinophilic count or isolated increased C-reactive protein, without overt clinical manifestations of vasculitis activity or asthma/rhino-sinusal exacerbation, will not be considered as activity of the EGPA and will not lead to an increase of the prednisone dose.

Instruction for corticosteroids tapering according to EGPA clinical 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 vasculitis flare: prednisone dose could be increase until 20 mg/day or double-blind could be stopped and optimal therapy chosen by the clinician in charge of the patient according to the severity of the clinical flare. In all cases, the patients will be followed until month 28.

If the subject's first relapse is managed with the use of an increase in prednisone dose, tapering will be recommenced as soon as the relapse has been appropriately controlled, as per standard of care practice. Once the minimally effective dose of prednisone is achieved, any down-tapering below this dose level will be at the discretion of the investigator, based on the clinical condition of the subject. In the event of a second or subsequent relapse, any further prednisone tapering, post-relapse, will be conducted at the discretion of the investigator.

Osteoporosis prophylaxis will also be recommended as standard of care for all patients according to the French recommendations for patients being treated with corticosteroids

7.3 Description of the traceability elements that accompany the experimental medications

7.3.1. Origins and storage conditions:

- **Rituximab 500 mg / 50 mL** for intravenous use after dilution, concentrate for solution for infusion of 1 vial containing 10 mg/mL rituximab.

Origin: supply and labelling free of charge, by Roche

Storage: in a refrigerator (2 °C – 8 °C). Keep the container in the outer carton in order to protect from light.

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

- **Azathiorine 25 mg and placebo**

Origin: supply and labelling by HAC Pharma

Storage: Do not store above 25°C. Store in its original packaging away from light

7.3.2. Supply

Supply: the supply order will be sent by the eCRF.

The shipments will be adapted to the patient's randomisation group. It will contain:
Experimental group: rituximab and placebo of azathioprine 25 mg
Conventional group: azathioprine 25 mg (placebo of rituximab will be supplied by the pharmacies)

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 of rituximab or placebo

The hospital pharmacy will be in charge of preparation and blindness of rituximab or placebo. Infusion bags will be prepared by the hospital pharmacy with respect to patient's group and disease status.
The preparation of rituximab infusion will be made in accordance to SMPC of Mabthera®.
Each bag will be labelled with all mandatory mentions (labels supplied by the sponsor), and its shelf life.
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.

Dispensing should be recorded on a specific traceability document.

7.3.5 Administration and follow up

Each administration should be recorded on a specific traceability document.

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.

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

7.3.6. Methods for monitoring compliance with the treatment

Rituximab and placebo-rituximab will be administered intravenously and will be easily monitored for compliance.
For azathioprine, placebo-azathioprine and corticosteroids, a logbook for the adhesion to the treatment will be completed by the patients during 28 months and transmitted to the investigators at each visit.

7.3.7. Accountability and destruction

Used and unused experimental medications must be accounted by the CRA in open, during or/and at the end of the study. After completion, study drug medication (unused) might be destroyed after sponsor authorization.

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

Authorized treatments will include:

- Corticosteroid-induced osteoporosis prophylaxis with calcium and vitamin D supplementation, and bisphosphonates as appropriate
- *Pneumocystis jiroveci* prophylaxis, with cotrimoxazole or pentamidine aerosol or atovaquone according to the FVSG and TASK force recommendations for all patients during the entire duration of the trial [42,44] (highly recommended)

- Vaccines for influenza virus and *Streptococcus pneumoniae*
- Proton pump inhibitors, hypokaliemia prophylaxis with potassium supplementation.

Prohibited treatments will include:

- Any other immunosuppressive or immunomodulatory agent administered for the control of vasculitis or any other inflammatory disorders,
- Allopurinol or febuxostat which may enhance azathioprine toxicity.

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 EGPA activity or remission and to determine BVAS. Asthma and rhino-sinusal manifestations will be recorded. Prednisone dosage will be also collected.

The Birmingham Vasculitis Assessment Score (BVAS) is a validated, clinician completed tool used for the comprehensive multisystem clinical assessment of disease activity in systemic vasculitis [46]. A copy of the BVAS questionnaire is provided section 18.3, page 87. The BVAS form is divided into 9 organ-based systems, with each section including symptoms/signs that are typical of that particular organ involvement in systemic vasculitis. The form is designed to record features that are attributable to current vasculitis, after exclusion of other causes such as infection, hypertension etc. The scoring sheet records the presence or absence of each item. Each item is weighted and a maximum total score applied to each system. The total score on all 9 organ systems gives an indication of the disease activity of each patient at the time of scoring and reflects the need for therapy. The investigator will be required to complete the BVAS form in the eCRF at Screening (Visit 1), Baseline (Visit 2), at month 1 and then every 3 months until study completion at Month 28 or Early Withdrawal, as specified in Table 3.

Vasculitis 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 [43].

Clinical flares attributable to vasculitis activity will be defined as the reoccurrence or new onset of disease attributable to active EGPA. A major flare will be defined as the re-occurrence or new onset of potentially organ- or life-threatening disease activity that cannot be treated with an increase of corticosteroids alone and requires further escalation of treatment (*i.e.*, the administration of cyclophosphamide). All other relapses will be classified as minor [43].

Based on recommendations from the EGPA Task Force, isolated asthma or sinusitis exacerbations with or without increased blood eosinophilia does not necessarily imply a relapse *per se* but these patients should be monitored closely because these symptoms may be early signs of a vasculitis flare [44]. Eosinophil-count increases, without any other clinical

EGPA manifestations; isolated asthma, sinusitis or rhinitis exacerbations, with or without concomitant eosinophil-count rise; will thus be recorded but not considered as relapse, and will be registered and analyzed separately.

An independent Endpoint Adjudication Committee will review in double-blind the classification of disease flare with particular emphasis on the distinction between vasculitis flare and asthma/rhino-sinusal exacerbations, and reasons for corticosteroid escalation.

For secondary endpoints, adverse event rate will be assessed, expressed as adverse events according to the CTCAE toxicity grading system.

The duration of remission, defined as the total accrued duration in weeks with BVAS=0 and prednisone dose ≤7.5 mg/day will be also assessed as previously described.

The area under the curve for corticosteroids in the two treatment groups will be analyzed.

To evaluate rhino-sinusal manifestations, sino-nasal outcome test-22 patients questionnaire will be used (see section 18.8, page 95) [47,48].The 22 item Sinonasal Outcome Test (SNOT-22) is a validated patient-reported outcome measure for disease-health related quality of life for sinonasal disease with simplified scoring. The minimally important difference is 9 [47]. A French version has been validated [48].

To evaluate asthma, pulmonary function test and asthma control questionnaire will be used (see section 18.7, pages 94) [49].The score on the ACQ-5 represents the mean of responses to five questions about the frequency or severity of asthma symptoms during the previous week, with each response scored on a scale of 0 to 6 and higher scores indicating poorer control. The minimal clinically important difference for the mean score is 0.5 points [49].

Finally, damage, functional disability and quality of life will be assessed using the validated Vasculitis Damage Index, HAQ and SF-36 questionnaires during follow-up, respectively (see sections 18.4, 18.5, 18.6, pages 88-92) [50].

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. The deaths will be also reviewed in double-blind by the

committee. It will be necessary for these cases to have the CD19 count, hemogram, the dosage of gammaglobulines -or IgG, and at least for sepsis the CD4 and CD8 count.
The committee will estimate the link between the experimental medications and the occurrence of the endpoint.

9. STATISTICAL ASPECTS

Statistical analyses will be performed in the Department of Epidemiology, Clinical Research Unit Paris Descartes, INSERM U 738, and supervised by Pr Philippe Ravaud.

9.1. Calculation of sample size

Total number of scheduled patients: 98 patients.
In absence of hypothesis on total duration of remission over the 28 month study period and based on the results of previous controlled trials from the French Vasculitis Study Group in EGPA, whatever the Five Factor Score, the proportion of patients experiencing vasculitis relapse or asthma-rhino-sinusal exacerbation is expected to be 35% at 28 months in the azathioprine control group, which means that a total of 35% of patients are expected to have an uncontrolled disease at 28 months in the azathioprine control group.
The primary hypothesis of the MAINRITSEG trial is a decrease of at least 66% of the rate of uncontrolled disease at 28 months, i.e. 12%. Based on this hypothesis, using a bilateral test, we calculated that 98 patients will be required, including patients lost to follow-up, for the study to have 80% power to detect a 66% reduction in the relative risk with a two-sided alpha level of 5%, 49 patients in each arm.

