**MAINRITSAN**

**A study comparing the efficacy of rituximab and azathioprine   
as maintenance therapy for ANCA-associated vasculitis:   
a prospective, multi-center, controlled, randomized study**

English title: Maintenance of remission using Rituximab in Systemic Anca   
associated vasculitis \*

\* The short English title was also kept for the French version

Version no. 7.0 dated 30/08/2012

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**SIGNATURE Page of the Biomedical Research PROTOCOL for the COORDINATING INVESTIGATOR and the SPONSOR's Representative**

Biomedical Research Code no. **P 070703**

Title: "MAINRITSAN" A study comparing the efficacy of rituximab and azathioprine as maintenance therapy for ANCA-associated vasculitis: a prospective, multi-center, controlled, randomized study.

Version no. 7.0 dated 30/08/2012 including all changes from Amendment No. 10

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SUMMARY

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| --- | --- |
| **Study title and code** | **MAINRITSAN**: A study comparing the efficacy of rituximab and azathioprine as maintenance therapy for ANCA-associated vasculitis: a prospective, multi-center, controlled, randomized study.  Code P 070703 |
| **Coordinating Investigator** | Prof. Loïc Guillevin  Pôle de Médecine Interne [Department of Internal Medicine]  Reference center "Maladies systémiques et autoimmunes rares, en particulier Vascularites nécrosantes et Sclérodermies systémiques" [Rare autoimmune and systemic diseases, especially necrosis vasculitis and systemic scleroderma]  Cochin Hospital, Assistance Publique – Hôpitaux de Paris [Public hospital of Paris]  27, rue du Faubourg Saint-Jacques, Paris, France  Tel: 33 1 58 41 13 21 / Fax: 33 1 58 41 14 60  Email: [loic.guillevin@cch.aphp.fr](mailto:loic.guillevin@cch.aphp.fr) |
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| **Primary objective** | To evaluate the efficacy of Rituximab as a maintenance therapy for patients in remission from antineutrophil cytoplasmic autoantibodies (ANCA)-related systemic vasculitis after a first exacerbation or relapse. An evaluation is scheduled at the end of the 18-month maintenance therapy, and 10 months later (after discontinuation of the immunosuppressive therapy). This is the "endpoint" of the study. |
| **Secondary Objectives** | To compare the tolerance to Rituximab to that of Azathioprine (reference treatment)  To determine the predictive value of the reappearance of ANCA and/or the recurrence of an increase in circulating levels of B CD19+ lymphocytes (CD19+ only for patients included in the Rituximab arm) for relapses. |
| **Inclusion Criteria** | 1/ Age between 18 and 75 (age at the time of disease diagnosis).2/ ANCA-associated vasculitis: Wegener's granulomatosis (WG), microscopic polyangiitis (MPA) and limited renal forms (pauci-immune glomerulonephritis) with or without ANCA (at the time of diagnosis and remission). There are four types of ANCA-associated vasculitis: limited renal forms, Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome. Only the first three diseases on that list are considered in the study. However, certain types of vasculitis do not exhibit ANCA at the time of diagnosis. This absence will not be considered an exclusion criterion upon histological confirmation of the diagnosis.   * The patients diagnosed with Wegener's granulomatosis who meet the criteria of ACR 1990 and/or Chapel Hill nomenclature, and present either:   + a) Renal, cardiac, central neurological and/or digestive disease   + b) Other general clinical manifestations (non-infectious fever > 38°3C lasting > 1 week; change in general condition with a Karnofsky index < 40; weight loss  > 5 kg in < 3 months), |

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|  | * c) A massive intra-alveolar hemorrhage (drop in hemoglobin level greater than 3 g/dl; hypoxemia with O2 sat < 90%; respiratory distress syndrome), * d) Another limited form characterized by pulmonary, ocular or otorhinolaryngological granulomatous manifestations, * Microscopic polyangeitis meeting the criteria of the Chapel Hill nomenclature and exhibiting signs of a poor prognosis in accordance with the five factor score (renal failure with serum creatinine > 140 µmol/l; proteinuria with >1 g in 24-h urine; specific central nervous system disorders, cardiac and/or digestive disease).   3/ Patients in remission after the first induction therapy or a relapse, obtained with any treatment combining corticosteroids and at least one immunosuppressant, in accordance with the currently accepted good practice, with the exception of anti-CD20 and/or anti-TNFα.  4/ Patients who read and signed the informed consent form for their participation in the study.  **5/ The period between the end of the immunosuppressive therapy and randomization into the study must not exceed one month.** |
| **Exclusion criteria** | 1/ Churg-Strauss syndrome.  2/ Other types of systemic vasculitis.  3/ Secondary vasculitis (in particular paraneoplastic or infectious forms).  4/ Patients in whom remission was not induced by the corticosteroid and immunosuppressant therapy (disease still active).  5/ Patients previously treated with monoclonal antibodies such as anti-CD20 or anti-TNFα.  6/ History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies.  7/ Inability or refusal to read or sign the informed consent form for their participation in the study.  8/ Inability or refusal to follow the treatment or undergo follow-up examinations required for the study. Non-compliance.  9/ Allergy, known hypersensitivity or contraindication to the medications used and investigated in the study (Cyclophosphamide, Corticosteroids, Azathioprine, Rituximab).  10/ Patients receiving Allopurinol will not be included if the Allopurinol treatment cannot be discontinued (risk of enhanced Azathioprine toxicity).  11/ Pregnancy, lactation. Women of childbearing age must use a reliable form of contraception during the entire immunosuppressive therapy.  12/ Infection with HIV, HBV or HCV.  13) Progressive, uncontrolled infection requiring long-term treatment (tuberculosis, etc.).  14/ Other types of severe infection reported less than 3 months prior to randomization (CMV, HHV-8, etc.).  15/ Bacterial, viral, fungal or mycobacterial infection (with the exception of fungal infection of the nail bed) or any other progressive infection or significant episode of infection requiring hospitalization or treatment with anti-infective medication either intravenously within the 4 weeks preceding trial selection or orally within the 2 weeks preceding trial selection.  16/ History of deep tissue infection (fasciitis, abscess, osteomyelitis, articular septic arthritis) in the year preceding inclusion in the trial.  17/ History of severe chronic or recurrent infection, or any other underlying condition which predisposes the patient to severe infections. |

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|  | 18/ Administration of a live vaccine in the 4 weeks preceding inclusion in the trial.  19/ Known severe chronic obstructive pulmonary disease (FEV1 <50 % or functional dyspnea grade 3).  20/ NYHA stage III or IV heart failure 21/ Recent history of acute coronary syndrome.  22/ Progressive cancer or hematological malignancy diagnosed within the 5 years preceding the diagnosis of vasculitis. The patients with non-metastatic prostate cancer or basal cell carcinoma, or patients cured from cancer or a hematologic malignancy more than 5 years ago, and received no cancer treatment in the past 5 years may be included.  23/ Patients with systemic diseases which could render the effects of the study treatments (Azathioprine or Rituximab) unpredictable and inappropriate.  24/ Severe immunosuppression.  25/ Participation in another clinical research study within the 4 weeks preceding inclusion.  26/ Any medical or psychiatric condition which may prevent the administration of the treatments and patient follow-up in accordance with the protocol, and/or which would expose the patient to highly significant risks of adverse effects, based on the judgment of the study investigator.  27/ Not a member of a social security scheme |
| **Number of patients** | 56 subjects in each group, for a total of 112 subjects. |
| **Total duration of study** | 52 months |
| **Duration of participation for each patient** | 28 months |
| **Methodology** | Phase III, prospective, international, multi-center, comparative, controlled, randomized, open-label study, parallel-arm study |
| **Study treatments** | **Maintenance therapy**  Once remission is reached, centralized randomization will be carried out for the Rituximab and Azathioprine treatments. The two groups will be stratified based on a recent or recurrent disease (*a priori*, 66% of new patients and 33% of relapsers).  - **Rituximab** will be administered intravenously at a **fixed dose** of 500 mg during the first month following discontinuation of the immunosuppressive therapy that allowed the patient to go into remission (J0).   * Before each infusion, the patients will receive premedication consisting of an analgesic/antipyretic drug (Paracetamol), a brief intravenous infusion of 100 mg Methylprednisolone and 1 ampoule of 5 mg Dexchlorpheniramine. * Other injections of Rituximab will be administered at the D15, M6, M12 and M18 visits (5 infusions total), **(the dates of each infusion are defined based on the first infusion, in other words the third infusion will take place 5 1/2 months after the second infusion)**, regardless of the ANCA titer and the level of circulating CD19+ lymphocytes. * Quantitative immunoglobulin testing and lymphocyte CD19 immunophenotyping will be carried out before each infusion, namely at visits D0, D15, M6, M12 and M18, as recommended, and at visits M24 and M28. The ANCA titer will be measured every 3 months over a period of 2 years. These results will not be used to adjust the treatment, but they will be collected for data analysis and interpretation. |

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|  | - In the other arm, **Azathioprine** will be administered orally at a dose of 2 mg/kg/d during 12 months, then 1.5 mg/kg/d during 6 months, and finally 1 mg/kg/d over 4 months (treatment discontinuation after these 22 months). The daily dose, based on body weight, will be rounded to the nearest multiple dose of 25, without exceeding 200 mg/day. For example, a patient weighing 70 kg would take 150 mg/d of Azathioprine to receive a dose of 2 mg/kg/d. The maintenance therapy will be initiated within a month following the last cyclophosphamide administration. |
| **Examinations** | The Inclusion visit at D1, one visit at D15 only for the patients treated with Rituximab, then visits every 3 months up to M24, and a the End of Study visit at M28.  The initial test panel will be as follows:   * Standard laboratory tests: complete blood count, PT/APTT, blood electrolytes, renal function, lymphocyte immunophenotyping for CD3, CD4, CD8 and CD19, urine sediment testing, CRP, transaminases, alkaline phosphatases, GGT, protein electrophoresis, albumin and cryoglobulinemia. * ANCA by IF and ELISA * Serum bank, Plasma bank, Cell bank and DNA bank (these samples will be shipped to the coordinating center where they will be stored).   The patients will be monitored at each visit using the initial test panel until the end of the study.  At the D15 visit, complete blood count and creatinine levels will be measured only for the patients receiving Rituximab.  For the patients on Rituximab, quantitative immunoglobulin testing and lymphocyte CD19 immunophenotyping will be carried out before each infusion, namely at the D15, M6, M12 and M18 visits, as recommended, and at visits M24 and M28.  For the patients on Azathioprine, protein electrophoresis will be carried out every 6 months (M6, M12, M18 and M24). If protein electrophoresis reveals hypogammaglobulinemia, quantitative immunoglobulin testing will be carried out.  At each visit, in addition to the abovementioned tests, the BVAS and VDI scores will be determined by the investigator, and the patients will complete the SF36 and HAQ questionnaires.  Antinuclear and anti-DNA antibody testing will be done yearly and/or whenever the patient develops clinical signs requiring these tests.  Optional examination: a study may be conducted on the activity of thiopurine methyltransferase (TPMT) during the initial treatment period of the patients included in the Azathioprine arm. These results will not be used to adjust the dose of Azathioprine, but the patients whose TPMT activity is low are more at risk of side-effects. This is why closer monitoring, even treatment discontinuation (and withdrawal from the study) will be considered for patients exhibiting even small changes in laboratory values, notably for liver function tests (for example, an elevation of transaminases 1.5–2 times above normal) or the hematological tests (anemia <11 g/dL, neutropenia <1500/mm3, lymphopenia <500/mm3, thrombocytopenia <125000/mm3).  The second phase of the study will end 10 months after the 18-month maintenance therapy (i.e. 28 months after inclusion). |

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|  | <1500/mm3, lymphopenia <500/mm3, thrombocytopenia <125000/mm3).  The second phase of the study will end 10 months after the 18-month maintenance therapy (i.e. 28 months after inclusion). |
| **Primary and secondary endpoints** | Primary endpoint:  Number of major relapses (defined as the reappearance of clinical and/or biological signs of vasculitis activity which could lead to organ failure/destruction or be life-threatening) in each arm at the end of the  28-month period (18-month maintenance therapy + 10 months of follow-up).  Secondary endpoint:   * Number of side-effects and their severity, in each arm. * Number of patients with detectable ANCA in each group. * Mortality in each arm. * Number of minor relapses in each arm. * Cumulative dose and duration of the corticosteroid treatment in each arm 10 months after the end of the maintenance therapy. * The same endpoints will be assessed 6 months after the end of the maintenance therapy (post-treatment observation phase). The patients experiencing a relapse during this phase of the study will be treated with immunosuppressants, in accordance with the Good Clinical Practice (GCP), or possibly a new infusion of Rituximab (outside of the protocol) for those in the Rituximab arm. |

# INTRODUCTION

The treatment of systemic vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA) is partially regimented and consists of an initial treatment with corticosteriods and immunosuppressants to achieve remission followed by maintenance therapy with an immunosuppressant, usually azathioprine or methotrexate, for a minimum of 12 to 18 months. More than 80% of the patients achieve remission following initial treatment. However, despite maintenance therapy, regardless of the immunosuppressant selected, the rate of relapse is high at approximately 50% for those suffering from Wegener's granulomatosis (WG) and 33% for those suffering from microscopic polyangiitis (MPA).

Of the newest available biotherapies, numerous published cases have shown a specific efficacy in ANCA-positive vasculitis, particularly with anti-CD20 monoclonal antibodies, in patients resistant to standard treatments and/or with multiple relapses. Rituximab (the only anti-CD20 currently on the market) is widely used to treat lymphoma (label) and several autoimmune diseases (off-label). It is currently being evaluated as an initial treatment for WG in the USA (RAVE protocol, led by the Vasculitis Clinical Research Consortium). However, the main issue with ANCA-associated vasculitis is the maintenance of remission. As a result, it would be more beneficial and pertinent to evaluate the efficacy of rituximab as a maintenance therapy, which will hopefully provide an alternative immunosuppressive therapy and significantly reduce the number of relapses.

#### Literature Review: Treatment of ANCA-associated Vasculitis

**A) Treatment of Wegener's Granulomatosis**

A combination of corticosteroids and immunosuppressant(s) is the benchmark treatment for systemic forms of WG. Corticosteroids, alone, do not lead to, or maintain, remission. Some consider a combination of orally administered corticosteroids and cyclophosphamide to be the "gold standard" [1]. Nevertheless, even when this combination is prescribed for an extended period of time, relapses occur in more than half of patients [1] and a treatment of at least 18 months is needed to control the disease. One of the consequences of using immunosuppressants is the high rate of severe side-effects. Hoffman et al. [1] have shown that the risk of bladder cancer increases 33-fold, the risk of lymphoma by 11-fold, and the risk of solid tumor by 2.4-fold.

#### Corticosteroids

The initial dose of corticosteroids is 1 mg/kg/day. Depending on disease severity, this may be preceded by one or more bolus doses of methylprednisolone (7.5 to 15 mg/kg/day). After an initial treatment for 3 to 4 weeks, the corticosteroid dose must be reduced. Thus, the disease is essentially controlled with cyclophosphamide. The European Vasculitis Group (EUVAS) recommends reducing the dose more rapidly than that currently prescribed in France [2]. Nonetheless, regardless of the rate of corticosteroid tapering, all clinical results are objectively comparable and based on our experiences, it is currently not beneficial to continue prescribing corticosteroids in France for such an extended period of time.

#### Cyclophosphamide

An oral dose of 2 mg/kg/day has been commonly prescribed [1] [3], adjusted for age and therapeutic response, along with the development of side-effects. The duration of a cyclophosphamide treatment partly depends on the choice of maintenance therapy. A study by EUVAS [2] showed that WG can be controlled with 3–6 months of cyclophosphamide treatment, followed by minimum of 12 months of azathioprine.

Bolus doses of cyclophosphamide have also been recommended (especially by us [4] [5]) as initial treatment and in combination with corticosteroids. Therefore, cyclophosphamide is prescribed every 3 weeks at a dose of 0.5–0.7 g/m2. The intravenous or oral administration of cyclophosphamide over a short period of time produces the same results. However, the number of relapses is higher when the patients continue to receive bolus doses of cyclophosphamide after the onset of remission [4].

Furthermore, since high doses of intravenously administered cyclophosphamide can be detrimental for patients with renal failure, the dose must be adjusted based on renal function. Significant hydration is essential, possibly combined with the administration of MESNA during and after each cyclophosphamide infusion. These measures prevent hemorrhagic cystitis and bladder cancer.

#### Immunoglobulins

Immunoglobulins have the capacity to bind ANCA and decrease their activity. Intravenously administered immunoglobulins have been mainly used in patients experiencing a relapse. Studies have demonstrated significant efficacy with this treatment resulting in a decrease in ANCA titer [6, 7]. Results from a prospective study conducted by the Groupe Français d’Etude des Vascularites (GFEV) [French Group on Vasculitis Studies] confirmed that the patients unable to achieve remission with a combination of corticosteroids and immunosuppressant(s) were able to achieve remission when immunoglobulins were added to their treatment [8]. Immunoglobulins are administered intravenously at a dose of 2 g/kg/day once a month. The dose is administered over a period of 2 days. However, we recommend that the infusion be spread over 4 days for patients who suffer from renal failure. Overall, this treatment is very well tolerated.

#### Plasma Exchanges

There is currently no evidence that therapeutic plasma exchanges (TPE; [plasmapheresis]) may contribute to the treatment of ANCA-associated vasculitis. On the other hand, Pusey [9] has demonstrated the benefits of PE on renal function. A EUVAS study conducted in patients with serum creatinine levels > 500 µmol/L revealed that TPE could significantly reduce the number of patients requiring dialysis at 3 months and 12 months [10].

#### Other Immunosuppressive Therapies: The New and “Old" Medications

**Azathioprine** is the recommended first-line maintenance therapy. It is both effective and well tolerated. It induces fewer long-term side-effects than cyclophosphamide. The initial dose is 2–3 mg/kg/day.

**Methotrexate** is also considered a good maintenance therapy and has been prescribed in some cases of WG relapse [11]. The dose is 0.3 mg/kg/week. Despite some encouraging results, its efficacy is inferior to cyclophosphamide. Methotrexate has been the subject of numerous prospective studies (NIH, EUVAS and GFEV) [12]. A number of side-effects have been associated with this drug, including hepatotoxicity, hypersensitivity pneumonitis, and transient medullary hypoplasia, etc.

Other medications are occasionally prescribed despite their relevance not being confirmed in any of the controlled studies. Cyclosporine has limited indications. More recent medications (mycophenolate mofetil [13], deoxyspergualin and leflunomide [14]) have been tested in a limited number of patients. These medications were only prescribed as maintenance therapy in relapsing patients or in patients resistant to combinations of corticosteroids and cyclophosphamide. As a result, their use is not presently widespread. Anti-TNFα could also be used as rescue therapy in these vasculitis patients who do not respond to or fail corticosteroid treatment combinations with various immunosuppressants. In a pilot study [15], we showed that most patients treated with infliximab achieve remission. However, the long-term effects of this treatment are currently unknown.

#### The Special Case of Anti-CD20 Antibodies

Rituximab is the leading chimeric anti-CD20 monoclonal antibody produced by genetic engineering. Initially developed to treat low-grade CD20-positive B-cell lymphoma, it is now prescribed for a number of partial or complete B-cell medicated autoimmune diseases, most notably rheumatoid arthritis and lupus. The proposed B-cell depletion by rituximab upon binding to CD20 antigens appears to involve several mechanisms (cell-mediated lysis, complement-dependent or via apoptosis) for any condition involving autoantibodies. Clinical efficacy of rituximab has been demonstrated in rheumatoid arthritis, even though this disease is considered a T-cell mediated disease. However, the indirect, but essential, pathogenic role of B cells intervenes upstream in several steps of the inflammatory cascade (antigen presentation, production and regulation of various proinflammatory cytokines and autoantibodies)**.** Similar to the proposed roles for B and T cells in the immunopathogenesis of rheumatoid arthritis, B cell depletion induced by anti-CD20 antibodies appears to be an equally plausible treatment approach for Wegener's disease. In fact, it has been recognized that B cells and ANCA have direct and indirect implications in the growth of vasculitis lesions and granulomatosis [16, 17, 18, 19].

#### Inconsistent Clinical Data for Rituximab in WG Based on Anatomical and Clinical Characteristics of the Disease?

Since 2001, 16 studies have been published evaluating rituximab in combination with immunosuppressants to treat resistant or recurrent forms of WG [20, 21, 22, 23, 24]. Although the results are contradictory, an encouraging trend did emerge, which motivated the "Vasculitis Consortium" to undertake a multi-center prospective study in the USA to determine whether rituximab could produce comparable or superior efficacy compared to cyclophosphamide as initial treatment for ANCA-associated vasculitis.

Follow-up of patients indicated that remission could be maintained for 16 to 35 months (median: 21 months) after the last injection. Partial responses and failures were observed in 2/31 (6.5%) and 6/31 (19.5%) patients treated with rituximab and cyclophosphamide, respectively. Detailed analysis of the treatment responses, in particular those reported in the studies of Keogh *et al.* [21] and Aries *et al.* [25], showed a priori contradictory results with complete responses observed in 10/10 and 2/8 of patients, and failures in 0/10 versus 5/8 of patients, respectively.

As other WG specialists have done, we will treat the two phenotypes of the disease separately — predominantly granulomatous and inflammatory vasculitis.

Different responses were reported in patients based on their general disease characteristics, where predominantly vascular manifestations (glomerulonephritis, intra-alveolar hemorrhage, peripheral neuropathy, uveitis, arthralgia, purpura, cerebral angiitis, etc.) recorded within days or weeks after treatment were different compared to those presenting with predominantly granulomatous signs (ENT signs, pulmonary nodules, orbital pseudotumors, subglottic stenosis, etc.), which showed slower improvement or sometimes none at all. The response appears to be worse in the presence of an orbital tumor and/or subglottic stenosis.

A more refined analysis of the predominantly granulomatous cases identified a second subgroup that responds better with rituximab than patients with an orbital tumor or tracheal stenosis. This subgroup exhibits pulmonary nodules and nasal polyps, whose response is gradual and delayed, sometimes by several months [24, 26].

Through monitoring titres, ANCA levels typically show a gradual decline, followed by their disappearance, but in some cases, ANCAs persist over the long term, making these results unreliable predictors of clinical response.

If rituximab is likely to be a short-term loading treatment (4 infusions per week or 2 infusions every 2 weeks), uncertainties regarding response duration and the need for additional maintenance infusions arise. ANCA-associated vasculitis, particularly WG, is characterized by a high risk of relapse.

Monitoring circulating levels of B lymphocytes may provide a useful decision making tool regarding additional rituximab infusions as secondary prophylaxis for patients in remission.

Immunophenotyping of residual circulating CD19 and/or CD20 cells indicated that B cells become rapidly undetectable after an effective treatment with rituximab with a subsequent tendency for the levels in peripheral blood to increase again, usually after the 6th month. Certain patients exhibit a more prolonged effect and very low levels of circulating B cells, which is maintained near the detection limit up to the 20th month. Some authors have suggested a correlation between the restoration of circulating B cells and the occurrence of clinical relapses [27]. However, this correlation is hypothetical, as the treatment response is based on the suppression of ANCAs and B cells, whereas this family of vasculitis, in particular Wegener's disease, also involves T cell mechanisms.

Few data are available on the possible development of human anti-chimeric antibodies (HACA) targeting rituximab after successive treatments; their effect on the maintenance of rituximab efficacy or tolerance remains unclear. The tolerance to rituximab is relatively good.

Bacterial or viral infections are relatively rare or less severe. In contrast, cases of progressive multifocal leukoencephalopathy (PML) caused by the reactivation of the JC virus, have been reported primarily in cases of lymphoproliferative syndrome. A few rare cases of PML in lupus patients were recently reported by ROCHE Laboratories. Since these cases almost always involved patients who received multiple treatments for relapses, and are thus already heavily treated and/or still undergoing other immunosuppressive therapies in combination with rituximab, the direct causality of these latter treatments for the occurrence of this appalling infection is unclear, but advocates the need to investigate new indications for anti-CD20s in controlled studies.

#### B) Treatment of Microscopic Polyangiitis

The same approach is used for the treatment of MPA and WG, at least for the severe cases of the disease. Both a retrospective analysis [28] and therapeutic study [29] that we conducted indicated that only severe cases of MPA respond to combinations of corticosteroids and cyclophosphamide. The addition of cyclophosphamide offers no significant benefit to MPA patients with no poor prognosis risk factors (FFS = 0). We therefore recommend treating severe cases of MPA with the treatment recommended for WG, while less severe cases should first be treated with corticosteroid as first line therapy.

#### Benefits/Risks

* + - **Benefits**

The expected benefits are a reduction in the incidence of disease relapses (which is approximately 40% following 28 months after achievement of remission with azathioprine) and a reduction in the number of side-effects in the rituximab arm.

Other parameters may also be improved: quality of life, reduced need for patient care associated the chronic disease activity, and a reduction in sequelae.

#### Foreseeable and Known Risks for Research Participants

* Toxicity due to prolonged corticosteroid therapy, which is expected to be comparable in the two study arms due to the identical initial treatment plans. This corticosteroid therapy is the standard of care treatment (no additional risk).
* Toxicity associated with azathioprine: In previous studies of severe forms of vasculitis, azathioprine and corticosteroids were used as the standard maintenance therapy, due to its usual excellent tolerance, in lieu of cyclophosphamide. Digestive intolerance (in 5% of the patients) or hepatic intolerance (moderate cytolysis in 7% of patients, reversible after treatment discontinuation) may occur in these patients (the only reasons for azathioprine discontinuation in a recent GFEV–WEGENT study).

A possible side-effect of azathioprine is a decrease in white blood cells, which can lead to infections. It can also cause a decrease in red blood cells (anemia) or platelets, which requires close monitoring of blood samples to modify the treatment dose. A transient decrease in fertility is also often observed with this disease. Gastrointestinal disorders (nausea, vomiting, diarrhea), abnormal liver function (reversible after treatment discontinuation), and hypersensitivity reactions (shivering, myalgia, arthralgia, skin rashes, pancreatitis, acute respiratory disease) are more rarely observed.

* Toxicity associated with rituximab: Rituximab is usually well tolerated, but the known possibility of allergic reactions means that is should be administered in a hospital setting with close monitoring over the few hours following the injection. Monitoring of complete blood count is essential to ensure that white blood cell counts do not drop. Unlike immunosuppressants, there is no cancer risk with rituximab. However, similar to immunosuppressants, it can cause an increase in infections. These infections can sometimes be severe. Among them was a fatal case of encephalitis; however, this complication is extremely rare. This complication was also reported in patients taking cyclophosphamide (Endoxan). Rituximab does not increase the frequency of infections compared to immunosuppressants normally used to treat the disease.

Infusion-related reactions with Rituximab administration may occur, especially during the first infusion. These events mainly include fever, shivering and shaking. Other less frequent symptoms such as skin redness, angioedema, nausea, rash/hives, asthenia, headaches, throat irritation, rhinitis, vomiting and pain at the tumor site may appear, but less commonly.

Less frequently observed are exacerbations of pre-existing heart disease, such as angina or heart failure. Symptoms occurring during the first infusion decrease considerably for the subsequent infusions.

Hematologic disorders (neutropenia, thrombocytopenia) may occur, but they are usually mild and reversible. Rare cases of hemolytic anemia due to rituximab have also been observed. Cardiovascular events have also been reported with the most frequent being hypotension and arterial hypertension.

Gastrointestinal perforations have been reported in patients treated with a combination of rituximab and chemotherapy for disorders other than vasculitis.