9.2. Description of statistical methods to be used

All analyses will be performed on an intent-to-treat basis: all patients will be considered in the analysis and will be analyzed in the group to which they had been assigned.

For descriptive analyses, qualitative variables will be reported with absolute and relative frequencies, and quantitative variables with median (interquartile range [IQR]).

A random-effects Cox proportional hazards for recurrent events will be used to analyse primary outcome (total duration of remission over the 28 month study period) with a random effect at center levels and Kaplan-Meier curves will be plotted for each treatment. Censoring values will be related to deceased patients and to patients lost to follow up. Assumption of proportionality will be assessed with a Kolmogorov-type Supremum test. Survival secondary outcomes will be analyzed with the same model.

To compare differences in changes in values between the 2 treatment groups for quantitative secondary variables, a constrained Longitudinal Data Analysis (cLDA) model will be used (Liang and Zeger, 2002). In this model, both the baseline and post baseline values will be modelled as dependent variables, and the true baseline means will be constrained to be the same for the 2 treatment groups. Hence, this analysis will provide an adjustment for the observed baseline difference in estimating the treatment effects. The differences from week 0 will be estimated at each time in each group by the time-by-treatment interaction. Random effects at patient and center levels will be added to these models. The main assumption of this mixed model is that baseline and post-baseline measures are jointly multivariable normal variables.

Qualitative secondary outcomes will be analyzed using a mixed logistic regression model with a random effect at center levels.

Stratification factors used in randomization (newly-diagnosed vs. relapsing, vasculitis severity (FFS=0 vs. FFS ≥1), ANCA status (MPO or PR3 vs. none), induction therapy (CYC vs. RTX vs. CS alone) will be entered in models as fixed effect. The stratified model will be the main model. There will be no unstratified model.

Data analysis will involve use of SAS 9.4 (SAS Institute, Cary, NC).

Safety analysis (e.g., % of patients with at least one serious adverse events) will be performed with a mixed logistic regression model taken into account centers and stratification factors.

Analyzed adverse events

The proportion of patients over the 28 month study period with adverse events, serious adverse events and selected severe adverse events will be reported including grade 3 or 4 adverse effects (Common Terminology Criteria for Adverse Events), necessitating hospitalization, all cause deaths, cancers or infusion reactions (within 24hours of infusion) that contraindicated further infusions.

Blinded statisticians will perform the statistical analyses at an independent center in the Department of Epidemiology, Paris Descartes University, INSERM U 738 (Pr Philippe Ravaud).

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

An analysis plan will be developed and validated with the scientific committee before statistical analysis.

No interim analysis is scheduled in this research.

10. SAFETY ASSESSMENT - RISKS AND RESTRICTIONS OF THE RESEARCH

10.1. 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.

10.2. Definition according to the notice to sponsors of clinical trials for medications (ANSM)

- **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

10.3. The investigator’s roles

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

The investigator must notify the sponsor, **immediately on the day when the sponsor becomes aware**, of all the serious adverse events, except those that are listed in the protocol or in the investigator's brochure as not requiring immediate notification.

These serious adverse events are recorded in the "adverse event" section of the case report form and the investigator must immediately notify the sponsor's Vigilance division (see 10.3).

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 (v4.03) [National Cancer Institute].

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

10.4. Specific features of the protocol

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

10.4.1. 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. They include the events associated with:

Normal and natural evolution of the pathology

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

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
- Stay in the Emergency Unit less than 12 hours

10.4.2. 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 10.4.1 as not requiring notification:

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"

For serious adverse events related to the experimental medication(s) and which are expected:

- the link for the SmPC for the "**Azathioprine 25mg**" speciality : link in Appendix 18.9 should be consulted.
- the link for the SmPC for the "**Mabthera**": link in Appendix 18.13 should be consulted.

Other events that require the investigator to immediately notify the sponsor

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.

Notification is required if the exposure involves:

- the mother,

- the father if the experimental medication is genotoxic.

10.5. 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 18.10). 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 DRCI, fax No. **01 44 84 17 99**.

For this study 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 DRCI can be contacted via email: vigilance.drc@aphp.fr.

In utero exposure

The investigator completes the "form for monitoring a pregnancy that developed during a biomedical research", found in Appendix 18.11 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 DRCI, fax No. **01 44 84 17 99**.

10.6. 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

10.7. The sponsor's roles

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

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

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 du Médicament (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 EUDRA vigilance 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.

Specific cases of serious adverse events of special interest:
At the request of ANSM, the sponsor may be asked to declare serious adverse events of special interest, in accordance with the same procedures and deadlines as SUSARs.

Specific case of double-blind trials
As a general rule, the sponsor declares a suspected unexpected serious adverse reaction to the competent authorities and to the CPP after having broken the blind on the experimental medication.
In exceptional situations, and if the ANSM grants permission when requested by the sponsor in the sponsor's clinical trial authorisation application, the methods for unblinding and for declaring suspected unexpected serious adverse reactions can be modified.

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.

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.

10.8. 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.
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.

10.8.1. General information about the DSMB

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

- to continue the research with no modifications
- to continue the research with a modification to the protocol and/or to the monitoring of subjects
- to temporarily halt inclusions
- to permanently terminate the research in light of:
    - safety data: serious adverse reactions
    - efficacy data: proven futility or efficacy

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

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

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

10.8.2. 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.

10.8.3. 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.

11. SPECIFIC RESEARCH COMMITTEEs

11.1. Scientific committee

The Scientific Committee of this trial has been involved in the design of the trial, the definition of objectives and endpoints, the writing of the protocol and the analysis plan.

It is composed by:

- Dr Xavier Puéchal, FVSG
- Dr Benjamin Terrier, FVSG
- Pr Loïc Guillevin, FVSG
- Pr Philippe Ravaud, Statistician

11.2. Endpoint Adjudication Committee

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

It will review in double-blind the classification of disease flare with particular emphasis on:

- the distinction between vasculitis flare and asthma/rhino-sinusal exacerbations,
- and reasons for glucocorticoid escalation.

12. DATA MANAGEMENT

12.1. 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 (ACQ, SNOT-22, HAQ and SF36) which will be collected on forms and secondly input in an electronic database.

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

For this research, no data will be directly collected in the CRF.

The source document is the patient's medical record.

Data collected in the medical record and the CRF and 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, serum protein electrophoresis, calcemia, phosphoremia, glycemia, urine analysis, CD19+ cells (blinded results), CD4+ and CD8+ cells and as appropriate troponin and NT-pro-BNP
- ANCA using immunofluorescence and ELISA
- Imaging tests as appropriate: chest X-ray, thoracic CT-scan, echocardiogram, echocardiography, cardiac MRI: only in the patient's medical record.
- prednisone tapering
- azathioprine dosage
- rituximab dosage

12.2. Right to access source data and documents

12.2.1. 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).

12.2.2. 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.

12.2.3. 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.

12.3. 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-CRF, 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 Tréluyer.

12.3.1. Data entry

Data entry will be carried out on an electronic case report form system (e-CRF), filled in on the internet after each visit by the investigator-physicians or by a clinical research technician supervised by the investigator.in each center. Access to the on-line data entry form by the investigator-physicians or the clinical research technician will be restricted by an access code and a personal and unique password system for each user. Each investigator will, in addition, have access to a specific profile that attributes or withholds access to certain functions of the system (entering data, or simply viewing the data of the enrolled patient or all the study data, possibility of change and validation by the CRAs, etc…). Data will be stored on a secure server, with data encrypted during transmission and automatic internal saving of a copy on the server that will host the electronic case report form.

12.3.2. 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".

12.3.3. 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.

12.4. 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.

13. 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. This research is considered at risk level C (moderate risk).

13.1. 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 centers.

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.

13.2. Level of center monitoring

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

13.3. Quality control

Management and quality control of patient data will be made jointly by the Clinical Research Unit URC/CIC Paris Descartes Necker-Cochin and coordinating investigator.

A blinded 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 DRCI and in accordance with the French Good Clinical Practices as well as with the legislative and regulatory provisions in force.

A non blinded Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the quality control to the pharmacy.

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.

13.4. 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 centers 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 print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the research. The investigator must archive a copy of the authenticated document that was delivered to the sponsor.