#### Justification

* Improved treatment of the disease by reducing the number of relapses
* A decrease in the number of side-effects

#### Population

Patients diagnosed with ANCA-associated vasculitis: WG, PMA, and limited renal forms (pauci-immune glomerulonephritis) with/without ANCAs (at the time of diagnosis and remission).

#### References

See References section in Appendix I

#### Legal and Ethical Declarations

The study will be conducted in accordance with:

* The current version of the protocol
* The current version of the Declaration of Helsinki
* The guidelines of the Bonnes Pratiques Cliniques françaises (French Good Clinical Practice), version dated 30 November 2006.

# STUDY OBJECTIVE(S)

This is a therapeutic, multi-center, prospective, randomized, open-label study comparing the efficacy of azathioprine and rituximab in combination with low dose corticosteroids for the treatment of ANCA-associated vasculitis.

#### Primary Objective

The primary objective of this study is to evaluate the efficacy of rituximab as maintenance therapy for patients in remission from ANCA-related systemic vasculitis after a first exacerbation or relapse.

**An interim analysis will be conducted after half of the patients have been enrolled, and the final analysis will be conducted at M28 (10 months** after discontinuation of immunosuppressive therapy). This is the study "endpoint".

#### Primary Endpoint

The primary endpoint of this study is the number of major relapses (defined as the reappearance of clinical and/or biological signs of vasculitis activity which could be life threatening or lead to organ failure or destruction) in each arm at the end of the 28-month study period (18-month maintenance treatment + 10 months of follow-up).

#### Secondary Objectives

The secondary objectives are:

* To evaluate rituximab tolerance compared to azathioprine (reference treatment);
* To determine if reappearance of ANCA and/or increase in circulating levels of CD19+ B lymphocytes (CD19+ only for patients in the rituximab arm) is predictive of relapse occurrence.

#### Secondary Endpoints

The secondary endpoints include:

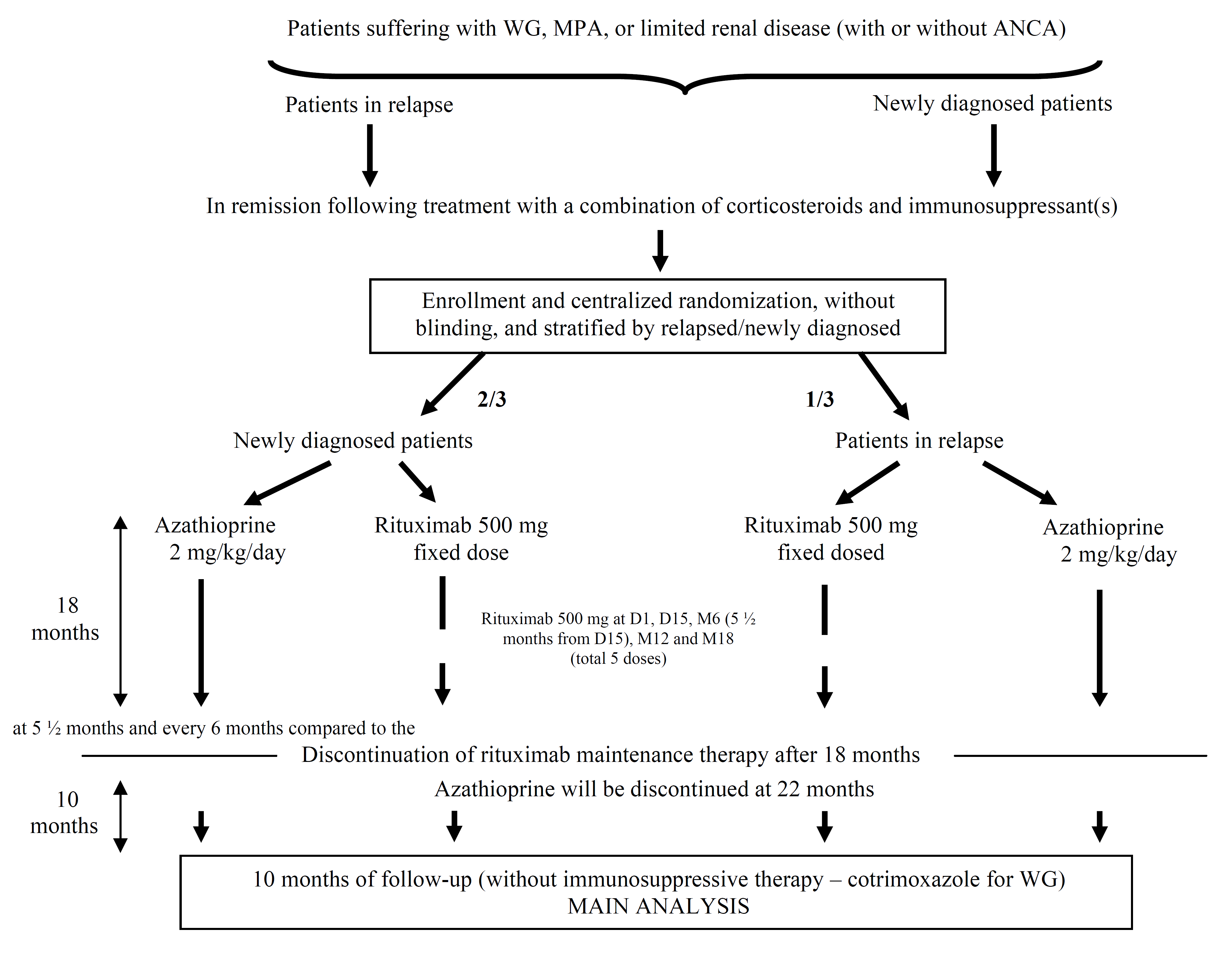
* Number and seriousness of side-effects in each treatment group.
* Number of patients with detectable ANCA in each treatment group.
* Mortality in each treatment group.
* Number of minor relapses in each treatment group.
* Cumulative corticosteroid dose and duration of treatment in each group 10 months after completion of maintenance therapy.
* The same endpoints will be assessed 6 months after the completion of maintenance therapy (post-treatment observation phase). Patients experiencing a relapse during this phase of the study will be treated with immunosuppressants in accordance with Good Clinical Practice (GCP), or with a new rituximab infusion (outside of the protocol) for those in the rituximab arm.

# STUDY DESIGN

#### Methodology

The MAINRITSAN study is a phase III, prospective, international, multi-center, comparative, controlled, randomized, open-label study comparing azathioprine and rituximab in combination with low-dose corticosteroids for the treatment of ANCA-associated vasculitis. The study will be conducted with two parallel arms.

The design of the study is as follows:



#### Projected Study Schedule

Patients will be enrolled over a period of 2 years.

A 28-month period for following the patients will begin at the onset of the maintenance therapy.

* + - Total study duration: 52 months
    - Expected enrollment period: 2 years. This period may be extended if the number of desired participants is not reached after 2 years.
    - Duration following the patients: 28 months (18 months of treatment + 10 months of follow-up), or less if complete remission has not been achieved, in the event of relapse, or if the patient was withdrawn from the study for another reason.

#### Patient Follow-up: Visits and Examinations

* + - **Screening Visit:**
* Serology for HIV, hepatitis B, and hepatitis C
* Confirmation of the patient's immunization status

#### Enrollment Visit: Initial Test Panel: D1

* Collection of clinical data and diagnostic test results at the initial diagnosis
* Collection of clinical signs and diagnostic tests from the last episode of disease exacerbation
* Record treatment for most recent episode of disease presentation (newly diagnosed or last relapse before enrollment)
* Record treatments given at the initial diagnosis
* Collection of clinical data and results of diagnostic results at enrolment (remission)

The initial test panel described below will be performed within 15 days of study enrollment:

* + - Standard laboratory tests: complete blood count, PT/aPTT, blood electrolytes, renal function tests (creatinine and creatinine clearance using the MDRD formula), lymphocyte immunophenotyping for CD3, CD4, CD8 and CD19, urine sediment testing (proteinuria per sample and/or over 24 h), hematuria, leukocyturia and red cell casts), CRP, liver function (transaminases, alkaline phosphatase, GGT), protein electrophoresis, albumin, cryoglobulinemia.
    - ANCA by IF and ELISA
    - For rituximab patients, dose of immunoglobulins and CD19+ titres before each infusion
    - For azathioprine patients, protein electrophoresis and, if protein electrophoresis reveals hypogammaglobulinemia, quantitative immunoglobulin testing will be performed.
* Serum bank, Plasma bank, Cell bank, and DNA bank creation: 7 ml blood sample for each bank.
* BVAS
* VDI
* Two questionnaires (quality of life [SF36] and the physical function health assessment questionnaire [HAQ]) will be printed from a CleanWEB electronic case report form (e-CRF), completed by the patient and then submitted to the investigator.The investigator will send these two questionnaires to URC Paris Centre, using a prepaid, stamped envelope provided to the patient at the enrolment visit.

#### D15 Follow-up Visit (only for patients receiving rituximab): Infusion No. 02 of Rituximab

* Clinical examination
* Laboratory tests: Complete blood count, CRP, blood electrolytes, PT/aPTT, renal function tests
  + - (creatinine and creatinine clearance using the MDRD formula), lymphocyte immunophenotyping for CD3, CD4, CD8 and CD19, immunoglobulin titres prior to infusion
* Record vasculitis treatments and concomitant treatments
* Record AEs/SAEs

#### Follow-up Visits: Every 3 months up to M24 (M3, M6, M9, M12, M15, M18, M21, M24) and a final visit at M28.

The patients will be monitored every 3 months up to visit M24, and finally at visit M28, the End of Study visit, with the initial test panel:

* + - Standard laboratory tests: complete blood count, PT/APTT, blood electrolytes, renal function (creatinine and creatinine clearance using the MDRD formula), lymphocyte immunophenotyping for CD3, CD4, CD8, urine sediment testing (proteinuria [from sample and/or 24 h collection], hematuria, leukocyturia, and red cell casts), CRP, liver function (transaminases, alkaline phosphatase, GGT), protein electrophoresis, albumin.
    - For rituximab patients, quantitative immunoglobulin testing and lymphocyte CD19 immunophenotyping will be performed, as recommended, before each infusion, namely at the D15, M6, M12 and M18 visits, and at visits M24 and M28.
    - For azathioprine patients, protein electrophoresis will be performed every 6 months (M6, M12, M18, and M24). If protein electrophoresis reveals hypogammaglobulinemia, quantitative immunoglobulin testing will be performed.
    - ANCA by IF and ELISA every 3 months up to M24 and M28.

If possible, the ANCA screening should always be conducted in the same laboratory.

* + - Serum bank, Plasma bank and Cell bank creation: 7 ml blood sample for each bank.
    - Antinuclear and anti-DNA antibody testing will be performed yearly and/or whenever the patient develops clinical symptoms requiring these tests.
    - Optional examination (depending on the local practices at each study center): a study may be conducted examining thiopurine methyltransferase (TPMT) activity during the initial treatment period for patients included in the azathioprine arm. These results are not expected to be used to adjust the azathioprine dose, but patients with low TPMT activity are more at risk of adverse effects. As a result, closer monitoring, even treatment discontinuation (and withdrawal from the study), will be considered for patients exhibiting even small changes in laboratory values, notably for liver function tests (for example, an elevation of transaminases 1.5-2 times above normal) or hematology tests (anemia <11 g/dL, neutropenia <1500/mm3, lymphopenia <500/mm3,

thrombocytopenia <125000/mm3).

* BVAS score at each visit
* VDI score (every 6 months up to the M24 visit and at visit M28)
* Two questionnaires (quality of life [SF36] and physical function health assessment [HAQ]) will be completed by the patient at each visit.

The patient questionnaires (SF36 and HAQ) will be assembled in a patient booklet given to the patients at visit M3. After each visit, the patients are to return the completed questionnaires to the management center, URC Paris Centre, using a prepaid stamped envelope provided in the booklet.

* Provide a treatment compliance diary to the patients at visits M3, M6, M9, M12, M15, M18, M21, and M24 (one diary every 3 months)
* Record vasculitis treatments and concomitant treatments
* Record AEs/SAEs

The second phase of the study is expected to end 10 months after the end of the 18-month maintenance phase (i.e. 28 months after enrollment).

Visit dates are based on the study protocol, with a +/- 7-day window for each visit, to accommodate rescheduling or in case of unrelated practical reasons.

#### Composition, Storage and Transport of the Serum Banks, Plasma Banks, Cell Banks, and DNA Banks

**Serum Bank**: A 7 mL blood sample will be collected in two dry tubes, with or without agar (red stopper), centrifuged, and serum extracted that will be stored at - 80°C at the study center where the patient was enrolled. Serum banks will be transported and delivered at – 20°C to the coordinating center in Cochin after the end of the follow-up period for all patients at each center.

**Plasma Bank**: A 7 mL blood sample will be collected in two EDTA tubes (lavender stopper), centrifuged, and supernatant extracted that will be stored at - 80°C at the study center where the patient was enrolled. The plasma banks will be transported at – 20°C by a carrier and delivered by courier to the coordinating center at Cochin Hospital. This plasma bank sample will be shipped at the same time as the serum bank sample, after completion of the follow-up period for all patients at each center.

The serum and plasma samples may all be shipped to the coordinating center by courier together with the DNA and cell samples, but this shipment must be refrigerated (+ 4°C).

**Cell Bank**: A 7 mL blood sample will be collected into two ACD tubes (pale yellow stopper), stored at room temperature, and immediately delivered by courier to the coordinating center at room temperature.

**DNA Bank**: A 7 mL blood sample will be collected into two ACD tubes (pale yellow stopper) at the enrollment visit only, stored at room temperature, and immediately delivered by courier to the coordinating center at room temperature.

At the end of the study, all serum, plasma, and DNA samples will be stored at -80°C in a previously declared and pre-existing sample bank, located at Cochin Hospital, at the Centre de référence Maladies Rares, Pavillon St Jacques, managed by Pr. Mouthon.

At the end of the study, all cell samples will be stored in liquid nitrogen in previously declared and pre-existing sample bank, located at Cochin Hospital in the laboratory of Hematology, Pavillon Jean Dausset, also managed by Prof. Mouthon.

An addendum to the patient information sheet and informed consent form that must be signed by the patient and investigator, will be provided to each patient to notify them of changes concerning the storage of their samples in a sample bank at the end of the study, during the 15-year storage period initially planned.

#### Patient Enrollment and Randomization Procedures

Patients will be recruited from multiple centers across the entire territory of France, by physicians belonging to the French Vasculitis Study Group GFEV) and the National Reference Center for rare diseases and necrotizing vasculitis (“Maladies rares:, Vascularites nécrosantes project). The DIRC and the Committee for the Protection of Persons (CPP) Ile de France III (Cochin) have been notified of the investigational centers planned for this study, with the possibility of further amendments to include other centers wishing to participate.

Potential participants will initially be contacted over the phone by the coordinating Investigator, the Senior Scientist (Dr. Christian Pagnoux) and/or the 2 official collaborators (Prof. Luc Mouthon, Dr. Pascal Cohen), in Paris (Department of Internal Medicine of Prof. Guillevin, Cochin Hospital, Paris).

Patient inclusion and exclusion criteria will be verified during this phone conversation.

After the patient has read and signed the informed consent form, the investigator will complete an online enrollment form that is accessible on the Internet 24/7 via the e-CRF (each investigational center will be provided secure access at the time of site initiation visit).

Patient randomization will be performed using a computer-based random assignment system for balanced random assignment of patients to treatment groups. The system is linked to the e-CRF to facilitate automated randomization of the patients enrolled in this study.

The randomization list will be established by Unite de Recherche Clinique (URC) Paris Centre in collaboration with the Agence Générale des Equipements et Produits de Santé (AGEPS), then integrated into the online randomization system (CleanWeb). The randomization process for each patient will be triggered at the time of enrollment via the e-CRF. Each patient will be assigned an 8-character identification code.

The 8-character patient identification code will be created as follows:

* The first 3 digits correspond to the site number of the investigating center
* The next 3 digits correspond to the randomization number
* The 2 letters corresponding to the patient initials (last name, first name).

The URC and AGEPS will be immediately notified of any patient enrollment/randomization through an automatic email/fax from the e-CRF (CleanWeb) system. The AGEPS will ship the treatments (rituximab or azathioprine) to the site pharmacy (PUI) of each investigational center as soon an enrolment is confirmed and within 72 hours of receipt of the fax.

#### Participation Period

Patient participation is expected to last a total of 28 months (18 months of treatment and 10 months of follow-up).

#### SCHEDULE OF ASSESSMENTS

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | | **Enrollment Visit D1** | **Visit D15 for Rituximab Patients** | **Visit M3** | **Visits M6, M9, M12, M15, M18, M21,  and M24** | **End of Study Visit M28** |
| **CLINICAL DATA ENTERED IN THE CASE REPORT FORM** | **Clinical data** | **** | **** | **** | **** | **** |
| **Progress report** | **** | **** | **** | **** | **** |
| **BVAS \*** | **** |  | **** | **** | **** |
| **VDI** | **** |  | **** | **** | **** |
| **Treatments** | **** | **** | **** | **** | **** |
| **Adverse Events, SAEs** |  | **** | **** | **** | **** |
|  | |  |  |  |  |  |
| **RITUXIMAB Injection** | | **D1 + 4 days** | **** |  | ** M6, M12 and M18** |  |
| **AZATHIOPRINE Dispensing (for 3 months)** | | **D1 + 4 days** |  | **** | ** M6, M9, M12, and M15, M18, and M21** |  |
| **Compliance Monitoring Booklet Provided to Patients  (1 yellow booklet for 3 months)** | | **D1 + 4 days**  **** |  | **** | **** |  |
|  | |  |  |  |  |  |
| **HIV and Hepatitis B and C Serology and Confirmation of Immunization Status** | | **Screening visit** |  |  |  |  |
| **Complete blood count, CRP, blood electrolytes, PT/aPTT** | | **** | **** | **** | **** | **** |
| **Immunophenotyping for CD3, CD4, CD8** | | **** | **** | **** | **** | **** |
| **CD19 level (Rituximab Arm Only)** | | **** | **** |  | ** M6, M12, M18, and M24** | **** |
| **AST, ALT, Alk. phos., GGT** | | **** |  | **** | **** | **** |
| **Albumin and Total Gamma Globulins** | | **** |  | **** | **** |  |
| **Protein Electrophoresis  +/- Ig titre** | | **** | **IgG, IgM, IgA dosage** |  | ** M6, M12, M18, and M24** | **** |
| **Urinary Sediment Test (urine test strip, urine microscopy and culture, proteinuria in g/L and/or g/24h)** | | **** | **Proteinuria in g/L and/or g/24h** | **** | **** | **** |
| **Renal Function (creatinine, clearance per MDRD)** | | **** | **** | **** | **** | **** |
| **Antineutrophil Cytoplasmic Antibodies (ANCA) by IF and ELISA §§** | | **** |  | **** | **** | **** |
| **Antinuclear Antibodies and anti-DNA** | | **** |  |  | * **M12 and M24** |  |
| **Cryoglobulins** | | **** |  |  |  |  |
| **Serum bank, Plasma bank, Cell bank and DNA bank** | | ****  **+ DNA bank at enrollment** |  | **** | **** | **** |
| **SF36 and HAQ questionnaires**  **completed by the patient (blue booklet)** | | **** | ****  **Booklets provided to patients** | ****  **Booklets provided to AZATHIOPRINE patients** | **** | **** |

\* BVAS = 0, if the patient has no signs of activity.

§§ If ANCAs are detected by immunofluorescence, systematic ELISA tests must be performed to precisely identify the type of antibody. The dates indicated relate to ANCA-positive patients at the enrollment visit +.

#### For each patient, only the ANCA screening must be performed in the same laboratory and within each investigation center.

¶ Patients must complete the HAQ and SF36 questionnaires themselves. If the patient is unable to complete the questionnaires (e.g., coma), it must be mentioned in a notation added to the questionnaire. Annotations should also be added to the questionnaire if the patient suffers from psychomotor difficulties (neuropathy, apathy, moderate confusion, etc.) and a close relative (family) may help the patient complete these questionnaires. Under no circumstances should the study investigator complete these questionnaires (aside from a note providing a reason for the patient not completing the form).

After M28, patients will be monitored every 3 or 6 months, based on their clinical condition (and/or persistence of ANCA for patients suffering from CSS or MPA), up to the 5 years after the diagnosis (post-hoc follow-up as part of the GFEV vasculitis registry), then at a frequency chosen by the study investigator responsible for the patient.

Patient participation in this study implies that they will not be able to participate in another biomedical study for a period of 28 months. However, they may participate in other observational or biological studies independent of the present study ("ancillary" studies, particularly biobanks, serum banks, and gene banks). Patients participating in such studies must read and sign the informed consent forms according to standard regulations.

#### Data Collected

Clinical and paraclinical signs will be recorded in an electronic case report form (e-CRF) accessible on the Internet using a secured access code (identifier and password) specific to each scientific investigator responsible for a patient. The data transferred will be anonymized and encrypted. This system will allow for rapid assessment of the results.

The items chosen for this form will be based on the e-CRFs previously used in numerous GFEV prospective studies.

# POPULATION SELECTION

#### Number of Patients

A total of 112 patients is planned for the study (56 in each arm).

#### Inclusion Criteria

The patients who meet the following criteria may be included in the study:   
1/ Between 18 and 75 years of age **(at the time of disease diagnosis)**.

2/ ANCA-associated vasculitis: WG, MPA, and limited renal forms (pauci-immune glomerulonephritis) with or without ANCA (at the time of diagnosis was well as remission). There are four types of ANCA-associated vasculitis: limited renal forms, Wegener's granulomatosis, microscopic polyangiitis, and Churg-Strauss syndrome. Only the first three of these diseases will be investigated in the study. However, ANCA are absent in certain types of vasculitis at the time of diagnosis. Their absence will not be considered an exclusion criterion as long as histological confirmation of the diagnosis was obtained.

* Wegener's granulomatosis which meet ACR 1990 criteria and/or Chapel Hill nomenclature, with either:
  + a) Renal, cardiac, nervous system, and/or digestive system disorders
  + b) Other general clinical manifestations (non-infectious fever > 38°3C lasting > 1 week; change in overall condition with a Karnofsky score   
    < 40; weight loss > 5 kg in < 3 months),
  + c) A massive intra-alveolar hemorrhage (drop in hemoglobin level greater than 3 g/dl; hypoxemia with O2 sat < 90%; respiratory distress syndrome),
  + d) Another rare form characterized by pulmonary, ocular or otorhinolaryngological granulomatous presentations,
* Microscopic polyangiitis meeting the Chapel Hill nomenclature criteria and exhibiting signs of a poor prognosis in accordance with the five factor score (renal failure with serum creatinine > 140 µmol/l; proteinuria with >1 g in   
  24-h; specific central nervous system disorders, cardiomyopic and/or gastrointestinal involvement).

3/ Patients in remission following a first induction therapy or a relapse, achieved with any treatment regimen combining corticosteroids and at least one immunosuppressant, in accordance with the currently accepted good practice, with the exception of anti-CD20 and/or anti-TNFα. A period of 10 to 15 days is required between the onset of remission and the start of maintenance therapy.

4/ Patients who have read and signed the informed consent form for their participation in   
the study.

5/ A maximum period of 1 month between the end of their previous immunosuppressive therapy and randomization into the study.

Biological criteria defining satisfactory bone marrow, liver, and kidney functions for inclusion in the study are the following:

* Bone marrow function: Bone marrow reserve will be evaluated using complete blood count and platelet count.
* Liver function will be evaluated by transaminase and alkaline phosphatase levels.
* Renal function will be evaluated based on creatinine level and calculated clearance.

All these tests are scheduled to be performed in the study as part of the initial testing during the enrollment visit.

#### Exclusion Criteria

Patients who meet at least one of the following criteria will be excluded from the study:

1/ Churg-Strauss syndrome.

2/ Other types of systemic vasculitis.

3/ Secondary vasculitis (particularly paraneoplastic or infectious forms).

4/ Patients who have not achieved remission with corticosteroid and immunosuppressant therapy (disease still active).

5/ Patients previously treated with monoclonal antibodies such as anti-CD20 or anti-TNFα.

6/ History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies.

7/ Inability or refusal to understand or sign the informed consent form to participate in the study.

8/ Inability or refusal to follow the treatment or undergo required follow-up examinations for the study. Non-compliance.

9/ Allergy, known hypersensitivity or contraindication to the medications being used and investigated in the study (cyclophosphamide, corticosteroids, azathioprine, rituximab).

10/ Patients being treated with allopurinol will not be included if allopurinol treatment must be continued (risk of increased azathioprine toxicity).

11/ Pregnancy, lactation. Women of childbearing potential must use a reliable method of contraception during the entire immunosuppressive treatment period.

12/ HIV, HBV or HCV infection.

13/ Progressive, uncontrolled infection requiring long-term treatment (tuberculosis, etc.).   
14/ Other types of severe infection reported less than 3 months prior to randomization   
(CMV, HHV-8, etc.)

15/ Bacterial, viral, fungal or mycobacterial infection (with the exception of fungal infection of the nail bed) or any other progressive infection or significant episode of infection requiring hospitalization or treatment with anti-infective medication either intravenously within 4 weeks or orally within 2 weeks prior to enrollment.

16)/ History of deep tissue infection (fasciitis, abscess, osteomyelitis, articular septic arthritis) in the year prior to enrollment in the trial.

17/ History of severe chronic or recurrent infection or any other underlying condition which predisposes the patient to severe infections.

18/ Administration of a live vaccine in the 4 weeks prior to enrollment in the trial.   
19/ Known severe chronic obstructive pulmonary disease (FEV1 < 50% or grade 3 functional dyspnea).

20/ NYHA stage III or IV heart failure.   
21/ Recent history of acute coronary syndrome.

22/ Progressive cancer or hematological malignancy diagnosed in the 5 years prior to the vasculitis diagnosis. Patients with non-metastatic prostate cancer or basal cell carcinoma, or patients cured from cancer or a hematologic malignancy more than 5 years ago, and who have not received any cancer treatment in the past 5 years, may be included.

23/ Patients with systemic diseases which could render the effects of the study treatments (azathioprine or rituximab) unpredictable and inappropriate.

24/ Severe immunosuppression.

25/ Participation in another clinical research study within the 4 weeks prior to enrollment.

26/ Any medical or psychiatric condition which may prevent the administration of the study treatments and patient follow-up according to the protocol, and/or which, based on the judgment of the study investigator, would expose the patient to an increased risk of adverse effects.

27/ Non-affiliation to a social security program (beneficiary or rights-holder).

# END OF STUDY AND PREMATURE STUDY WITHDRAWAL

#### End of Study

The patients will complete the study after 28 months of being followed.

#### Premature Withdrawal From Study

1. Reasons and description

Patients may choose to withdraw from the study at any time and for any reason. Withdrawal of a patient from the study may also be initiated by an investigator or the sponsor. All patient withdrawals from the study must be documented, and the investigator must specify the reason for the withdrawal (e.g. patient not compliant with study visits despite reminders, patient is uncooperative, lack of treatment efficacy, etc.)

1. Procedures

Criteria and reasons for early withdrawal or exclusion from the study

Early withdrawal or exclusion of a patient from the study must be reported. The failure must be recorded and the patient withdrawn from the study based on the following criteria:

* + - Major relapse: reappearance of the initial clinical signs or appearance of new clinical signs and symptoms representative of active disease. Thus, BVAS will be > 0. Some of these symptoms may be life-threatening or involve a major organ (e.g., kidney, cardiac, pulmonary or cerebral) corresponding to the definition of a major relapse. These relapses will require higher doses of corticosteroids and an immunosuppressant.