13.5. 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 DRCI'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 DRCI 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.

13.6. 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.

13.7. 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 center will sign a responsibility commitment (standard DRCI 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.

14. ETHICAL AND LEGAL CONSIDERATIONS

14.1. 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 thirty days between the time when the subject receives the information and the time when he or she signs the consent form.

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.

14.2. Subject prohibited from participating in another research or an exclusion period anticipated after the research, if applicable

The exclusion period for this trial is 3 months but patients who have participated in the REOVAS trial would be authorized to participate in the MAINRITSEG trial.

14.3. Compensation for subjects

None but patients are followed according to standard of care by experimented physicians.

14.4. Registration on the national register of subjects participating in biomedical research relating to the products listed in Article L. 5311-1 of the French Public Health Code.

According to the French Public Health Code, this registration will take place before the beginning of the trial.

14.5. Legal obligations

14.5.1. The sponsor's role

Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this research and by delegation, the Clinical Research and Development Department (DRCI) 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.

14.5.2. 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.

14.5.3. 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.

14.5.4. Commitment to compliance with the MR 001 "Méthodologie de Référence"

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

14.6. Modifications to the research

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, prior to starting the research, a favourable opinion from the CPP and authorisation from the ANSM within the scope of their respective authorities.

The information sheet and the consent form can be revised if necessary, in particular if there is a substantial modification to the research or if adverse reactions occur.

14.7. Final research report

The final biomedical research report referred to in Article R1123-60 of the French Public Health Code is drawn up and signed by the sponsor and the investigator. A summary of the report written according to the competent authority's reference plan will need to be sent to the competent authority and ethical review board within one year after the end of the research, meaning the end of the participation of the last research subject.

15. FUNDING AND ASSURANCE

15.1. Funding sources

The present study will be submitted for funding to the PHRC-2015.

In addition, Roche SAS has shown interest in this project. Should AP-HP accept to sponsor and give funding for this PHRC, Roche SAS will provide rituximab for free for all the participants randomized in the experimental arm (see intentional letter from Roche SAS).

15.2. 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.

16. PUBLICATION RULES

AP-HP will be mentioned in the affiliations of the authors' publications of this research which will also indicate the administrator AP-HP (DRCI) and funding's source (PHRC national), according to the following indications.
A copy of the manuscript will be shared with DRCI.

The publication rules will follow the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.
The first author will be the coordinating investigator of the trial and all those designated as authors should meet all four criteria for authorship:
1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

16.1. Mention of the AP-HP manager (DRCI) in the acknowledgements of the text

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16.2. Mention of the financier in the acknowledgements of the text

"The research was funded by a grant from Programme Hospitalier de Recherche Clinique – PHRC-2015 (Ministère de la Santé)"

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

16.3. Anticipated calendar for publication

Last patient is expected to reach the month 28 visit on February 2022. .
Submission for publication of the main results is scheduled for Q4 2022.

17. BIBLIOGRAPHY

1. Churg J, Strauss L. Allergic granulomatosis, allergic angiitis, and periarteritis nodosa. Am J Pathol 1951;27:277-301.

2. Lanham JG, Elkon KB, Pusey CD, Hughes GR. Systemic vasculitis with asthma and eosinophilia: A clinical approach to the Churg-Strauss syndrome. Medicine (Baltimore) 1984;63:65-81.

3. Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 1990;33:1094-100.

4. Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P **for the French Vasculitis Study Group**. Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. Medicine (Baltimore) 1999;78:26-37.

5. Comarmond C, Pagnoux C, Khellaf M, et al. **for the French Vasculitis Study Group.** Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): Clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. Arthritis Rheum 2013;65:270-81.

6. Moosig F, Bremer JP, Hellmich B, et al. A vasculitis centre based management strategy leads to improved outcome in eosinophilic granulomatosis and polyangiitis (Churg-Strauss, EGPA): Monocentric experiences in 150 patients. Ann Rheum Dis 2013;72:1011-7.

7. Sable-Fourtassou R, Cohen P, Mahr A, et al. **for the French Vasculitis Study Group.** Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. Ann Intern Med 2005;143:632-8.

8. Sinico RA, Di Toma L, Maggiore U, et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. Arthritis Rheum 2005;52:2926-35.

9. Mahr A, Guillevin L, Poissonnet M, Ayme S. Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome in a French urban multiethnic population in 2000: A capture-recapture estimate. Arthritis Rheum 2004;51:92-9.

10. Watts RA, Lane SE, Bentham G, Scott DG. Epidemiology of systemic vasculitis: A ten-year study in the united kingdom. Arthritis Rheum 2000;43:414-9.

11. Samson M, **Puéchal X,** Devilliers H, et al. **for the French Vasculitis Study Group.** Long-term outcomes of 118 patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) enrolled in two prospective trials. J Autoimmun 2013;43:60-9.

12. Cohen P, Pagnoux C, Mahr A, et al. **for the French Vasculitis Study Group.** Churg-Strauss syndrome with poor-prognosis factors: A prospective multicenter trial comparing

glucocorticoids and six or twelve cyclophosphamide pulses in forty-eight patients. Arthritis Rheum 2007;57:686-93.

13. Guillevin L, Lhote F, Gayraud M, et al. **for the French Vasculitis Study Group.** Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. Medicine (Baltimore) 1996;75:17-28.

14. Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Le Toumelin P **for the French Vasculitis Study Group.** The five-factor score revisited: Assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. Medicine (Baltimore) 2011;90:19-27.

15. **Puéchal X,** Pagnoux C, Baron G, et al. **for the French Vasculitis Study Group.** Does adding azathioprine to glucocorticoid induction increase the remission rate and prevent relapses in patients with systemic necrotizing vasculitides without poor-prognosis factors? A multicenter, double-blind randomized controlled trial (abstract). Arthritis Rheumatol 2015;67,11(Suppl.10): Accessed September 29, 2015.

16. Ribi C, Cohen P, Pagnoux C, et al. **for the French Vasculitis Study Group.** Treatment of Churg-Strauss syndrome without poor-prognosis factors: A multicenter, prospective, randomized, open-label study of 72 patients. Arthritis Rheum 2008;58:586-94.

17. Pagnoux C, Mahr A, Hamidou MA, et al. **for the French Vasculitis Study Group.** Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N Engl J Med 2008;359:2790-803.

18. **Puéchal X,** Pagnoux C, Perrodeau E, **for the French Vasculitis Study Group.** Long-term outcomes among participants in the WEGENT trial of remission-maintenance therapy for granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis. Arthritis Rheumatol 2016;68:690-701.

19. Ntatsaki E, Carruthers D, Chakravarty K, et al. BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. Rheumatology 2014;53:2306-9.

20. Manger BJ, Krapf FE, Gramatzki M, et al. IgE-containing circulating immune complexes in Churg-Strauss vasculitis. Scand J Immunol 1985;21:369-73.

21. Bottero P, Bonini M, Vecchio F, et al. The common allergens in the Churg-Strauss syndrome. Allergy 2007;62:1288-94.

22. Falk RJ, Terrell RS, Charles LA, Jennette JC. Anti-neutrophil cytoplasmic autoantibodies induce neutrophils to degranulate and produce oxygen radicals in vitro. Proc Natl Acad Sci U S A 1990;87:4115-9.

23. Xiao H, Heeringa P, Hu P, et al. Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. J Clin Invest 2002;110:955-63.