A relapse will be considered minor of it is not life-threatening and does not involve a major organ. These relapses which are not life-threatening and do not involve major organ damage are to be recorded in the e-CRF, but will not be considered a reason for withdrawal from the study. For these patients, a modest increase in corticosteroid, up to 20 mg/day during 3 weeks, is allowed to control a relapse, with gradual tapering over a maximum of 6 weeks, returning to the dose level used before the minor relapse.

If an increased dose of corticosteroids to 20 mg/day is insufficient for these patients, or if another immunosuppressant must be prescribed to control the minor relapse (BVAS unchanged or increased at 4 weeks, or not reduced by at least 50% by the 6th week), they will be considered as treatment failures and/or major relapses, and they will be withdrawn from the study.

* + - Any side-effect due to the investigational medication (rituximab) justifying its discontinuation.

If the patient experiences a severe allergic reaction during the first infusion, the administration of the treatment will discontinued permanently.

* + - Any side-effect due to azathioprine justifying its discontinuation
    - Withdrawal of consent
    - Patients lost to follow-up (intent-to-treat analysis)
    - Investigator’s decision

Data collection and schedule for these patients

Data obtained from these patients will be recorded regularly on the e-CRF at least every 3 months, until the M28 visit. The investigators will continuously keep the study coordinators informed of the health status and progress of the patient.

For subjects who are lost to follow-up, the e-CRF must be completed until the last visit performed. The investigator and collaborators will provide the reason for the patient’s absence at a visit and his/her health status.

Replacement of patients, if necessary

Patients withdrawn prematurely or excluded from the study will not be replaced. The intent-to-treat analysis will include treatment failures, patients lost to follow-up or with missing data, patients who died, and those who interrupted treatment due to intolerance or side-effects.

Follow-up procedures for these patients

After a relapse or premature withdrawal from the study, patients will continue to be followed until the end of the study, at a minimum according to the visit schedule outlined in the protocol, and the investigator will continue to complete the e-CRF until M28. After exiting the study,

these patients will continue to be followed regularly according to current recommendations [standard of care] in France.

1. Consequences

The patients withdrawn from the study may not be rescreened for the study. Their randomization number must not be reused.

# TREATMENTS

#### Induction Therapy

According to current recommendations in France, induction therapy includes a combination of corticosteroids and an immunosuppressant, namely bolus doses of cyclophosphamide (oral cyclophosphamide and methotrexate are accepted induction therapies). The clinician is free to define the initial treatment, provided that it does not include monoclonal antibodies such as anti-CD20 or anti-TNFα. Plasma exchanges and/or immunoglobulins administered intravenously may also be used as part of the initial treatment.

Corticosteroid treatment is left to the investigator’s discretion and should be gradually tapered as the disease improves. The tapering schedule outlined in the IMPROVE protocol (EUVAS protocol) (see Appendix V) offers guidelines for reduction in corticosteroid therapy.

#### Remission Criteria

Remission will be considered achieved when the BVAS score is 0 [30]. This corresponds to an absence of clinical signs of the disease and laboratory evidence of a least stabilized kidney function. Persistence of ANCA is not an exclusion criterion as remission can be achieved despite the persistence of ANCA.

#### Description of the Maintenance Treatments in this Study Traitement d’entretien

Once remission is achieved, centralized randomization will be performed to the rituximab and azathioprine treatment arms, stratified by disease characteristic: newly diagnosed or disease relapsing (*a priori*, 66% of newly diagnosed and 33% relapsers).

#### Study Medication

**Rituximab** will be administered intravenously at a **fixed dose of 500 mg** in the first month following discontinuation of the immunosuppressive therapy that led to remission.

The first infusion will occur 4 days after the enrolment visit, which corresponds to the time interval required for delivery of the vial of rituximab to the site pharmacy (72 hours between receipt of the supply request and arrival of the treatment at the site).

* Before each infusion, the patients will be treated with premedications consisting of an analgesic/antipyretic drug (paracetamol), a short intravenous infusion of 100 mg methylprednisolone and one 5 mg ampoule dexchlorpheniramine.
* Subsequent injections of Rituximab will be administered at the D15, M6, M12 and M18 visits (5 infusions total), regardless of the ANCA titre and the level of circulating CD19+ lymphocytes.
* Quantitative immunoglobulin testing and CD19 lymphocyte immunophenotyping will be performed as recommended before each infusion, namely at D15, M6, M12, and M18 visits. ANCA titres will be measured every 3 months for 2 years. These results will be collected for data analysis and interpretation only and not for adjusting treatment regimens.

Any recommended immunization as detailed in the adult immunization report should be followed prior to rituximab administration. Unless contraindicated, anti-pneumococcal and anti-haemophilus immunizations are recommended before starting rituximab therapy.

Forms will be completed by pharmacy or nursing staff (for the purposes of preparation and monitoring) at the time of the infusion to enable notification of possible side effects and/or serious side effects in the 4 hours following the infusion.

Rituximab infusions must be administered in an environment where full resuscitation facilities are immediately available.

In the event of an allergic reaction during the infusion, treatments for hypersensitivity reactions (adrenaline, antihistamines and glucocorticosteroids) must be readily available for immediate use.

To avoid any risk of hypotension related to the infusion of MabThera, this antihypertensive treatment must be interrupted 12 hours before rituximab infusion.

Rituximab infusion will be discontinued if signs of severe infusion related reactions to are detected, especially severe dyspnea or bronchospasms.

If the patient develops an initial allergic reaction during the first infusion, the administration of the product will permanently discontinued.

If a patient develops a mild-to-moderate reaction during the first infusion, an antihistamine and corticosteroid treatment will be recommended at the second infusion and patient care will be reinforced with closer monitoring.

#### The Azathioprine Arm

**Azathioprine** will be orally administered at a dose of 2 mg/kg/day for 12 months, followed by 1.5 mg/kg/day for 6 months, and finally 1 mg/kg/day for 4 months (with treatment discontinuation after 22 months). The daily dose, based on body weight, will be rounded to the nearest multiple of 25, without exceeding 200 mg/day (for example, a dose of 2 mg/kg/day, a patient weighing 70 kg would take 150 mg/day of azathioprine). Maintenance therapy will be initiated **in the month following discontinuation of the immunosuppressive therapy that led to the patient’s remission, and no later than 8 days after the patient was included in the study.**

#### Concomitant and Prohibited Therapies

Any concomitant medication administered during the study must be recorded in the e-CRF.

#### Approved Adjuvant Therapies:

* + - **Prescription of trimethoprim/sulfamethoxazole** (80 mg at 400 mg/day) is required in the two treatment arms if the levels of circulating CD4 T lymphocytes is lower than 250/mm3 and the patient is not allergic to trimethoprim/sulfamethoxazole.

In the event of persistent lymphopenia, any patient allergic or intolerant to cotrimoxazole (trimethoprim/sulfamethoxazole) will be treated monthly with pentamidine aerosol. After 18 months of maintenance therapy, this treatment will also be prescribed (160 mg/800 mg x 2/day) in WG patients for a period of 2 years, as recommended by current standard of care guidelines.

#### Prescriptions of calcium, vitamin D3, potassium (in accordance with standard of care), and a prescription of biphosphonates (as recommended by the World Medical Association for cortisone-related osteoporosis) will be prescribed to the patients under long-term corticosteroid therapy.

#### Prophylactic therapy for tuberculosis

Patients with a history of untreated, spontaneously healed tuberculosis, or who were recently in contact with a tuberculosis patient, may be offered prophylactic tuberculosis therapy following testing performed in accordance with standard recommendations (tuberculin test, thorax radiography) [49]. This will consist of dual therapy: rifampicin (Rifadine® 10 mg/kg/day) + isoniazid (Rimifon® 4 mg/kg/day as a single daily dose for 3 months) or Rifinah® (rifampicin + isoniazid: 2 tablets/day as a single daily dose for 3 months). Where rifampicin is contraindicated or results in toxicity, or for cirrhotic patients, isoniazid alone (Rimifon®) 4 mg/kg/day may be prescribed as an alternative for 9 months. Since Rifampicin reduces their efficacy, the dose of corticosteroids must be increased by 30% for the patients prescribed rifampicin.

#### Other Adjuvant Therapies

Treatments commonly used to prevent and, if necessary, correct hypokalemia and other metabolic or hormonal disorders induced by corticosteroid therapy, must be prescribed in accordance with standard of care.

#### Prohibited Therapies

Allopurinol is contraindicated in combinations with azathioprine and must be discontinued in patients taking azathioprine (enhances hematological toxicity). Patients who must continue to take allopurinol will not be included in the study.

All other immunosuppressants and immunomodulators specifically intended to control vasculitis (colchicine, Disulone, Plaquenil, Danatrol, etc.) are prohibited for the duration of the study. If the disease worsens and requires more intensive treatment, the patient will be withdrawn from the study (premature withdrawal) and will receive treatment in accordance with current standard practices for vasculitis.

Any attenuated live vaccine or any treatment causing lymphocyte depletion is prohibited for the duration of the study.

#### Packaging and Labelling of the Investigational Medication

The Unité Essais Cliniques (Clinical Study Unit) of the AGEPS will be responsible for supplying rituximab and azathioprine as well as packaging and labeling the treatments in accordance with Section 12 of the current Good Manufacturing Practice guidelines. A removable label, applied on each treatment kit, will be used to track the administration of each treatment.

#### Storage Conditions for the Investigational Medication

The treatment kits will be stored in their original packaging, away from light, in dedicated areas between 2-8°C for rituximab and at a temperature not exceeding 25°C for azathioprine.

#### Dispensing Conditions for the Investigational Medication

The AGEPS of Paris will be responsible for managing, packaging, and shipping treatments.

#### Azathioprine

Kits will contain a 3 month supply of treatment including supplies for an additional 15 days (visit schedule window).

The first 3-month treatment kit for azathioprine will be sent after patient randomization.

Azathioprine will be dispensed directly to patients by the site pharmacy (PUI) at each center during the scheduled visits, every 3 months for a period of 22 months.

AGEPS will ship the remaining treatment kits to the centers upon receipt of a fax requesting a refill. The e-CRF will be programmed to automatically send the refill request faxes three weeks before the expected dates for visits M3, M6, M9, M12, M15, and M18.

Prescriptions specific to the MAINRITSAN study and azathioprine will be provided to the investigators in the e-CRF at the Enrollment visit and M3, M6, M9, M12, M15, M18, and M21 visits.

The removable labels found on each treatment kit will be attached to the prescription forms at the time of dispensing.

#### Rituximab

The first two vials of Rituximab will be sent after patient randomization (for infusion visits D1 and D15).

Vials corresponding to the remaining treatments will be sent to the centers by the AGEPS upon receipt of a fax requesting a refill. The e-CRF will be programmed to automatically send the refill request faxes three weeks before the expected dates for visits M6, M12, and M18.

Prescriptions specific to the MAINRITSAN study and rituximab will be provided to the investigators in the e-CRF at the Enrollment visit and D15, M6, M12, and M18 visits.

The two removable labels found on each vial will be attached to the prescription form and the nursing report [site record], respectively.

#### Accountability / Compliance / Disposal of the Products

* + - At each visit, patients will be asked to return their empty, opened, and full boxes and blister packs of azathioprine. These products will be kept at the pharmacy until the clinical research associate assesses the inventory and, in turn, patient compliance.

Following this accounting by the CRA, returned products will be destroyed at the site pharmacy (PUI) of each investigational center.

* + - The department will discard all empty or opened vials of rituximab.
    - Along with the first azathioprine treatment kit or the first rituximab infusion, all patients will receive their first patient diary (for 3 months) to collect the doses of corticosteroids and azathioprine (for the patients randomized into this arm) and to report any side effects or serious side effects occurring between visits.

The patients will receive a new diary every 3 months. The patients will bring these diaries to each study visit with the investigator in order to record all side effects in the e-CRF.

#### Patient Card

In accordance with the requirements of the Good Manufacturing Practice dated May 26, 2006, all patients will be issued a patient card with the statement "Please keep this card with you at all times". The card must also specify the name, address and telephone number of the investigational center and the coordinating study center (Pôle Médecine, Hôpital Cochin), the research code, the patient identification code, and the starting date of the treatment.

Front of card:

**PATIENT CARD**

***Please keep this card with you at all times***

**Last name:……………………………………. First name:…………………………….**

***Patient identification code:*** *| | | | / | | | | / | | |*

Center No. / Randomization No. / Initials (N-P)

**I am participating in the MAINRITSAN study*:*** A study comparing the efficacy of rituximab and azathioprine as maintenance therapy for ANCA-associated vasculitis: a prospective, multi-center, controlled, randomized study **sponsored by the AP-HP [Public Hospitals of Paris]**

I am currently receiving the following treatment:

❑ Azathioprine administered orally at a dose of 2 mg/kg/day for 12 months, then 1.5 mg/kg/day for 6 months, and finally 1 mg/kg/day for 4 months (with treatment discontinuation after 22 months). Start date of treatment: \_\_\_/\_\_\_/\_\_\_\_\_\_

❑ Rituximab administered intravenously at a fixed dose of 500 mg. One injection at D1, D15, M6, M12 and M18.

Date of the first injection: \_\_\_/\_\_\_/\_\_\_\_\_\_

Back of card:

**PATIENT CARD**

***Please keep this card with you at all times***

I am monitored by Dr…………………………………………   
at ………………………………………….…………..hospital

………………………………………………………………...

# EVALUATION OF EFFICACY

#### Description of the efficacy endpoints

The primary endpoint of the study is the number of major relapses (BVAS > 10)

in each arm at the end of 28-month maintenance therapy (18 months of treatment + 10 months of follow-up).

The secondary endpoints are the number and seriousness of the side-effects in each arm, the number of patients with detectable ANCAs in each arm, the rate of mortality in each arm, the number of minor relapses in each arm, the cumulative dose and duration of corticosteroid therapy in each arm after 10 months of maintenance therapy, and these same endpoints 6 months after the end of maintenance therapy (post-treatment follow-up phase).

Our definitions of remission and relapses are based on those recently formulated and adopted by the working group of experts of EUVAS/EULAR (Hellmich et al., *Annals of Rheumatic Disease*, 2007 May;66(5):605-17).

* *Complete remission*: defined as the disappearance of all clinical, biological and immunological signs of disease activity, allowing continuation of stable maintenance, immunosuppressive therapy. A BVAS score = 0 is required to confirm complete remission has occurred. ANCA eradication is not required to assert that remission has occurred. As the ANCA titer may increase before a relapse; it is recommended to monitor these patients more closely.

Remission may be accompanied by sequelae such as proteinuria, kidney failure, sinusitis, etc. (list not exhaustive). The clinician will ask for the specialists’ opinions to confirm a diagnosis of remission with sequelae. Remission with sequelae will be considered to be complete remission. The persistence of one of these clinical elements (with the exception of sequelae) is not sufficient to be considered confirmation of complete remission.

* *Sustained remission*: complete remission as defined above, lasting at least 6 months.
* *Response:* defined as improvement but without complete regression of the signs of disease activity (clinical and biological) for at least one of the major organs targeted by the illness, such as the regression of pulmonary alveolar hemorrhage on imaging modalities, improvement in renal function with sustained microhematuria or proteinuria which may be considered not to be a sequelae of the disease. The BVAS score must have decreased by at least 50% with respect to the initial score. The serological status of ANCAs is not used for the diagnosis of complete remission or response. In these cases of partial remission, the initial treatment of the disease will be maintained or modified based on the opinion of the clinician and study coordinator.

For this study, response is evaluated at the month 3 visit (M3). The response will be considered partial if clinical signs indicating that the disease is active or progressing persist, in particular with a BVAS > 6, an inflammatory syndrome and/or eosinophilia >1000/mm3. This situation would justify an increase in Azathioprine/Placebo to 3 mg/kg/day, however this is not mandatory (decision of the study investigator).

* *Failure:* defined as an exacerbation of the symptoms of the disease, including damage to at least one of the major organs (FFS > or =1) at any time, or signs of persistent disease activity despite an increase of Azathioprine to 3 mg/kg/day.  
  In these "forms of good prognosis" of failure, another immunosuppressive therapy should be proposed a priori, by boluses of Cyclophosphamide.
* *Relapse*: defined as the reappearance of clinical and/or biological signs of vasculitis activity. The BVAS is a few points higher than during remission. The relapse must be documented. An isolated elevated ANCA titer (MPA and CSS) or eosinophil counts (CSS) cannot be considered as indications of a relapse.
  + *Major relapse:* defined as the reappearance of clinical and/or biological signs of vasculitis activity which could lead to organ failure or destruction or could be life-threatening (in particular kidney, cardiac or pulmonary failure).
  + *Minor relapse:* defined by the reappearance of clinical and/or biological signs of vasculitis activity but not involving organ failure or destruction and not life-threatening.

# EVALUATION OF SAFETY

#### Description of the Safety Parameters

* **Definition of an adverse event or effect (AE)**: An adverse event is considered any undesirable or unexpected harmful manifestation or worsening of a pre-existing condition occurring in an individual participating in biomedical research, whether or not the event is considered to be related to the study treatment.
* **Adverse effects of an investigational medication**: Any harmful, undesired reaction to

an investigational medication, regardless of the dose administered.

* **Definition of a serious adverse event or effect (SAE)**:Any undesirable event or effect that leads to death, is life-threatening, requires hospitalization or prolongation of hospitalization, results in a significant or permanent disability or handicap, or causes a congenital abnormality or deformity, related to the medication, regardless of the dose administered.

Cancer, pregnancy, medication overdose or drug abuse will be reported as a serious adverse event.

Hospitalization scheduled prior to the start of the study will not be considered a serious adverse event.

* **Unexpected adverse effect to an investigational medication**: Any adverse effect whose nature, severity or development is not in accordance with the information provided in the Summary of Product Characteristics at the time the medication was approved, or in the Investigator’s Brochure if not approved.
* **New data:** Any new data related to safety that could lead to a reassessment of the benefits/risks of the study or the investigational medication, or could be sufficient to consider changes in the administration of the investigational medication in the study.

#### Methods and Schedule

* + 1. **Scientific Committee**

The MAINRITSAN study Scientific Committee will include the clinicians who initiated this study (Prof. Guillevin and Dr. Pagnoux), the biostatistician in charge of the project (Dr. Mahr), representatives of the Sponsor (Mr. Vacher, Ms. Mebarek) and the Clinical Research Unit (Prof. Tréluyer; Ms. Poignant, CRA in charge of the study) appointed for the study.

The Scientific Committee will meet before the study is started, then at least every 3 months. Scientific Committee meetings will provide an opportunity to review study progress in the different areas and to provide feedback to each recruiting center.

The committee’s mission is to approve all the major decisions requested by the coordinating investigator pertaining to study conduct and compliance with the protocol and ethics. Il vérifie le respect de l’éthique. They will inform the Centre de Méthodologie et de Gestion for the study (Center for Methodology and Management) of the study progress and of any problems and on the results. They will make decisions regarding any relevant protocol modification required to continue the study, namely:

* Measures to facilitate patient recruitment in the study;
* Protocol amendments before they are presented to the CPP,
* Decisions regarding opening or closing study sites,
* Measures ensuring the highest level of safety for individuals participating in the study,
* Discussions on the results and the publication strategy for these results.

The Scientific Committee may recommend (on the advice of the Data Monitoring Committee) to extend or suspend the study if the rate of patient recruitment is too low, if the number of patients lost to follow-up is too high, for major protocol violations, or for medical and/or administrative reasons.

If new analyses, not included in the protocol, are proposed for the samples provided by the study subjects, the Scientific Committee will review these proposals and define the data access restrictions and rules for publishing these results.

The Scientific Committee will monitor the tolerance to the study products or the therapeutic approach by reviewing, discussing, and validating the Annual Tolerance Report, to be submitted to the Health Authority and the CPP.

#### Committee Validating the Critical Cases

The committee validating the critical cases is composed of 3 independent members, specialists of vasculitis, who will meet once after the follow-up period to perform a evaluation of the relapses while blinded to the patients’ treatment arms.

#### Procedures for Recording and Reporting Adverse Events

* + 1. **Non Serious Adverse Events (AE):**

Any adverse event considered non serious, according to the abovementioned definition, which occurs during or after the study must be reported in the appropriate section of the e-CRF.

A single event must be reported per page. The event may correspond to a symptom, diagnosis, or an additional test result judged to be significant. All clinical or paraclinical elements to describe the corresponding should be reported.

#### Serious Adverse Events (SAE):

Investigators must immediately, or as quickly as possible, report any of the serious adverse events defined in the SAE grid *(see Appendix VI)* to the AP-HP Sponsor.

The investigator is to complete the SAE forms of the CRF, and send printed and signed copies to the Département à la Recherche Clinique et Développement (DRCD) (Department of Clinical Research and Development) by fax at 01 44 84 17 99 within 48 hours (if possible immediately followed by a phone call to 01 44 84 17 23 if the patient died or has a life-threatening condition).

The investigator must also inform the Clinical Research Associate responsible for the study of the occurrence of the SAE.

For each serious adverse event, the investigator must submit one report explaining the causal link of the event with each experimental medication and any other treatments.

It may be impossible to obtain information on the description and evaluation of an adverse event within the time allocated for the initial report.

The investigator must also report the clinical progress of the patient, as well as the results of any clinical tests diagnostic test, and/or examinations, or other information required for an adequate analysis of causality:

* either in the initial SAE report (if the abovementioned information is immediately available),
* or as soon as possible, by completing and faxing a new SAE report (clearly identified as follow-up SAE report with the follow-up number).

All reports submitted by investigators must identify each subject participating in the study, using the unique patient identification code.

In case of the death of a study subject, the investigator will provide any additional information requested by the Sponsor (hospitalization report, autopsy report, etc.).

Any new information discovered during this study or related to this study, originating from

published data or ongoing research must be reported to the Sponsor.

* Reporting serious adverse events to Health Authorities

The Pôle de Pharmacovigilance (Pharmacovigilance Unit) of the DRCD will be responsible for submitting this report after evaluating the seriousness of the adverse event, its causal link to each experimental drug and any other treatments, as well as the unexpected nature of the adverse event.

Any suspicion of a serious unexpected adverse effect must be reported by the Sponsor to the competent authorities within the notification period required by law.

Any safety-related data or new information that could significantly modify the evaluation of the benefits/risks ratio concerning the investigational medication or the study, or that could result in changes in administration of the investigational medication or the conduct of the study must be reported by the Sponsor to the competent authorities, the CPP, and the study investigators.

#### Procedures During and After the Study

Any patient exhibiting an adverse event must be monitored until the event is resolved or stabilized.

* If the event is not serious, its progress must be recorded on the applicable e-CRF page.
* If the effect is serious, an SAE report must be sent to the DRCD.

For the duration of the MAINRITSAN study, investigators are required to inform the Sponsor of the occurrence of an event of this nature (within 24 hours, if the event appeared over the course of the 24-month period of the study). The investigators will be required to complete the SAE report form provided within the initial study documents (protocol), also available on the GFEV website, on the e-CRF, or upon request from the sponsor or coordinating investigator. The study may be suspended for further investigation or interrupted, if serious adverse events are reported more in of the two treatment arms.

# STATISTICAL ANALYSIS

The statistical analysis will be performed at the Centre d’Epidémiologie Clinique [Centre for Clinical Epidemiology], Hôtel-Dieu Hospital in Paris, by Prof. Philippe Ravaud.

#### Data Analysis and Statistical Methods

The study is conducted as an intent-to-treat analysis with per-protocol analysis. Data stratification is based on whether the disease is a first presentation of disease (2/3 of patients to be enrolled) or a relapse (1/3 of patients to be enrolled, based on the 30–50% rate of relapse normally observed with ANCA-associated vasculitis). The 2 treatment arms (Azathioprine vs Rituximab) will be compared using survival curves established from the date of start of maintenance therapy until the date of relapse. The difference will be estimated using the log-rank test.

The primary endpoint is the maintenance of remission for 28 months after the start of maintenance therapy with Rituximab or Azathioprine (namely, 18 months of maintenance therapy and 10 months of follow-up after treatment discontinuation). The WEGENT study showed that 40% of patients who received Azathioprine had a relapse in the 28 months that followed the onset of maintenance therapy. In the Rituximab arm, the expected proportion of patients who will relapse is estimated at 15%, for a 25% reduction in the number of relapses.

#### Required Sample

Based on a two-sided statistical test with 80% power and an alpha level of 5%, 54 subjects per treatment arm will be required to carry out this analysis. Allowing for a 5% rate of patients lost to follow-up or excluded for protocol violation, 112 patients (56 in each arm) are required to be enrolled in the study.

An additional 6 patients will be enrolled over the total of 112 patients initially calculated. Therefore, a total of 118 patients will be enrolled, 59 in each treatment arm.

(Amendment no. 6, April 2010).

#### Feasibility

This objective could be achieved in less than 3 years, by mobilizing all centers that participated in the GFEV over its many years, as well as those identified as expertise and resource centers under the French National Plan on Rare Diseases and renowned scholarly associations (Société National Française de Médecine Interne, Société Française de Rhumatologie, Société de Néphrologie, Société de Pneumologie (French), Club Rhumatismes et Inflammation, etc.).

The data collected in the course of the study will be recorded in electronic case report forms, (e-CRF CleanWEB) entered on-line after each visit by the study investigators of each center.

These e-CRFs include various items already used in previous GFEV protocols, adapted specifically for this study. The access to the online e-CFR data collection forms will be restricted to study investigators via an access code and a personal password that is unique to each user. Each investigator will also have access to a specific profile allowing them (or not) to use selected system functions (read or display the data of the enrolled patient, or all study data, the option to update and validate by clinical research associates, etc.). The data will be stored on a secure server with encrypted data transfers and automatic internal backups on the server. The server (at AP-HP, Bessières) will host the Cleanweb information management software solution.

Two parties will have joint responsibility for patient data management and quality control: the Clinical Research Associates (CRA) of the Clinical Research Unit (CRU; Paris Centre) and the study investigators and collaborators of the Cochin Hospital (Medical Unit) under Prof. Guillevin.

#### Interim analysis

An interim analysis will be carried out after 50% of the total number of patients has been enrolled. This analysis would reveal any potential difference between the two study arms, which could, in the interests of patients, lead to to suspension of the study or protocol amendment. The results of this interim analysis will be presented to the Independent Monitoring Committee.

# ACCESS RIGHTS TO THE SOURCE DATA AND DOCUMENTS

The persons granted direct access to the source data and documents in accordance with the current laws and regulations, namely Articles L.1121-3 and R.5121-13 of the French Public Health Code (e.g., investigators, personnel in charge of quality control, monitors, clinical research assistants, auditors and any other personnel called on to take part in this study), must take all precautions necessary to maintain the confidentiality of any information related to the investigational medications, the assessments, and the study participants, notably their identity and the results obtained. Therefore, the data collected by these individuals for quality control or audits will remain anonymous.

# QUALITY CONTROL AND ASSURANCE

The research will be supervised in accordance with the Sponsor's standard operating procedures.

The conduct of the research at the study sites and patient care will be carried out in accordance with the current Declaration of Helsinki and current Good Clinical Practice (GCP).

#### Monitoring Procedures

The MAINRITSAN study presents a risk level of D.

The corresponding level of monitoring is as follows:

* + - Baseline monitoring: source documents, inclusion criteria, exclusion criteria, primary endpoint, adverse events, treatments
    - Verification of informed consent
    - Monitoring of SAEs, tolerance and new cases

The clinical research associates representing the Sponsor will visit the study sites according to the schedule described in the protocol, the number of patients enrolled at each center, and the risk level assigned to the study.