24. Heeringa P, Brouwer E, Tervaert JW, Weening JJ, Kallenberg CG. Animal models of anti-neutrophil cytoplasmic antibody associated vasculitis. Kidney Int 1998;53:253-63.
25. Kiene M, Csernok E, Muller A, Metzler C, Trabandt A, Gross WL. Elevated interleukin-4 and interleukin-13 production by T cell lines from patients with Churg-Strauss syndrome. Arthritis Rheum 2001;44:469-73.
26. **Terrier B,** Bieche I, Maisonobe T, et al. Interleukin-25: A cytokine linking eosinophils and adaptive immunity in Churg-Strauss syndrome. Blood 2010;116:4523-31.
27. Vaglio A, Strehl JD, Manger B, et al. IgG4 immune response in Churg-Strauss syndrome. Ann Rheum Dis 2012;71:390-3.
28. Takemura S, Klimiuk PA, Braun A, Goronzy JJ, Weyand CM. T cell activation in rheumatoid synovium is B cell dependent. J Immunol 2001;167:4710-8.
29. Wong FS, Wen L, Tang M, et al. Investigation of the role of B-cells in type 1 diabetes in the nod mouse. Diabetes 2004;53:2581-7.
30. Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363:221-32.
31. Jones RB, Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 2010;363:211-20.
32 Guillevin L, Pagnoux C, Karras A, et al. **for the French Vasculitis Study Group.** Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med 2014; 371:1771-80.
33. Koukoulaki M, Smith KG, Jayne DR. Rituximab in Churg-Strauss syndrome. Ann Rheum Dis 2006;65:557-9.
34. Pepper RJ, Fabre MA, Pavesio C, et al. Rituximab is effective in the treatment of refractory Churg-Strauss syndrome and is associated with diminished T-cell interleukin-5 production. Rheumatology (Oxford) 2008;47:1104-5.
35. Cartin-Ceba R, Keogh KA, Specks U, Sethi S, Fervenza FC. Rituximab for the treatment of Churg-Strauss syndrome with renal involvement. Nephrol Dial Transplant 2011;26:2865-71.
36. Thiel J, Hassler F, Salzer U, Voll RE, Venhoff N. Rituximab in the treatment of refractory or relapsing eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). Arthritis Res Ther 2013;15:R133.
37. Novikov P, Moiseev S, Smitienko I, Zagvozdkina E. Rituximab as induction therapy in relapsing eosinophilic granulomatosis with polyangiitis: A report of 6 cases. Joint Bone Spine 2016;83:81-4
38. Mohammad AJ, Hot A, Arndt F, et al. Rituximab for the treatment of eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Ann Rheum Dis 2016;75:396-401.

39. **Puéchal X.** Therapeutic immunomodulation in eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Joint Bone Spine 2016;83:7-10.

40. Bouldouyre MA, Cohen P, Guillevin L. Severe bronchospasm associated with rituximab for refractory Churg-Strauss syndrome. Ann Rheum Dis 2009;68:606.

41. Emery P, Fleischmann R, Filipowicz-Sosnowska A, Schechtman J, Szczepanski L, Kavanaugh A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis Rheum 2006;54:1390-400.

42. Charles P, Bienvenu B, Bonnotte B, et al. **for the French Vasculitis Study Group.** Rituximab: Recommendations of the French Vasculitis Study Group (FVSG) for induction and maintenance treatments of adult, antineutrophil cytoplasm antibody-associated necrotizing vasculitides. Presse Med 2013;42:1317-30.

43. Hellmich B, Flossmann O, Gross WL, et al. EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: Focus on anti-neutrophil cytoplasm antibody-associated vasculitis. Ann Rheum Dis 2007;66:605-17.

44. Groh M, Pagnoux C, Baldini C, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) Consensus Task Force recommendations for evaluation and management. Eur J Intern Med 2015;26:545-53.

45. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med 2014;371:1189-97.

46. Mukhtyar C, Lee R, Brown D, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis 2009;68:1827-32.

47. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-itemSinonasalOutcomeTest. Clin Otolaryngol. 2009;34:447-54.

48. de Dorlodot C, Horoi M, Lefebvre P, et al. French adaptation and validation of the sino-nasal outcome test-22: a prospective cohort study on quality of life among 422 subjects. Clin Otolaryngol 2015;40:29-35.

49. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14:902-7.

50. Exley AR, Bacon PA, Luqmani RA, et al. Development and initial validation of the Vasculitis Damage Index for the standardized clinical assessment of damage in the systemic vasculitides. Arthritis Rheum 1997;40:371-80.

51. Mabthera Investigor's Brochure. *Current Version*

18. LIST OF APPENDIX

18.1 Birmingham Vasculitis Activity Score (BVAS)
18.2 Vasculitis Damage index (VDI)
18.3 Short Form 36 Health Survey (SF36) questionnaire
18.4 Health Assessment Questionnaire (HAQ) questionnaire
18.5 Asthma Control Questionnaire (ACQ)
18.6 Sino-Nasal Outcome Test-22 questionnaire (SNOT-22)
18.7 Patient's card
18.8 Logbook for the adhesion to the treatment
18.9 SmPC for the "Azathioprine 25mg" speciality
18.10 Form for reporting Serious Adverse Events (SAE)
18.11 Form monitoring a pregnancy that developed during a biomedical research
18.12 Abacuses for azathioprine/placebo
18.13. Link for the SmPC for the Mabthera
18.14. Information letter for patients included in the REOVAS study18.15. Information letter for the additional EGPA patients after remission achieved with an induction regimen treatment similar to the one used in the REOVAS trial.

18.1. 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 ☐

18.2 Vasculitis Damage index (VDI)

Ne cocher que les symptômes présents depuis plus de 3 mois, depuis le début de la maladie, quelle qu'en soit l'origine (1 point par atteinte cochée).

SIGNES MUSCULO-ARTICULAIRES
- Atrophie ou faiblesse ☐
- Arthrite érosive ☐
- Fracture ostéoporotique ☐
- Ostéonécrose aseptique ☐
- Ostéomyélite ☐

SIGNES CUTANEO-MUQUEUX
- Alopécie ☐
- Ulcère(s) cutané(s) ☐
- Ulcération(s) buccale(s) ☐

SIGNES OPHTALMOLOGIQUES
- Cataracte ☐
- Atteinte ou atrophie rétinienne ☐
- Baisse d'acuité visuelle / diplopie ☐
- Cécité monoculaire ☐
- Cécité binoculaire ☐
- Destruction orbitaire ☐

SIGNES ORL
- Perte d'audition ☐
- Obstruction, croûtes, écoulement nasal ☐
- Effondrement/perforation de cloison nasale ☐
- Sinusite chronique ☐
- Destruction osseuse ☐
- Sténose sous-glottique non opérée ☐
- Sténose sous-glottique opérée ☐

SIGNES PULMONAIRES
- HTAP ☐
- Fibrose pulmonaire/excavations ☐
- Infarctus pulmonaire ☐
- Fibrose pleurale ☐
- Asthme chronique ☐
- Insuffisance respiratoire chronique ☐
- Anomalies aux EFR ☐

SIGNES CARDIOVASCULAIRES
- Angor ou pontage ☐
- Infarctus du myocarde ☐
- Cardiomyopathie ☐
- Insuffisance cardiaque ☐
- Atteinte valvulaire ☐
- Péricardite-péricardectomie ☐
- HTA PA Diastolique > 95 mmHg et/ou traitée ☐

SIGNES VASCULAIRES PERIPHERIQUES
- Abolition d'un pouls ☐
- Sténose d'un gros vaisseau ☐
- Claudication artérielle ☐
- Phlébite compliqueé ☐

SIGNES DIGESTIFS
- Infarctus/résection intestinale ☐
- Claudication digestive-mésentérique ☐
- Pancréatite > 3 mois ☐
- Péritonite chronique ☐
- Sténose oesophagienne ☐

REINS
- Diminution de clairance > 50% ☐
- Protéinurie > 0.5g/jour ☐
- Insuffisance rénale chronique ☐
- Dialyse ☐

SYSTEME NERVEUX
- Trouble cognitif majeur ou psychose ☐
- Comitialité ☐
- Accident vasculaire cérébral ☐
- Atteinte de nerf crânien ☐
- Neuropathie périphérique ☐
- Myélite transverse ☐

AUTRES SEQUELLES ☐
- Ménopause ☐
- Cancer ☐
- Cystite/néoplasie de vessie liée au cyclophosp ☐
- Décrire

TOTAL = ☐ (= nombres de cases cochées)

18.3 Short Form 36 Health Survey (SF36)

MAINRITSEG Page 1 / 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

MAINRITSEG Page 2 / 4	Code d'identification patient |__|__|__| / |__|__|__|__| / |__| - |__|	Visite : |__|__| Date : |__|__| |__|__| |__|__|

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.

18.4 Health Assessment Questionnaire (HAQ) questionnaire

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 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

MAINRITSEG Page 4 / 4	Code d'identification Patient |__|__|__| / |__|__|__|__| / |__| - |__|	Visite : |__|__| Date : |__|__| |__|__| |__|__|

• **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

18.5 Asthma Control Questionnaire (ACQ)

QUESTIONNAIRE DE CONTRÔLE DE L'ASTHME

S'il vous plaît, merci d'indiquer la réponse qui correspond le mieux à votre asthme au cours de la semaine passée.

En général, au cours des 7 derniers jours, vous êtes-vous éveillé la nuit à cause de votre asthme ?	0 - Jamais 1 - Presque jamais 2 - Quelque fois 3 - Plusieurs fois 4 - Souvent 5 - Très souvent 6 - Je n'ai pas pu dormir à cause de mon asthme
En général, au cours des 7 derniers jours, comment étaient vos symptômes d'asthme (toux, essoufflement) le matin au réveil ?	0 - Aucun symptôme 1 - Symptômes très légers 2 - Symptômes légers 3 - Symptômes modérés 4 - Symptômes sérieux 5 - Symptômes graves 6 - Symptômes très graves
En général, au cours des 7 derniers jours, vous êtes-vous senti limité dans vos activités à cause de votre asthme ?	0 - Nullement limité 1 - Très discrètement limité 2 - Discrètement limité 3 - Modérément limité 4 - Très limité 5 - Extrêmement limité 6 - Totalement limité
En général, au cours des 7 derniers jours, avez-vous été essoufflé à cause de votre asthme ?	0 - Nullement 1 - Un petit peu 2 - Peu 3 - Modérément 4 - Beaucoup 5 - Très souvent 6 - Enormément
En général, au cours des 7 derniers jours, avez-vous eu la respiration sifflante ?	0 - Jamais 1 - Presque jamais 2 - Quelque fois 3 - Plusieurs fois 4 - Souvent 5 - Très souvent 6 - Tout le temps
En général, au cours des 7 derniers jours, combien de bouffées de votre bronchodilatateur à courte durée d'action (ex Ventoline©/Bricanyl©) avez-vous prise par jour ? *Si vous n'êtes pas sûr de la réponse, merci de demander de l'aide*	0 - Aucune 1 - 1à 2 bouffées la plupart des jours 2 - 3 à 4 bouffées la plupart des jours 3 - 5 à 8 bouffées la plupart des jours 4 - 9 à 12 bouffées la plupart des jours 5 - 13 à 16 bouffées la plupart des jours 6 - Plus de 16 bouffées la plupart des jours
Valeurs du VEMS en % des valeurs prédites	0 - Plus de 95 % 1 - Entre 90 et 95 % 2 - Entre 80 et 89 % 3 - Entre 70 et 79 % 4 - Entre 60 et 69 % 5 - Entre 50 et 59 % 6 - Moins de 50 %

18.6 Sino-Nasal Outcome Test-22 questionnaire (SNOT-22)

Sino-Nasal Outcome Test-22
(Test d'impact des symptômes sino-nasaux-22)

Vous trouverez ci-dessous une liste de symptômes et de conséquences sociales et/ou émotionnelles liées à votre pathologie nasale. Nous aimerions en apprendre davantage sur ces problèmes et apprécierions que vous répondiez aux questions suivantes au meilleur de vos capacités. Il n'y a pas de bonnes ou de mauvaises réponses et vous seul(e) pouvez nous donner ces informations. Veuillez évaluer vos problèmes, tels qu'ils se sont présentés durant les deux dernières semaines. Nous vous remercions pour votre participation

En considérant la sévérité du problème quand il survient et la fréquence avec laquelle il survient, veuillez coter chaque item ci-dessous en **entourant** le chiffre qui correspond à votre ressenti, en utilisant l'échelle suivante →	Aucun problème	Problème très léger	Problème léger	Problème modéré	Problème sévère	Problème très sévère
1. Besoin de se moucher	0	1	2	3	4	5
2. Eternuements	0	1	2	3	4	5
3. Nez qui coule	0	1	2	3	4	5
4. Toux	0	1	2	3	4	5
5. Ecoulement nasal postérieur (dans la gorge)	0	1	2	3	4	5
6. Ecoulement nasal épais	0	1	2	3	4	5
7. Oreilles bouchées	0	1	2	3	4	5
8. Vertiges	0	1	2	3	4	5
9. Douleur/pression dans l'oreille	0	1	2	3	4	5
10. Douleur/pression faciale	0	1	2	3	4	5
11. Difficulté pour s'endormir	0	1	2	3	4	5
12. Se réveiller la nuit	0	1	2	3	4	5
13. Manque d'une bonne nuit de sommeil (mauvaise qualité de sommeil)	0	1	2	3	4	5
14. Se réveiller fatigué	0	1	2	3	4	5
15. Fatigue (durant la journée)	0	1	2	3	4	5
16. Baisse de productivité (rendement, efficacité)	0	1	2	3	4	5
17. Baisse de concentration	0	1	2	3	4	5
18. Frustration/agitation/irritabilité	0	1	2	3	4	5
19. Baisse de moral (tristesse)	0	1	2	3	4	5
20. Gêne/inconfort	0	1	2	3	4	5
21. Perturbation du goût, de l'odorat	0	1	2	3	4	5
22. Obstruction/congestion nasale	0	1	2	3	4	5
	TOTAL:	____	____	____	____	____

TOTAL GÉNÉRAL : _____

Fig. 1. French version of the 22-item Sino-Nasal Outcome Test (SNOT-22). Symptoms are rated from 0 ('no problem') to 5 ('problem as bad as it can be'). The theoretical range of measure is 0–110, with higher score indicating poorer nasal function or related symptoms.

18.7 Patient's card

CARTE PATIENT

Merci de garder cette carte en permanence avec vous

Nom :…….. Prénom : ……..

Je participe à la recherche MAINRITSEG
MAINtien de la rémission avec le RITuximab verSus l'azathioprine pour les patients
ayant un diagnostic récent ou une rechute de Granulomatose Éosinophilique avec polyangéite.
Essai prospectif, randomisé, contrôlé, en double aveugle.
dont le promoteur est l'Assistance Publique – Hôpitaux de Paris

Code d'identification dans la recherche :

|__|__|__| - |__|__|__|__| - |__|__|

Je reçois le traitement suivant :

Traitement standard : azathioprine par voie orale (2 mg/kg/jour) pendant 24 mois + 4 perfusions de placebo de rituximab par voie intraveineuse (tous les 6 mois pendant 18 mois).

OU

Traitement expérimental : perfusions d'une dose fixe de 500 mg de rituximab tous les 6 mois pendant 18 mois (4 perfusions) par voie intraveineuse + placebo d'azathioprine par voie orale pendant 24 mois.

Date de début de traitement : __ __ /__ __ /__ __ __ __

Traitements dispensés (n°trimestriels) :
Visite J0 : __ __ __ __ Visite M3 : __ __ __ __ Visite M6 : __ __ __ __ Visite M9 : __ __ __ __

Visite M12 : __ __ __ __ Visite M15 : __ __ __ __ Visite M18 : __ __ __ __ Visite M21 : __ __ __ __ __

Version n°1 du 24/08/2016

Je suis suivi(e) par le Dr……

A l'Hôpital ……..……..

☎……...

En cas de nécessité de connaître votre traitement en urgence, votre médecin peut contacter le Centre Anti-Poison de l'hôpital Fernand Widal, à Paris

☎: 01 40 05 48 48

18.8 Logbook for the adhesion to the treatment

Etude MAINRITSEG Carnet de suivi de l'adhésion au traitement	Code d'identification patient |__|__|__| / |__|__|__|__| / |__H__|	CARNET n° 1 / 9 De l'inclusion à la visite à 3 mois

Etude MAINRITSEG

MAINtien de la rémission avec le RITuximab verSus l'azathioprine pour les patients ayant un diagnostic récent ou une rechute de Granulomatose Éosinophilique avec polyangéite.
Essai prospectif, randomisé, contrôlé, en double aveugle.

CARNET N°1 POUR LE SUIVI DE L'ADHESION AU TRAITEMENT

DU |__|__| / |__|__| / |__|__| **au** |__|__| / |__|__| / |__|__|

Etude MAINRITSEG Carnet de suivi de l'adhésion au traitement	Code d'identification patient |__|__|__| / |__|__|__|__| / |__H__|	CARNET n° 1 / 9 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 28 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 au premier jour de prise de l'azathioprine ou du placebo (lundi, mardi, … ou dimanche) = semaine 1.

La semaine 2 et les semaines suivantes commenceront ce même jour.

Ce carnet vous permet de noter toutes les semaines (une ligne par semaine), les doses d'azathioprine/placebo et de corticoïdes que vous prenez avec les dates correspondantes.

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.

Le délai maximum autorisé entre chacune de vos consultations est de 15 jours.

Etude MAINRITSEG Carnet de suivi de l'adhésion au traitement	Code d'identification patient _____/_____/__H__	CARNET n° 1 / 9 De l'inclusion à la visite à 3 mois

Semaine1 = 1er jour du traitement par azathioprine ou placebo : __ __ /__ __ /__ __ __ __ Jour de la semaine correspondant : _____

MOIS 1

	CORTICOIDES : dose en mg / jour	AZATHIOPRINE ou PLACEBO : dose en mg / jour	Les doses de traitement prescrites ont-elles été respectées ? Oui ☐ Non ☐ Si le traitement n'a pas été pris ou partiellement pris, indiquez le motif :
Semaine 1 __/__/__	__,__	___	☐ Oubli : pendant combien de jours : ___ ☐ Autre : précisez : _____
Semaine 2 __/__/__	__,__	___	☐ Oubli : pendant combien de jours : ___ ☐ Autre : précisez : _____
Semaine 3 __/__/__	__,__	___	☐ Oubli : pendant combien de jours : ___ ☐ Autre : précisez : _____
Semaine 4 __/__/__	__,__	___	☐ Oubli : pendant combien de jours : ___ ☐ Autre : précisez : _____

Etude MAINRITSEG Carnet de suivi de l'adhésion au traitement	Code d'identification patient _____/_____/__H__	CARNET n° 1 / 9 De l'inclusion à la visite à 3 mois

MOIS 2

	CORTICOIDES : dose en mg / jour	AZATHIOPRINE ou PLACEBO : dose en mg / jour	Les doses de traitement prescrites ont-elles été respectées ? Oui ☐ Non ☐ Si le traitement n'a pas été pris ou partiellement pris, indiquez le motif :
Semaine 5 __/__/__	__,__	___	☐ Oubli : pendant combien de jours : ___ ☐ Autre : précisez : _____
Semaine 6 __/__/__	__,__	___	☐ Oubli : pendant combien de jours : ___ ☐ Autre : précisez : _____
Semaine 7 __/__/__	__,__	___	☐ Oubli : pendant combien de jours : ___ ☐ Autre : précisez : _____
Semaine 8 __/__/__	__,__	___	☐ Oubli : pendant combien de jours : ___ ☐ Autre : précisez : _____

Etude MAINRITSEG Carnet de suivi de l'adhésion au traitement	Code d'identification patient _____/_____/___H___	CARNET n° 1 / 9 De l'inclusion à la visite à 3 mois

MOIS 3

	CORTICOIDES : dose en mg / jour	AZATHIOPRINE ou PLACEBO : dose en mg / jour	Les doses de traitement prescrites ont-elles été respectées ? Oui ☐ Non ☐ Si le traitement n'a pas été pris ou partiellement pris, indiquez le motif :
Semaine 9 __/__/__	__,__	___	☐ Oubli : pendant combien de jours : ___ ☐ Autre : précisez : _____
Semaine 10 __/__/__	__,__	___	☐ Oubli : pendant combien de jours : ___ ☐ Autre : précisez : _____
Semaine 11 __/__/__	__,__	___	☐ Oubli : pendant combien de jours : ___ ☐ Autre : précisez : _____
Semaine 12 __/__/__	__,__	___	☐ Oubli : pendant combien de jours : ___ ☐ Autre : précisez : _____

Etude MAINRITSEG Carnet de suivi de l'adhésion au traitement	Code d'identification patient _____/_____/___H___	CARNET n° 1 / 9 De l'inclusion à la visite à 3 mois

MOIS 4 : si la date de la visite à 3 mois est décalée (15 jours maximum autorisés)

	CORTICOIDES : dose en mg / jour	AZATHIOPRINE ou PLACEBO : dose en mg / jour	Les doses de traitement prescrites ont-elles été respectées ? Oui ☐ Non ☐ Si le traitement n'a pas été pris ou partiellement pris, indiquez le motif :
Semaine 13 __/__/__	__,__	___	☐ Oubli : pendant combien de jours : ___ ☐ Autre : précisez : _____
Semaine 14 __/__/__	__,__	___	☐ Oubli : pendant combien de jours : ___ ☐ Autre : précisez : _____

18.9 SmPC for the “Azathioprine 25mg” speciality

Link to the SmPC for the “Azathioprine MYLAN 25mg” speciality:

http://agence-prd.ansm.sante.fr/php/ecodex/frames.php?specid=63944066&typedoc=R&ref=R0177683.htm

18.10 Form for reporting Serious Adverse Events (SAE) version n°2 of 10/07/2017

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 (2 pages), signé et retourné sans délai au pôle 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 : MAINRITSEG

Code de la Recherche : P150922

Titre complet de la Recherche Biomédicale : MAINtien de la rémission avec le RITuximab versus l'azathioprine pour les patients ayant un diagnostic récent ou une rechute de Granulomatose Eosinophilique avec polyangéite (GEPA). Essai prospectif, randomisé, contrôlé, en double aveugle.

Date de notification : |__|__| |__|__| |2|0|__|__|
jj mm aaaa

Date de prise de connaissance de l'EIG par l'investigateur : |__|__| |__|__| |2|0|__|__|
jj mm aaaa

Risque : ☐ A ☐ B ☒ C ☐ D

Plan expérimental : ☐ Essai non comparatif
☒ Essai comparatif : ☒ Double aveugle ☐ Simple aveugle ☐ Ouvert
☒ Randomisé ☐ Non randomisé

2. Identification du centre Investigateur

Nom de l'établissement : .....
Ville et code postal : .....
Service : .....

Investigateur (nom/prénom) : .....
Tél : ..... Fax : .....

3. Identification et antécédents de la personne se prêtant à la recherche

Référence de la personne : |__|__|__| - |__|__|__|__|__| - |__|__| - |__|__|
n°centre – n° ordre d'inclusion – initiale nom – initiale prénom

Sexe : ☐ M ☐ F

Poids : |__|__|__| kg
Taille : |__|__|__| cm

Date de naissance :
|__|__| |__|__|__|__|
mm aaaa
Age : |__|__|__| ans

Date de signature du consentement : |__|__| |__|__| |2|0|__|__|
jj mm aaaa

Date de randomisation : |__|__| |__|__| |2|0|__|__|
jj mm aaaa

Antécédents médicaux-chirurgicaux/familiaux pertinents pour l'évaluation du cas (joindre un CRH anonymisé le cas échéant) :
.....
.....
.....
.....
.....
.....
.....

1er numéro de traitement attribué (azathioprine/placebo) : _____

Facteurs de stratification lors de la précédente rechute :
☐ patient nouvellement diagnostiqué ou ☐ patient en rechute
☐ FFS = 0 ou ☐ FFS ≥1
ANCA en ELISA (anti-MPO ou anti-PR3) : ☐ positifs ou ☐ négatifs
Traitement d'induction : ☐ corticoïdes seuls ou ☐ corticoïdes et cyclophosphamide ou ☐ corticoïdes et rituximab

4. Médicament(s) expérimental(aux) (ME) ou produit(s) assimilé(s) [préciser le(s)quel(s)] avant la survenue de l'EIG

(barrer l'encadré si traitement non débuté)

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie[1]	Posologie / jour	Date de début *(jj/mm/aaaa)*	En cours[2]	Date de fin *(jj/mm/aaaa)*
Rituximab ou placebo	----	----	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|
Azathioprine ou placebo	----	----	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|
	----	----	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|

5. Procédures et actes ajoutés par la recherche *(ex. : biopsies, IRM ...)*

(barrer l'encadré si procédures et actes non réalisés)

	Date de réalisation *(jj/mm/aaaa)*	Chronologie : Avant la survenue de l'EIG	Chronologie : Après la survenue de l'EIG
.....	|__|__| |__|__| |2|0|__|__|	☐	☐
.....	|__|__| |__|__| |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 y compris forme pharmaceutique et dosage	Indication	Voie[1]	Posologie / jour	Date de début *(jj/mm/aaaa)*	En cours[2]	Date de fin *(jj/mm/aaaa)*

PARTIE RESERVEE AU PROMOTEUR
REFERENCE VIGILANCE :

Référence GED : REC-DTYP-0192

.....	.....	.....	.....	__/__/____	☐	__/__/2_0__/__
.....	.....	.....	.....	__/__/____	☐	__/__/2_0__/__
.....	.....	.....	.....	__/__/____	☐	__/__/2_0__/__

(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'EI

Acronyme : MAINRITSEG

Référence de la personne se prêtant à la recherche : ___ - ____ - __ - __
(n°centre – n° ordre d'inclusion – initiale nom – initiale prénom)

7. Evènement indésirable grave [EIG]

Diagnostic : ☐ Définitif ☐ Provisoire
.....

Organe(s) concerné(s) :
.....

Symptôme(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 : __h__ 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 :
du __/__/2_0__/__
au __/__/2_0__/__ ☐ *en cours*

L'évènement a-t-il conduit à une interruption du/des ME/produit assimilé(s) à l'étude ?
☐ Non ☐ Oui Date : __/__/2_0__/__
L'arrêt de traitement a été : ○ Provisoire ○ Définitif
Le cas échéant, date de reprise du traitement à l'étude : __/__/2_0__/__
Récidive de l'EIG après ré-administration : ○ Non ○ Oui - Date : __/__/2_0__/__

L'évènement a-t-il conduit à une levée d'insu ?
☐ Non ☐ Oui Date : __/__/2_0__/__

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__/__

☐ 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 :
.....

Degré de sévérité :
☐ Léger ☐ Modéré ☐ Sévère

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 ○ Aggravation ○ Amélioration

☐ **Guérison :**
○ sans séquelles
○ avec séquelles, préciser lesquelles :
.....
Date : __/__/2_0__/__ (jj mm aaaa)
__heures __ min

Des mesures symptomatiques ont été prises :
☐ Non ☐ Oui Si oui, préciser : .....

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].....

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) ?**
Lequel : ..... ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable
Lequel : ..... ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable
○ **à la (aux) procédure(s)/acte(s) de la recherche biomédicale : La/le(s)quel(les) ?**
La/lequel(le) : ..... ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable
La/lequel(le) : ..... ☐ Relation certaine ☐ Relation probable ☐ Relation possible ☐ Relation improbable

☐ **Non :**
○ **à la progression de la maladie faisant l'objet de la recherche :** (à compléter)
○ **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 :	

18.11 Form monitoring a pregnancy that developed during a biomedical research

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 **Notification et suivi d'une grossesse apparue au cours d'une recherche biomédicale portant sur un Médicament ou produit assimilé**	**PARTIE RESERVEE AU PROMOTEUR** **REFERENCE INTERNE :**

Ce formulaire doit être dûment complété (2 pages), signé et retourné sans délai au pôle Vigilance du DRCD-Siège par télécopie au +33 (0)1 44 84 17 99

1. Identification de la recherche

Acronyme: MAINRITSEG
Code P : 150922

Notification initiale ☐ **Suivi de notification** ☐ **N° du suivi** |__|__|

Date de notification : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Date de prise de connaissance de la grossesse par l'investigateur : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Titre complet de la Recherche Biomédicale: MAINtien de la rémission avec le RITuximab versus l'azathioprine pour les patients ayant un diagnostic récent ou une rechute de Granulomatose Eosinophilique avec polyangéite (GEPA). Essai prospectif, randomisé, contrôlé, en double aveugle.

2. Identification du centre investigateur

Nom de l'établissement : .....
Ville et code postal : .....
Service : .....

Investigateur (nom/prénom) : .....
Tél : Fax :

3. Identification de la personne présentant une grossesse

Référence de la personne : |__|__|__| - |__|__|__|__|__|__| - |__| - |__| (n°centre - n° ordre d'inclusion - initiale nom - initiale prénom)

Date de naissance (jour/année): |__|__| |__|__|__|__|
Date d'inclusion : |__|__| |__|__| |2|0|__|__|
Date de randomisation : |__|__| |__|__| |2|0|__|__|

Date des dernières règles : |__|__| |__|__| |2|0|__|__|
Et/ou date début de grossesse : |__|__| |__|__| |2|0|__|__|

Cas particulier d'une exposition paternelle : ☐ Oui ☐ Non

Référence de la personne : |__|__|__| - |__|__|__|__|__|__| - |__| - |__| (n°centre - n° ordre d'inclusion - initiale nom - initiale prénom)

Date de naissance (jour/année) : |__|__| |__|__|__|__|
Date d'inclusion : |__|__| |__|__| |2|0|__|__|
Date de randomisation : |__|__| |__|__| |2|0|__|__|

Expositions : Préciser si exposition au tabac (paquets/année), à l'alcool (unités OH), à des drogues et autres expositions.
Préciser si l'exposition est antérieure à la grossesse, poursuivie ou arrêtée (mentionner la date d'arrêt le cas échéant).
☐ *Non Applicable car exposition paternelle*

4. Antécédents maternels

Médicaux :

Chirurgicaux :

Obstétricaux : |__|__| geste |__|__| pare
Préciser si fausse couche spontanée, grossesse extra-utérine, interruption de grossesse, mort *in utero*, malformation néonatale, pathologie néonatale non malformative … (*nombre, date et nature/raison si applicable).*

5. Médicament(s) expérimental(aux) administré(s) pendant la grossesse ou s'il s'agit une exposition paternelle

Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration Ou non administré	Date de dernière administration Ou en cours	Voie d'administration[1]	Posologie / 24h
Rituximab ou placebo	|__|__| |__|__| |2|0|__|__| ☐ Non administré	|__|__| |__|__| |2|0|__|__| ☐ En cours		
Azathioprine ou placebo	|__|__| |__|__| |2|0|__|__| ☐ Non administré	|__|__| |__|__| |2|0|__|__| ☐ En cours		

(1) Voie d'administration : VO=voie orale ; IM=intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)

6. Procédures et actes ajoutés par la recherche ***(Barrez l'encadré si procédures et actes non réalisés)***	Date de réalisation *(jj/mm/aaaa)*	Chronologie	
		Avant la grossesse	Au cours de la grossesse
	|__|__| |__|__| |2|0|__|__|		
	|__|__| |__|__| |2|0|__|__|		

Acronyme: **MAINRITSEG**

Référence de la personne : |__|__|__| - |__|__|__|__|__| - |__| - |__|
n° centre - n° ordre d'inclusion - initiale nom - initiale prénom

PARTIE RESERVEE AU PROMOTEUR
REFERENCE INTERNE :

7. Médicament(s) concomitants administré(s) dans le cadre du soin
(Cf. annexe « Liste relative aux médicaments concomitants » complétée : ☐ *Oui* ☐ *Non applicable)*

Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration	Date de dernière administration Ou en cours	Voie d'administration(1)	Posologie / 24h
	|__|__| |__|__| |2|0|__|__|	|__|__| |__|__| |2|0|__|__| ☐ En cours		
	|__|__| |__|__| |2|0|__|__|	|__|__| |__|__| |2|0|__|__| ☐ En cours		
	|__|__| |__|__| |2|0|__|__|	|__|__| |__|__| |2|0|__|__| ☐ En cours		

(1) Voie d'administration : VO=voie orale ; IM=intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)

8. Suivi de la grossesse

☐ Echographiques. Date(s) et résultats à préciser *(joindre les CR anonymisés)* :

☐ Autres examens. Date(s) et résultats à préciser *(joindre les CR anonymisés)* :

9. Grossesse en cours ☐ (faxer un nouveau formulaire complété à l'issue de la grossesse pour le suivi de la notification initiale)
ou issue de la grossesse ☐ (compléter ci-dessous)

☐ Fausse couche spontanée → Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :	Date : |__|__| |__|__| |2|0|__|__| Terme : |__|__| SA |__|__| J
☐ Grossesse extra-utérine	Date : |__|__| |__|__| |2|0|__|__| Terme : |__|__| SA |__|__| J
☐ Interruption de grossesse → Raison : → Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :	Date : |__|__| |__|__| |2|0|__|__| Terme : |__|__| SA |__|__| J
☐ Accouchement ☐ Spontané ☐ Provoqué ☐ Voie basse ☐ Césarienne	Date : |__|__| |__|__| |2|0|__|__| Terme : |__|__| SA |__|__| J

Naissance multiple : ☐ Non ☐ Oui, précisez le nombre :
Souffrance fœtale : ☐ Non ☐ Oui, précisez :
Placenta normal : ☐ Oui ☐ Non, précisez :
Liquide amniotique : ☐ clair ☐ autre, précisez :
Anesthésie : ☐ Générale ☐ Péridurale ☐ Rachianesthésie ☐ Aucune

10. Nouveau-né (Si naissance multiple, compléter les parties 1, 2, 3, 9 et 10 d'un nouveau formulaire et le faxer)

Sexe : ☐ Masculin ☐ Féminin
Poids : |__|__|__|__| grammes Taille : |__|__|__| cm Périmètre crânien : |__|__|__| cm
APGAR : 1 minute : _____ 5 minutes : _____ 10 minutes : _____

Malformation(s) néonatale(s) : ☐ Non ☐ Oui, précisez :

Pathologie(s) néonatale(s) non malformative(s) : ☐ Non ☐ Oui, précisez :

Le nouveau-né a-t-il bénéficié d'un suivi particulier à la naissance : ☐ Non ☐ Oui, précisez :

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

18.12 Abacuses for azathioprine/placebo

18-59 ans Posologie : 2 mg/kg		
Poids	Dose/j (mg)	
kg	Dose calculée	Arrondi
40	80	75
41	82	75
42	84	75
43	86	75
44	88	75
45	90	75
46	92	75
47	94	75
48	96	75
49	98	75
50	100	100
51	102	100
52	104	100
53	106	100
54	108	100
55	110	100
56	112	100
57	114	100
58	116	100
59	118	100
60	120	100
61	122	100
62	124	125
63	126	125
64	128	125
65	130	125
66	132	125
67	134	125
68	136	125
69	138	125
70	140	125
71	142	125
72	144	125
73	146	125
74	148	125
75	150	150
76	152	150
77	154	150
78	156	150
79	158	150
80	160	150
81	162	150
82	164	150
83	166	150
84	168	150
85	170	150
86	172	150
87	174	150
88	176	175
89	178	175
90	180	175
91	182	175
92	184	175
93	186	175
94	188	175
95	190	175
96	192	175
97	194	175
98	196	175
99	198	175
100	200	200
>100	200	200

60-74 ans Posologie : 1,5 mg/kg		
Poids	Dose/j (mg)	
kg	Dose calculée	Arrondi
40	60	50
41	61,5	50
42	63	50
43	64,5	50
44	66	50
45	67,5	50
46	69	50
47	70,5	50
48	72	50
49	73,5	50
50	75	75
51	76,5	75
52	78	75
53	79,5	75
54	81	75
55	82,5	75
56	84	75
57	85,5	75
58	87	75
59	88,5	75
60	90	75
61	91,5	75
62	93	75
63	94,5	75
64	96	75
65	97,5	75
66	99	75
67	100,5	100
68	102	100
69	103,5	100
70	105	100
71	106,5	100
72	108	100
73	109,5	100
74	111	100
75	112,5	100
76	114	100
77	115,5	100
78	117	100
79	118,5	100
80	120	100
81	121,5	100
82	123	100
83	124,5	100
84	126	125
85	127,5	125
86	129	125
87	130,5	125
88	132	125
89	133,5	125
90	135	125
91	136,5	125
92	138	125
93	139,5	125
94	141	125
95	142,5	125
96	144	125
97	145,5	125
98	147	125
99	148,5	125
100	150	150
>100	150	150

> 75 ans Posologie : 1 mg/kg		
Poids	Dose/j (mg)	
kg	Dose calculée	Arrondi
40	40	50
41	41	50
42	42	50
43	43	50
44	44	50
45	45	50
46	46	50
47	47	50
48	48	50
49	49	50
50	50	50
51	51	50
52	52	50
53	53	50
54	54	50
55	55	50
56	56	50
57	57	50
58	58	50
59	59	50
60	60	50
61	61	50
62	62	50
63	63	50
64	64	50
65	65	50
66	66	50
67	67	50
68	68	50
69	69	50
70	70	50
71	71	50
72	72	50
73	73	50
74	74	50
75	75	75
76	76	75
77	77	75
78	78	75
79	79	75
80	80	75
81	81	75
82	82	75
83	83	75
84	84	75
85	85	75
86	86	75
87	87	75
88	88	75
89	89	75
90	90	75
91	91	75
92	92	75
93	93	75
94	94	75
95	95	75
96	96	75
97	97	75
98	98	75
99	99	75
100	100	100
>100	100	100

18.13. Link for the SmPC for the Mabthera

Link to the SmPC for the “Mabthera 500 mg solution à diluer pour perfusion”

http://ec.europa.eu/health/documents/community-register/2017/20170516137895/anx_137895_fr.pdf

From page 47 to 89

18.14. Information letter for patients included in the REOVAS study

MAINRITSEG : extension de REOVAS

MAINtien de la rémission avec le **RIT**uximab ver**S**us l'azathioprine pour les patients ayant un diagnostic récent ou une rechute de **G**ranulomatose **É**osinophilique avec polyangéite.

Essai prospectif, randomisé, contrôlé, en double aveugle.

Promoteur : AP-HP

Lettre d'information à l'attention des patients

Pourquoi proposer une extension à l'étude REOVAS ?

Madame, Monsieur,

Vous participez actuellement à l'étude REOVAS, comparant 2 stratégies thérapeutiques pour obtenir une rémission au cours de la GEPA (granulomatose éosinophile avec polyangéite, Churg-Strauss) récemment diagnostiquée ou en rechute. Nous vous remercions de votre participation à cette recherche permettant d'améliorer la prise en charge de ces maladies rares.

Votre médecin va vous proposer de participer à l'extension de cette étude, appelée MAINRITSEG, qui consiste à comparer deux traitements pour prévenir au mieux les rechutes de votre vascularite.

En effet, lors des études précédentes réalisées dans votre maladie, nous avons constaté que certains malades rechutaient à distance de l'obtention d'une rémission. En effet, seulement 29 % des patients connaissaient une rémission persistante sur le long terme et des rechutes sont survenues chez plus de 40 % d'entre eux.

Dans d'autres vascularites associées aux ANCA, très proches de votre maladie, l'étude MAINRITSAN, conduite par le Pr Guillevin sous l'égide du Groupe Français d'Etude des Vascularites, a montré que le rituximab (en perfusions tous les 6 mois pendant 18 mois) avait une remarquable efficacité dans le maintien de la rémission. Dans cette étude, seulement 4 % des patients ont eu une rechute sévère après 28 mois de suivi.

Votre médecin va vous proposer de participer à l'étude MAINRITSEG, dont le but est de trouver un traitement optimal pour éviter les rechutes de votre maladie.

Si vous acceptez de participer à cette extension d'étude, vous pourrez être traité :

- soit par du rituximab, en perfusion, à raison d'une injection lors de l'entrée dans l'étude puis tous les 6 mois pendant 18 mois (4 perfusions au total nécessitant une hospitalisation de jour). Vous aurez aussi des comprimés de placebo d'imurel© (azathioprine) pendant 2 ans.

- soit par l'imurel© (azathioprine) en comprimés pendant 2 ans, traitement qui a démontré une efficacité dans la prévention des rechutes des vascularites associées aux ANCA. Vous aurez aussi des perfusions avec un placebo tous les 6 mois pendant 18 mois (4 perfusions au total nécessitant une hospitalisation de jour).

L'attribution du traitement par rituximab ou imurel© (azathioprine) se fera par tirage au sort.

Remarque importante : L'utilisation du placebo ne doit pas être source d'inquiétude pour plusieurs raisons :

- c'est un composant inactif (donc non dangereux) dont le but est de permettre d'avoir une évaluation non biaisée car ni le médecin ni vous ne saurez dans quel bras vous êtes.

- la poursuite du protocole permet d'avoir des visites trimestrielles avec un suivi très encadré permettant de dépister précocement les rechutes

- si une rechute venait à survenir, le traitement de la rechute a montré son efficacité.

Vous aurez une visite de surveillance trimestrielle et l'analyse finale de l'étude aura lieu 28 mois après la première perfusion. L'efficacité du traitement sera jugée sur la fréquence des rechutes dans chaque groupe.

Nous vous remercions encore pour votre forte implication dans la recherche sur les vascularites nous permettant de faire progresser la prise en charge de ces maladies et souhaitons que vous puissiez participer à cette nouvelle et prometteuse étude.

Dr Xavier Puéchal, investigateur coordonnateur.