* Initiation visit at each center: To implement the protocol and to become acquainted with the various parties in biomedical research.

The centers likely to start enrolling patients first will be initiated before patient enrollments begin. As the study progresses, other centers will be opened after the enrollment of the first patient.

* During subsequent visits, the clinical research associates will review the e-CRFs periodically as the study progresses (at a minimum, one monitoring visit after visit M12 and one after visit M24 at each center). The lead investigator at each center as well as other investigators recruiting patients or responsible for the follow-up of the patients participating in the study, will meet the clinical research associates at regular intervals.

The following items will be reviewed during these on-site visits, in accordance with the Good Clinical Practice (GCP):

* + Compliance with the protocol and the procedures defined for this study,
  + Verification of patients’ informed consent forms,
  + Review of the source documents and comparison with the data reported in the e-CRFs with respect to accuracy, missing data and data consistency, in accordance with the rules established by the Département à la Recherche Clinique et Développement (DRCD) (Department of Clinical Research and Development).
* Close-out visit (after the data freeze, a few months after visit M28): Collection of e-CRFs, biomedical research documents, archiving.

#### Data Entry in the Electronic Case Report Form

The information required by the protocol must be entered into the electronic case report form (e-CRFs). Each missing data item requires an explanation from the investigator.

The data must be entered in the e-CRF as soon as they are obtained, whether they are clinical or the result of diagnostic tests.

Anonymity of subjects will be assured using an 8-digit numerical code, including the first letter of the last name and the first letter of the first name of the study participant. This number will be used on all necessary documents. Anonymity will also be ensured by appropriate deleting of the personal data appearing on copies of source documents intended as research documents. The data converted to a digital file will be declared to the Commission Nationale de l'Informatique et des Libertés (CNIL) (National Commission for Data Protection and Liberties), in accordance with the adapted procedure.

The data collected in the course of the study are recorded in an electronic case report form (e-CRF) after each online visit by the study investigators of each center. These e-CRFs include various items already used in previous GFEV protocols (printed standard CRFs like the one used for the CHUSPAN2 protocol) and adapted specifically for this study. The access to the online e-CFR data collection forms will be restricted. The study investigators will use an access code and a personal password that is unique for each user. Each investigator will also have access to a specific profile allowing them (or not) to use selected system functions (read or display the data of the enrolled patient, or all study data, the option to update and validate by clinical research associates, etc.). The data will be stored on a secure server offering encrypted data transfers and automatic internal backups on the server.

The server (at AP-HP, Bessières) will host the Cleanweb information management software solution. Two parties will have joint responsibility for patient data management and quality control: the Clinical Research Associates (CRA) of the Clinical Research Unit (CRU; Paris Centre) and the study investigators and collaborators of the Cochin Hospital (Medical Unit) under Prof. Guillevin. The patients will complete two questionnaires (SF36 on quality of life and the physical self-maintenance scale HAQ) at visits D1, M3, M6, M9, M12, M15, M18, M21, M24 and M28. Copies of these questionnaires will be available in the patient booklets especially designed for that purpose. After each visit, the patients will return their booklet to the management center (URC Paris Centre), using the envelopes provided in the booklet.

# ETHICAL CONSIDERATIONS

*The Sponsor is defined by Law 2004-806 of August 9, 2004. For this study, the AP-HP is the Sponsor and the Department of Clinical Research and Development (DRCD) is responsible for the regulatory tasks.*

Before initiating a study, each investigator must give the sponsor representative a copy of his/her personal curriculum vitæ, dated and signed, and including his/her registration number at the National Board of Physicians.

#### Application for AFSSAPS Authorization

To be able to initiate the study, both the AP-HP and the Sponsor must submit an Authorization Request file to AFSSAPS, the relevant authority. The authority, defined in Article L. 1123-12, is responsible for making decisions regarding the safety of the participants in a biomedical study, specifically that the safety and quality of the products used during the study are in accordance with the current reference standards, their condition of clinical use and patient safety with respect to the procedures performed and methods used, as well as the arrangements made for patient follow-up.

#### Opinion Request to the Comité de Protection des Personnes (CPP)

Article L.1123-6 of the Public Health Code stipulates that the study protocol must be submitted by the Sponsor to an Institutional Review Board. The Sponsor must communicate the opinion of the IRB to the competent authority before the study is launched.

#### Amendments

The Department of Clinical Research and Development (DRCD) must be kept informed of any plans by the coordinating investigator to modify the protocol.

The investigator must indicate whether or not these changes will be substantial.

A substantial amendment is a modification likely to change, one way or another, the protection provided to patients taking part in the biomedical study (modification of an inclusion criterion, extension of an enrollment period, addition of new centers, etc.)

After the study is underway, any substantial amendment of the study initiated by the Sponsor must receive approval from the committee and an authorization from the relevant authority before it can be implemented. If the amendment is authorized, the committee must ensure that any new consent form required is signed by, and collected from, the patients taking part in the study.

Furthermore, any study extension (substantial amendment of the treatment plan or the populations, extension of the treatments and/or therapeutic interventions not originally included in the protocol) must be considered as a new study.

For any substantial amendment, the sponsor must submit (after paying a fee) a new Authorization Request file to the AFSSAPS and/or a new opinion request form to the Institutional Review Board.

#### Declaration of the CNIL

The law provides that the electronic file containing the personal data collected for the study must be specified before the study actually begins.

A specific reference methodology used to process personal data for the purpose of the biomedical research, defined by Law 2004-806 of August 9, 2004 as part of Articles L.1121-1 ff. of the Public Health Code, was established by the Commission Nationale de l'Informatique et des Libertés (CNIL) (National Commission for Data Protection and Liberties) in January 2006.

This methodology offers a simplified declaration procedure when the type of data collected during the study is compatible with the list provided by the CNIL in the reference document.

When a clinical research associate representing the Sponsor conducts quality control on the data, and this control is compatible with the simplified CNIL procedure, the DRCD, as the Sponsor, will ask the person responsible for the computerized file to commit himself/herself in writing to the conditions of the simplified MR06001 reference methodology.

#### Informed Consent Form

Written informed consent must be obtained before any assessment described in the study protocol can be performed.

The patients included in this study will be provided with descriptions of the study protocol, both orally and in writing. These patients must sign the Informed Consent Form if they agree to participate in the study. The patients will be given time to consider their decision. The patients retain the option of withdrawing from the study at any time, through a simple request on their part or their treating physician, or from the study investigator *(see Informed Consent Form Version No 4.0 dated August 12, 2009)*

#### Final Study Report

The final study report will be prepared through a collaboration between the coordinator and the study biostatistician. This report will be submitted to each investigator to obtain their input. Once a consensus is reached, the final version must be signed by each investigator and sent to the Sponsor as soon as possible, after the end of the study. A report prepared according to the reference plan of the relevant authority must be sent to the authority and the Institutional Review Board (IRB) no later than one year after the end of the study, corresponding to the last follow-up visit of the last subject enrolled. This period is reduced to 90 days if the study is discontinued prematurely.

# DATA PROCESSING AND STORAGE OF STUDY-RELATED DOCUMENTS AND DATA

The study documents which fall under the scope of the laws on biomedical research must be archived by all parties for a period of 15 years after the end of the study *(see Good Clinical Practice, Section 8: Essential Documents)*

Indexed archiving includes:

* Copies of the AFSSAPS authorization letters and the CPP favorable opinion,
* All successive versions of the study protocol (identified by Version No. and version date),
* All correspondence with the Sponsor
* Consent forms signed by the subjects kept in a sealed envelope (for minors, signed by the legal guardian) with the corresponding list or enrollment registry,
* The completed and validated case report forms for each subject enrolled,
* All study specific appendices,
* The final study report outlining the statistical analysis and quality control performed on the study data (copy sent to the Sponsor),
* Any audit certificates for audits performed over the course of the study

The database used for the statistical analysis must also be archived by the person responsible for the analysis (hard copy or digital form).

# FINANCING AND INSURANCE

#### Insurance

The Assistance Publique-Hôpitaux de Paris (AP-HP) (Paris Public Hospitals) is the sponsor of this study. As stipulated by the laws on biomedical studies, the organization has acquired insurance from GERLING KONZERN for the entire duration of the study, guaranteeing its own civil responsibility and that of all study contributors (physicians or personnel involved in carrying the study) (Law no. 2004-806, Art L.1121-10 of the Public Health Code).

The AP-HP reserves the right to stop the study at any time for medical or administrative reasons. In such an event, the investigators will be notified.

#### Scientific Commitment

Every investigator is bound to comply with the obligations under the law and to carry out the research in accordance with current Good Clinical Practice as well as the current terms of the Declaration of Helsinki. For this purpose, a copy of the scientific commitment (Department of Clinical Research and Development document) dated and signed by each investigator in each clinical department at a participating center will be submitted to a Sponsor representative.

# PUBLICATION RULES

All data are the property of the Assistance Publique-Hôpitaux de Paris (AP-HP) (Paris Public Hospitals). They may not be used or transmitted to a third party without the prior consent of that organization.

Those listed as first authors on any publications will be those who actually participated in the design of the protocol, execution of the protocol, and reporting of the results. The study investigators who enrolled patients will be listed as authors in ascending order by the number of patients actually enrolled in the study, and in accordance with the number of authors authorized by the solicited journal. The last author will be the Groupe Français d’Etude des Vascularites (GFEV) [French Group on Vasculitis Studies]. The other investigators will be cited in an appendix to the article.

The AP-HP must be identified as the Sponsor of this biomedical study and, if applicable, as financial support. The wording "Assistance Publique-Hôpitaux de Paris" must appear in the address of the authors.

# APPENDICES

**Appendix I: References**

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# Appendix II - Classification Criteria

|  |  |  |
| --- | --- | --- |
|  | **Table 1** | Wegener's granulomatosis.  Criteria of the American College of Rheumatology (1990) |
| The presence of 2 to 4 of the following criteria in a patient suffering from vasculitis | | |
| classifies the condition as Wegener's granulomatosis, | | |
| with a sensitivity of 88.2% and a specificity of 92%. | | |
| 1 | Nasal or oral inflammation (epistaxis, oral ulcers or facial pain) | |
| 2 | Abnormal chest radiograph (nodules, cavities, fixed infiltrates) | |
| 3 | Abnormal urinary sediment (microscopic hematuria or red cell casts) | |
| 4 | Granulomatous inflammation on biopsy (in the wall or around arteries or arterioles) | |

|  |  |  |
| --- | --- | --- |
| **Table 2** | Names and definitions of the different types of vasculitis adopted by the Consensus Conference on the Nomenclature of Systemic Vasculitis (Chapel Hill, North Carolina, USA) in 1993 | |
| **Large vessel vasculitis** | | |
| * Giant cell arteritis  (temporal arteritis) | | Granulomatous arteritis of the aorta and its major branches with a predilection for the extracranial branches of the carotid artery.  *Often involves the temporal artery. Usually occurs in patients older  than 50 and is often associated with polymyalgia rheumatica.* |
| * Takayasu arteritis | | Granulomatous inflammation of the aorta and its major branches.  *Usually occurs in patients younger than 50.* |
| **Medium-sized vessel vasculitis** | | |
| * Polyarteritis nodosa | | Necrotizing vasculitis of medium-sized or small arteries without glomerulonephritis or vasculitis in the arterioles, capillaries or venules. |
| * Kawasaki disease | | Arteritis involving large, medium-sized, and small arteries, and associated with the mucocutaneous lymph node syndrome.  *Coronary arteries are often involved. Aorta and veins may be involved. Usually occurs in children.* |
| **Small vessel vasculitis** | | |
| * Wegener's granulomatosis\*\* | | Granulomatosis inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels (capillaries, venules, arterioles, arteries)  *Necrotizing glomerulonephritis is common.* |
| * Churg-Strauss syndrome\*\* | | Eosinophil-rich and granulomatosis inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels and associated with  Asthma and eosinophilia. |
| * Microscopic polyangiitis\*\* | | Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (capillaries, venules, arterioles).  *Necrotizing arteritis involving small and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs.* |
| * Henoch-Schönlein purpura | | Vasculitis, with IgA-dominant immune deposits, affecting small vessels (capillaries, venules, arterioles).  *Typically involves skin, gut, and glomeruli and is associated with arthralgias and arthritis.* |
| * Essential  cryoglobulinemic vasculitis | | Vasculitis with cryoglobulin immune deposits, affecting small  vessels (capillaries, venules, arterioles) and associated with  cryoglobulins in serum.  *Skin and glomeruli are often involved.* |
| * Cutaneous leukocytoclastic angiitis | | Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis. |
| \* Large vessels refer to the aorta and the largest branches. Medium-sized vessels refer to the main visceral arteries (renal, hepatic, coronary, and mesenteric) Small vessels refer to venules, capillaries, arterioles, and the intraparenchymal distal arterial radicals connected to arterioles. Some small and large vessel vasculitides may involve medium-sized arteries, but large and medium-sized vessel vasculitides do not involve vessels smaller than arteries. Italicized text represents usual, but not essential, components.  \*\* Strongly associated with ANCA. | | |

**Appendix III – BVAS 2003**

#### BVAS 2003 – VASCULITIS ACTIVITY SCORE 2003 TOTAL

***Select only the signs indicative of an active disease (use the VDI to score items of sequelae lasting more than 3 months). If all the signs recorded indicate a chronically and*** *slightly active (smouldering/grumbling) disease,* ***and there is no new, recent or worse sign, please check the box in the bottom right corner. The scores indicated are for a disease that recently became active or is slightly active, "grumbling" (check the box in the bottom right corner.).***

**Yes**

1. **General signs** | | **(maximum 3)**

Myalgia | | 1

Arthralgia or arthritis | | 1

Fever? 38°C | | 2

Weight loss? 2 kg | | 2

1. **Cutaneous signs** | | **(maximum 6)**

Necrosis | | 2

Purpura | | 2

Ulcer(s) | | 4

Gangrene | | 6

Other lesion(s) linked to the vasculitis | | 2

1. Mucosal and ocular diseases | | **(maximum 6)**

Mouth ulcers / granuloma | | 2

Genital ulcers | | 1

Lacrimal or salivary gland inflammation | | 4

Exophthalmos | | 4

Episcleritis | | 2

Conjunctivitis / blepharitis / keratitis | | 1

Gradual loss of vision / blurred vision | | 3

Sudden vision loss / blindness | | 6 Uveitis | | 6

Retinal vasculitis | | 6 Thrombosis / Hemorrhage / Retinal exudates

1. **ENT signs** | | **(maximum 6)**

Epistaxis / nasal scabs

Nasal ulcers or granuloma | | 6

Sinusitis | | 2

Subglottic stenosis | | 6 Transmission hearing loss (conductive) | | 3

Perception hearing loss (sensory) | | 6

1. **Pulmonary signs** | | **(maximum 6)**

Wheezing / sibilants | | 2

Nodules / Excavated nodules | | 3

Pleural effusion | | 4

Radiological pulmonary infiltrate | | 4

Endobronchial stenosis | | 4

Intra-alveolar hemorrhage | | 6

Respiratory distress | | 6

**Yes**

1. **Cardiovascular signs** | | **(maximum 6)**

Loss of a pulse | | 4

Valvular disease | | 4

Pericarditis | | 3

Angina | | 4

Cardiomyopathy | | 6

Congestive heart failure | | 6

1. **Abdominal disease** | | **(maximum 9)**

Peritonitis | | 9

Bloody diarrhea | | 9

Abdominal pain (digestive angina) | | 2

|  |  |  |
| --- | --- | --- |
| **8. Renal signs** | | | **(maximum 12)** | |
| Hypertension | | | | 4 |
| Proteinuria > 1+ | | | | 4 |
| Hematuria > 10 RBC/field | | | | 6 |
| Creatininemia 125–249 µmol/l | | | | 4 |
| Creatininemia 250–499 µmol/l | | | | 6 |
| Creatininemia > 500 µmol/l | | | | 8 |

Increase in creatininemia > 30% or reduction   
of creatinine clearance > 25% | | 6

1. **Neurological disease** | | **(maximum 9)**

|  |  |  |
| --- | --- | --- |
| Headaches | | | | 1 |
| Meningitis | | | | 3 |
| Confusion, awareness disorder | | | | 3 |
| Seizures (not hypertensive) | | | | 9 |
| Spinal cord lesions (myelitis) | | | | 9 |
| Stroke | | | | 9 |
| Cranial nerve disease | | | | 6 |
| Sensory peripheral neuropathy | | | | 6 |
| Motor peripheral neuropathy | | | | 9 |

1. **Other specific disease** | |

Specify:………………………………………………………

…………………………………………………………………

…………………………………………………………………

……………………………………………………..

CHECK THIS BOX ONLY IF **ALL** THEDISEASES NOTED ARE OLD AND

PERSISTENT (not new or worse)

**Appendix IV - MAINRITSAN: Classification Grid for Adverse Events for a Biomedical Study on a Medication**

**Classification Grid for Adverse Events for a Biomedical Study on a Medication or Similar Product**

Study Risk: |\_D\_| Independent Monitoring Committee: Yes  No

|  |  |  |  |
| --- | --- | --- | --- |
| SAE Grid for the Biomedical Study (Art. R. 1123-54 of the French Public Health Code)  • MAINRITSAN: A study comparing the efficacy of rituximab and azathioprine as maintenance therapy for ANCA-associated vasculitis: A prospective, multi-center, controlled, randomized study • P 070703 | | | |
| **DO NOT NOTIFY the sponsor BY FAX**  **(no completion of the SAE report form)**  **but rather report on the adverse event CRF pages** | | **IMMEDIATE NOTIFICATION by the investigator to the sponsor** **(fax the SAE report form to 01 44 84 17 99)**  **and report on the adverse event CRF pages** | |
| **Other events** | **Expected Non Serious**  **Adverse Reactions**  Known to be related:  to the investigational medication(s) or to the study procedures. | **Expected Serious Adverse Reactions**  Known to be related:  to the investigational medication(s)  or to the study procedures. | **Unexpected Serious  Adverse Reactions** |
| **EVENTS MAY BE SERIOUS but not related to the investigational medication(s) or to the study procedures:**  Anything that is related to the natural and usual  course of the disease  Hospitalizations scheduled for monitoring of  the disease  Hospitalizations in case of relapse of the disease | **Description: AE that does not require hospitalization and is not life-threatening**  Related to rituximab:  -Reactions related to the infusion: fever, chills, tremors, skin redness, angioedema, nausea, joint rash, asthenia, headaches, throat irritation, rhinitis, vomiting, pain  -hypotension, hypertension  -Hematological events: thrombocytopenia, neutropenia  Related to Imurel:  - Bone marrow failure, leukopenia, thrombocytopenia, anemia.  - Moderate cholestasis and impaired liver function (liver failure), pancreatitis confirmed by laboratory tests.  - Arterial hypotension, asthenia, malaise, dizziness, nausea, vomiting, diarrhea, fever, chills  - Muscle and joint pain.  - Moderate alopecia.  - Common ENT infections.  Related to corticosteroid therapy:   * Electrolyte disorders: moderate hypokalemia, metabolic alkalosis, fluid retention, HTN/ -Menstrual irregularities/ -Musculoskeletal disorders: muscle atrophy preceded by muscle weakness/ - Skin disorders: acne, purpura, ecchymosis, hypertrichosis, delayed healing/ - Neuropsychiatric disorders: euphoria, insomnia, excitation | **SAE description that requires hospitalization or is life-threatening**  Related to rituximab:  -Severe infections, Encephalitis  -Hematological events, neutropenia, thrombocytopenia, severe anemia,  hemolytic anemia  -Angina, heart failure  -Gastrointestinal perforations  -Tumors/cancers  Related to Imurel:  - Severe bone marrow failure, megaloblastic erythropoiesis and macrocytosis, severe hematological disorder.  - Severe cholestasis and impaired liver function, severe pancreatitis, transaminases > 3x normal, hepatitis  - Manifestations of hypersensitivity, exanthemic-type severe skin reaction,  skin rash; renal function abnormalities and hemolytic anemia  - Infections, pneumonitis  - Arrhythmia  - Necrotizing enterocolitis, GI perforation, hepatic veno-occlusive disease  - Squamous cell skin carcinoma, malignant Non-Hodgkin’s lymphoma, cervical cancer, Kaposi sarcoma, vulvar cancer  Related to corticosteroid therapy:  - Congestive heart failure / - Endocrine and metabolic disorders: iatrogenic Cushing’s syndrome, ACTH secretion inertia, sometimes permanent adrenal cortex atrophy, reduced glucose tolerance, discovery of latent diabetes/ - Musculoskeletal disorders: muscular dysfunction due to corticosteroid-induced myopathy, osteoporosis, pathological fractures in particular vertebral compression or fracture of the femoral neck, aseptic osteonecrosis of the femoral heads / -Serious gastrointestinal disorders: gastroduodenal ulcers, small intestine ulcer, perforations and GI bleeding / -Serious Neuropsychiatric disorders: delusions of manic appearance, delirium or confusional states, seizures, severe depressive states during or after discontinuing the treatment / -Eye disorders: cataracts and some forms of severe glaucoma, serous chorioretinopathy | This column will be completed as reports are made by the investigators.  Report all events with one of the severity criteria\* noted below, except for those identified in the other columns  \*Severity criteria:  1- Death  2- Life-threatening  3- Requiring or extending hospitalization  4- Lasting sequelae  5- Congenital abnormality or defect  6- Event considered serious by the investigator (specify the reason)  NOTE: Any discovery of a PREGNANCY during a biomedical research study must be reported to the sponsor immediately and must be monitored until delivery. |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Last name, first name and signature of the coordinating investigator: Prof. L. Guillevin  Scientific Director Dr. C. Pagnoux | Last name, first name and signature of the Clinical Research Unit (CRU) manager:  Prof. J.M. Treluyer | Last name, first name and signature of the project lead: Y. Vacher | Last name, first name and signature  of the pharmacovigilance manager:  H. Brocvielle | Last name, first name and signature of the medical coordinator: O. Chassany |

Final version DRCD-PV-12/12/2006 AP-HP [Public Hospitals of Paris] Département de la Recherche Clinique et du Développement [Clinical Research and Development Department], Délégation Interrégionale à la Recherche Clinique Ile de France   
[Ile de France Inter-regional Clinical Research Delegation]

Date: 07 05 2008

**Appendix V – Tapering off schedule for corticosteroids according   
to the protocol**

**EUVAS IMPROVE**

DOSES OF CYCLOPHOSPHAMIDE AND CORTICOSTEROIDS ACCORDING   
TO THE EUVAS IMPROVE PROTOCOL

1. Induction phase

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| time from entry  (weeks)1 | Prednisolone  (mg/kg/day) | plus either | Cyclophosphamide  (oral)  (mg/kg/day)2 | or | Cyclophosphamide  (pulse)  (mg/kg)2 | Puls no. |
| 0 | 1 |  | 2 |  | 15 i.v. | 1 |
| 1 | 0.75 |  | 2 |  |  |  |
| 2 | 0.5 |  | 2 |  | 15 i.v. | 2 |
| 4 | 0.4 |  | 2 |  | 15 i.v. | 3 |
| 7 | 0.3 |  | 2 |  | 15 i.v. or 3x5 p.o.3 | 4 |
| 10 | 0.28 |  | 2 |  | 15 i.v. or 3x5 p.o.3 | 5 |
| 134 | 0.25 |  | 2 |  | 15 i.v. or 3x5 p.o.3 | 6 |

Initial administration of an IV bolus of methylprednisolone is authorized at a dose of 15 mg/kg. If justified, this bolus may be repeated on the 2nd and 3rd days, i.e. a total of 3 boluses maximum, distributed over 3 consecutive days. This decision is left up to the clinician in charge of the patient.

The initial dose of oral prednisolone will be limited to 80 mg/day for patients who weigh more than 80 kg.

2. Maintenance phase: dose tapering regimen

|  |  |  |
| --- | --- | --- |
| Time from entry  (months) | Action | Prednisolone  (Pred)  (mg/day) |
| 3 | Reduce Pred. start MMF/AZA | 15 |
| 4 | Reduce Pred | 12.5 |
| 5 | Reduce Pred | 10 |
| 6 | Reduce Pred | 7.5 |
| 12 | Reduce Pred and MMF/AZA | 5 |
| 18 | Reduce Pred and MMF/AZA | 2.5 |
| 24 | Stop Pred | 0 |
| 42 | Stop MMF/AZA | 0 |
| 483 | Study end | 0 |

**Appendix VI – Scientific Agreement Form, with e-CRF**

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***SCIENTIFIC AGREEMENT FORM***

**Biomedical research study code: P............................**

**Study title:………………………………………………………………………………….**  
**………………………………………………………………………………………………**  
**………………………………………………………………………………………………**

Protocol version number and date:

1. The investigator declares to direct and supervise the conduct of the above-mentioned biomedical research study at his/her research site.
2. The investigator is qualified by his/her training and his/her professional experience to conduct this research as demonstrated by the signed and dated curriculum vitae (with his/her registration number from the Ordre des Médecins [French medical association] and his/her Adeli number [health professional registration]), which he/she has provided to the sponsor.
3. The investigator certifies that he/she is committed to conducting this research according to Good Clinical Practices and in accordance with the Law dated 20 December 1988 amended by Law 2004-806 dated 9 August 2004, its decrees and implementing legislation.
4. The investigator agrees to respect the laws of medical ethics defined by the World Medical Association in the Declaration of Helsinki and the rules of confidentiality.
5. The investigator is aware of the prerequisites of this research, the protocol and its appendices. In particular, he/she agrees to follow the protocol during the research and to ensure proper management of the study products where necessary.
6. The investigator acknowledges receipt of all necessary information for proper use of the CleanWEB™ online case report form and agrees not to disclose his/her personal login and password to a third party.
7. The investigator certifies that he/she has the means necessary to properly conduct this research in terms of availability, staff, recruitment of individuals, technical facilities and environment.
8. The investigator agrees to obtain the free and informed consent of any individual who may participate in the research or his/her legal representative, as applicable. This consent will be obtained by the investigator himself/herself or by his/her designated collaborating physicians, after providing the individual with objective information, the informed documents, and being notified in writing, if possible, after the individual has had time to reflect. At the end of the research, all of the original consent forms obtained will be archived by the site and an additional copy of all consent forms will be provided to the sponsor in a sealed envelope.
9. The investigator agrees to periodic visits by representatives of the sponsor, if applicable. He/she will make available all source documents and materials related to the research to ensure quality control of the data recorded in the electronic case report form. The investigator agrees to periodically notify the sponsor of the number of enrolled subjects at his/her research site.
10. The investigator, or his/her designated collaborating physicians, if applicable, will notify the sponsor within 48 hours, according to the instructions of the research protocol, of serious adverse events or new information that arises during the research, using the forms provided.
11. The investigator agrees to store, for each of the patients until the end of their monitoring, a paper copy of the validated e-CRF (initially generated in PDF format by the CleanWEB software), automatically dated and signed by the investigator as well as all source documents relevant within the context of this research.
12. The investigator agrees to the principle of control in the event of an audit by the sponsor and/or inspection by the health authorities. He/she also agrees to respond as soon as possible to any request for information or data by the sponsor.
13. The investigator agrees to notify the AP-HP [Public Hospitals of Paris] of any publication mentioning this research and to cite the AP-HP as sponsor of the research. He/she also agrees, if necessary, to collaborate with the research coordinator in the writing of the final study report.
14. The principal investigator is the sponsor’s main contact person at each site. He/she agrees to provide training on the protocol and to supervise the work of the local team, for which he/she provided a list of names to the sponsor.

Date: …………/…………/………… *stamp of the department*

Name and signature of the principal investigator: