MAINEPSAN Study

A Prospective Comparative Randomized Double-blind Placebo-controlled In-Parallel Groups Multicenter, Study to Evaluate the remission MAINtenance using Extended administration of Prednisone in Systemic anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis.

CATEGORY 1 PROTOCOL INVOLVING HUMAN INDIVIDUALS AND CONCERNING A DRUG

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Summary of Changes to the Protocol

The protocol history is provided below:

Protocol History	
Version and Date of Protocol	**Comments**
Version 1.0, Date : 26.06.2018	Original Version
Version 2.0, Date 18.09.2018	Modified due to CPP request
Version 3.0 Date 04.01.2018	Modified due to DSMB advice:

Key changes in the current version of the protocol are summarized below:

Change and Rationale	Affected Sections
CPP request 6.09.2018	Statistics
DSMB advice 31.12.2018	-non inclusion criteria changed: Patients who have white blood neutrophils count ≤ 1500/mm3 -non inclusion criteria added: Patients with severe hypogammaglobulinemia (invase bacterial or fungal infection with IgG < 5 g/L or IgG < 3 g/L in patients without infection) - An individual subject unblinding can be performed in case of adrenal insufficiency suspicion - In case of a physiological stress situation a hydrocortisone prescription is authorized

CONTENTS

ABREVIATIONS LIST

AAV:	ANCA-associated Vasculitis
ACR:	American College of Rheumatology
AE:	Adverse Event
ANCA:	Anti-Neutrophil Cytoplasmic Antibody
ANSM:	Agence Nationale de Sécurité du Médicament
BVAS:	Birmingham Vasculitis Activity Score
CDA:	Combined damage assessment
CRA:	Clinical Research Associate
CTACE:	Common Terminology Criteria for Adverse Events
D	Day
DSMB:	Data and Safety Monitoring Board
EDTA:	European Dialysis and Transplantation Association
EGPA:	Eosinophilic Granulomatosis with Polyangiitis
ENT:	Ear, nose and throat
EULAR:	EUropean League Against Rheumatism
ERA:	European Renal Association
ETV:	Early Termination Visit
FFS:	Five Factor Score
FVSG:	French Vasculitis Study Group
GCPs:	Good Clinical Practices
GPA:	Granulomatosis with PolyAngiitis
HCL:	Hospices Civils de Lyon
IP:	Investigational Product
IRB:	Institutional Review Board
MPA:	Microscopic PolyAngiitis
MPO:	Myeloperoxidase
PR3:	Proteinase 3
RTX	Rituximab
SAE:	Serious Adverse Events
SFU:	Safety Follow-Up
SUSARs:	Suspected Unexpected Serious Adverse Reactions
UNS:	UNScheduled
VDI:	Vasculitis Damage Index
W	Week

1. PROTOCOLE SYNOPSIS

Full title:	MAINtenance of remission using Extended administration of Prednisone in Systemic anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV). A prospective, multicentric, randomized, controlled, double-blind trial.
Acronym:	MAINEPSAN
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Scientific justification:	Immunosuppressive therapy of granulomatosis with polyangiitis (GPA, Wegener's) and microscopic polyangiitis (MPA) has transformed the outcome from death to a strong likelihood of disease control and temporary remission. However, most patients have recurrent relapses that lead to damage and require repeated treatment associated with long-term morbidity and death. Rituximab has been shown to be as effective as cyclophosphamide to induce remission in severe GPA and MPA patients, with an acceptable safety profile. Randomized controlled trials showed significantly lower relapse rate with rituximab than azathioprine treatment during maintenance (PHRC 2008). Nevertheless, although rituximab is becoming the standard of care for maintenance therapy in these patients, relapse still occur and the optimal duration of prednisone therapy remains debated. On the one hand, most US studies use early withdrawal (6-12 months) because of feared side effects. On the other hand, most European trials propose late withdrawal (>18 months) given a lower observed relapse rate on long-term low dose glucocorticoids treatment. In a systematic review and meta-analysis, glucocorticoids regimen was the most significant variable explaining the variability between the proportions of ANCA-associated vasculitis patients with relapses. However, it was an indirect estimation of treatment effect because of the absence of dedicated randomized trial. This meta-analysis concluded that combined longer-term (i.e. >12 months) use of low dose prednisone is associated with a 20% reduction of relapse compared to early withdrawal (i.e. ≤12 months). The relapse rate in patients with early glucocorticoids (10-12 months) withdrawal was provided in two studies of meta-analysis and was of 37 and 34%, respectively. By contrast, the relapse rate in patients with late prednisone withdrawal (18-24 months) after rituximab maintenance treatment was 16% at 28 months (10 months after last RTX maintenance infusion) and 23% at 36 months (18 months after last RTX maintenance infusion) in the MAINRITSAN trial. Of note, the decision to withdraw glucocorticoids after 18 months was left to physician's discretion in this study and two thirds of the non-severe relapses occurred when patients were off prednisone. The trial detailed here is the first prospective trial evaluating the length of glucocorticoid administration as maintenance adjunctive treatment for patients with GPA or MPA.

Primary objective and assessment criterion:	**<u>Primary objective:</u>** To compare relapse rate of patients continuing low-dose prednisone treatment until 13 months of treatment (Visit Month 13) versus those who will have prednisone treatment cessation after one month (visit Month 1), on remission maintenance with rituximab therapy, after achievement of remission of GPA or MPA. GPA or MPA remission is defined as patients maintaining a BVAS=0 at Month 30 (36 months after initiation of first RTX maintenance infusion and 18 months after last RTX maintenance infusion), in patients with newly-diagnosed or relapsing GPA or MPA and who will all have already received glucocorticoids for 12 months after diagnosis or last flare before Day 1. **<u>Primary assessment criterion:</u>** The primary endpoint is the relapse rate at Month 30 (18 months after last RTX maintenance infusion), relapse being defined as BVAS >0.
Secondary objectives and assessment criteria:	**<u>Secondary objectives:</u>** - To compare the rate of AE and SAE between Day 1 and Month 30, - To compare the rate of predefined severe events related to glucocorticoids between Day 1 and Month 30 including osteoporotic fracture and weight gain, - To compare the duration of complete remission, defined as the total accrued duration in weeks with BVAS=0 between Day 1 and Month 30, - To compare the rate of minor and major vasculitis relapse at Month 30, - To compare the side effect related to low dose prednisone by GTI toxicity scale between Day 1 and Month 30, - To compare the prednisone use between Day 1 and Month 30, - To compare the number of deaths between Day 1 and Month 30, - To compare variation of the bone mineral density and remodeling markers between Day 1 and Month 30, - To compare weight gain between Day 1 and Month 30, - To compare the sequelae assessed by the Vasculitis Damage Index (VDI) and Combined Damage Assessment Index (CDA) between Day 1 and Month 30, - To compare functional disability (HAQ scale), quality of life (SF36) and healthcare resource utilization between Day 1 and Month 30. **<u>Secondary assessment criteria:</u>** - Percentage of patients with at least one AE between Day 1 and Month 30, - Percentage of patients with at least one minor or major vasculitis flare (BVAS>0) or one predefined severe event corresponding to AE of grade 3 to 5 of the Common Terminology Criteria (CTCAE), including severe side effect related to glucocorticoids (infection requiring hospitalization or intravenous antibiotics, osteoporotic fracture, diabetes requiring medication, cardiovascular event, osteonecrosis, psychiatric or mood disorder requiring drug administration, weight gain >10 kg), between Day 1 and Month 30, - Percentage of patients with at least one SAE between Day 1 and Month 30 corresponding to any AE that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or congenital anomaly/birth defect or any other AE considered "medically significant", - Percentage of patients with minor (reappearance or worsening of disease with a BVAS >0, not corresponding to a major relapse but requiring mild treatment intensification) or major vasculitis (occurrence or new onset of potentially organ- or life-threatening disease activity that cannot be treated with an increase of glucocorticoids alone and requires further escalation of treatment) between Day 1 and Month 30 (BVAS >0) and time to first vasculitis relapse, - Variation of the GlucoCorticoids Toxicity Score (GTI score) between Day 1 and Month 30,

	- Prednisone area under the curve of administrated dose between Day 1 and Month 30, - Number of deaths, whatever the cause at Month 30, - Variation of the bone mineral density between Day 1 and Month 30, - Weight gain between Day 1 and Month 30, - Variation of BVAS (vasculitis activity), VDI and CDA (damage), HAQ (disability), SF-36 (quality of life) between Day 1 and Month 30, - Healthcare resource utilization during the study between Day 1 and Month 30 being defined as the percentage of patients being hospitalized at least once except only for rituximab infusions.
Experimental design:	Prospective, multicenter, randomized, double-blind, placebo-controlled trial comparing 5 mg daily prednisone cessation at Month 1 and at Month 13 post-randomization, during remission maintenance therapy with rituximab in patients with MPA and GPA. During Screening period (5 weeks before Day 1), eligible patients should be in remission (BVAS=0) for MPA or GPA, must have received a prednisone dose from 5 to 10 mg/day and the first two rituximab maintenance infusion 6 month before Day 1 (J1 and J15 infusions). From Screening to Day 1, if prednisone dose is between 6 to 10mg/day, a 5-weeks-run-in period must be performed with a decreasing dose to reach 5 mg/jour at Day 1. At Day 1 (12 months after treatment initiation of vasculitis/relapse), patients, still in remission (BVAS =0) will be randomized at 1:1 ratio in two arms : - **Conventional arm – Short treatment duration:** Patients will carry out a progressive stop of prednisone (decrease of 1 mg / week during the first 4 weeks of treatment) until stop of the prednisone obtained in M1. Then, they will receive a placebo of prednisone 5 mg up to the end of the 13th month of treatment (M13 visit). - **Experimental Arm – Long treatment Duration:** Patients will receive a daily dose of 5mg of prednisone for 12 months and then perform a gradual discontinuation of prednisone therapy (decrease of 1mg per week) for 4 weeks until the end of the 13th month of treatment (M13 visit). In both randomization arms, patients will receive the third rituximab maintenance infusion at D1, the fourth at M6 and the fifth at M12 (5 rituximab maintenance infusions of 500 mg fixed dose given in 18 months).
Target Population:	Patients with newly diagnosed or relapsing MPA and GPA will be randomized after remission achievement, 12 months after initiation of treatment for vasculitis onset or flare. During this 12 months, patients are treated with rituximab (500 mg fixed low-dose) maintenance therapy every 6 months. Eligible patients are those in remission and receiving a prednisone dose of 5-10 mg/day, 12 months after vasculitis onset or flare, before the third rituximab maintenance infusion (scheduled for Day 1).
Inclusion criteria:	- Patients who have been informed about the study and have given his/her written consent prior to participation in the study, - Patients with newly-diagnosed or relapsing MPA or GPA according to the ACR 1990 criteria and/or revised Chapel Hill Consensus Conference definition, independently of ANCA status, - Patients aged of 18 years or older, - Patients in remission (BVAS =0) for MPA or GPA achieved with rituximab or cyclophosphamide or methotrexate,

	- Patients who will all have already received glucocorticoids for 12 months ± 2 weeks after diagnosis or last flare before Day 1. - Patients having received 500 mg pre-emptive low-dose rituximab maintenance infusions at remission achievement (4 to 6 months after initiation of induction therapy and possibly 15 days after, according to the MAINRITSAN study), so 6 month ± 2 weeks before Day 1. - Patients receiving from 5 to 10 mg/day prednisone dose within 35 days before Day1 (= before the third rituximab maintenance infusion). After Inclusion, a Run-in period will be performed during a maximum of 35 days to decrease prednisone dose and reach 5 mg daily at D1. The randomization will be performed in patients i) still in remission (BVAS = 0) and ii) all receiving prednisone daily dose of 5 mg for the third rituximab maintenance infusion.
Non-inclusion criteria:	- Patients with EGPA, or other vasculitides, defined by the ACR criteria and/or the Chapel Hill Consensus Conference, - Patients with vasculitis with active disease defined as a BVAS >0, - Patients with acute infections or chronic active infections (including HIV, HBV or HCV), - Patients with active or recent cancer (<5 years) or myelodysplasia, except basocellular carcinoma and low activity prostatic cancer controlled by hormonal treatment, Pregnant women and lactation: women of childbearing potential will have to follow an effective method of contraception for the total duration of the study, - Patients with contraindication to use rituximab, - Patients with other uncontrolled diseases, including drug or alcohol abuse, severe psychiatric diseases, that could interfere with participation in the trial according to the protocol, - Patients included in other investigational therapeutic study within the previous 3 months excepted for the PNEUMOVAS trial, - Patients suspected not to be observant to the proposed treatment, - Patients who have neutrophils count ≤ 1500/mm^3 - Patients who have platelet count ≤ 100 000/mm^3 - Patients with severe hypogammaglobulinemia (invasive bacterial or fungal infection with IgG < 5 g/L or IgG < 3 g/L in patients without infection) - Patients who have ALT or AST level greater than 3 times the upper limit of normal that cannot be attributed to underlying MPA-GPA disease, - Patients unable to give written informed consent form prior to study participation. - Patients under legal protection - Patient not affiliated to a social security scheme or other social protection scheme.
Criteria for withdrawal:	Consent withdrawal
Control Group:	Decreasing dose of prednisone 1 mg/week until discontinuation at the end of Month 1 (Month 1 visit). A placebo treatment will continue until the end of Month 13 (M13 visit).
Experimental Group:	Prednisone treatment will be continued at 5 mg / day until the end of Month 12 (M12 visit), then a decrease of 1 mg of Prednisolone/week will be achieved from Month 12 to discontinuation of corticosteroid therapy at the end of Month 13 (M13 visit).
Other procedures added by the research:	All patients received a standard maintenance treatment with ritruximab preemptive low-dose (500 mg) infusions given every 6 months within 18 month. The first maintenance rituximab infusion has been given 6 months prior to Day 1; when remission is obtained, 4 to 6 months after the initiation of the induction treatment. A

	second additional 500 mg rituximab may have been given, 15 days after the first maintenance rituximab infusion according to the MAINRITSAN's study, when cyclophosphamide or methotrexate was used as induction therapy. The (two) first rituximab maintenance infusion(s) is(are) followed by 3-low-dose additional rituximab infusions administered at Day 1, Month 6 and Month 12. Adrenal insufficiency will be sought in case of suggestive symptoms according to the physician's discretion. Hydrocortisone will be administered according to published recommendations if needed.
Benefit-risk ratio:	Foreseeable benefits are a superior efficacy of extended administration of low-dose prednisone compared to the conventional therapeutic strategy to maintain remission of vasculitis, and an improved outcome with higher rates of complete remission and lower cumulative morbidity in the experimental group. Foreseeable risks are those associated with toxicity of treatments. The rate of side effects related to low dose prednisone is expected to be low in regards low dose used (<7.5mg/day). In the control group, foreseeable risk linked with prednisone is lower. The rate of major relapse would correspond to at maximum 50% of all the relapses, i.e. an absolute theoretical difference of 10% between both arms.
Number of patients:	146 patients Based on the results of the previous MAINRITSAN trial from the French Vasculitis Study Group, in MPA and GPA, the proportion of patients receiving at least 18 months of prednisone and experiencing vasculitis relapse (minor or major) after rituximab maintenance is expected to be 14% at 30 months post-randomization in the late cessation group. Of note two thirds of minor relapses in this trial were observed in patients off prednisone. The same percentage (14%) of relapse was observed in the meta-analysis for the studies with no glucocorticoids withdrawal. On the other hand, previous studies in AAV reported a relapse rate of 34% and 37% in case of glucocorticoids cessation before 12 months, both after achievement of remission with cyclophosphamide. The primary hypothesis of the trial is a relative decrease of 60% of the relapse rate at 30 months post-inclusion, i.e. 14% vs 34%. Based on this hypothesis, using a bilateral test, we calculated that 140 patients would be required for the study to have 80% power to detect an absolute 20% reduction with a two-sided alpha level of 5%, 70 patients in each arm. Given an expected loss of follow-up or withdrawal of consent of patients, 73 patients per arm will be necessary.
Location of the study:	This protocol is redacted as part of a national research with participation of the French Vasculitis Study Group (FVSG) network, The investigator list is presented in appendices
Study duration:	Recruitment period: 24 months Study participation for each patient: 30 months Total duration: 54 months
Number of inclusions expected per center and per month:	2 patients/year/center, i;e. 146 patients
Statistical analysis:	Relapse rate will be compared using a binomial GEE model with an identity link to estimate the risk difference for the correlated data (correlation will be due to a multicenter trial). Results will be presented as absolute risk difference with 95% confidence intervals (CIs). An offset term (Log follow-up duration) could be added to the model. As a sensitivity analysis, the Kaplan-Meier curves will be used to

	display the probability of remaining relapse-free according to treatment group and a marginal Cox model test will be used to compare overall survival (results will be presented as hazard ratio with 95% CIs).
Expected impacts:	This trial will be the first prospective, randomized and controlled study evaluating efficacy and safety of extended administration of prednisone to maintain remission in MPA and GPA patients. This study, if it demonstrated a benefit of extended treatment of prednisone compared to conventional therapeutic strategy,it would improve the management of patients with MPA and GPA. the increase in the duration of administration of low-dose prednisone would be retained as the standard of care for the maintenance treatment of GPA and PAM.

2. SCIENTIFIC JUSTIFICATION FOR THE RESEARCH

2.1. Hypothesis for the Research

The MAINEPSAN study aims to compare the relapse rate of patients continuing low-dose prednisone treatment until 24 months after the vasculitis diagnosis or flare versus those who will have prednisone treatment cessation at 12 months after the vasculitis diagnosis or flare, in GPA and MPA on remission maintenance with low-dose pre-emptive rituximab therapy, after achievement of remission, in relapsing or newly-diagnosed vasculitis.

2.2. Description of Knowledge - Granulomatosis with Polyangiitis and Microscopic Polyangeiitis

2.2.1. ANCA-associated vasculitides

Systemic vasculitides are inflammatory diseases of blood vessels, among which anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are the most severe diseases with life-threatening manifestations or complications [1].

Anti-neutrophil cytoplasmic antibody-associated vasculitides include granulomatosis with polyangiitis (GPA, Wegener's), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss) [1]. They are classified as AAV because most patients with generalized disease have antibodies against proteinase 3 (PR3) or myeloperoxidase (MPO) ANCA [1]. Anti-neutrophil cytoplasmic antibody-associated vasculitides affect small-to-medium-size blood vessels, with a predilection for the respiratory tract and kidneys [1].

2.2.2. Clinical Manifestations of ANCA-associated Vasculitides and Diagnosis

GPA is a systemic small- and medium-sized-vessel vasculitis which is characterized by the granulomatous inflammation of the upper and lower respiratory tract. GPA is an uncommon disease with an estimated annual incidence of 5-15 per million [2-4]. The histopathological

hallmark of this vasculitis is a necrotizing vasculitis of capillaries and veinules with neutrophilic granuloma formation [5]. Disease onset may be gradual with general symptoms including fever, myalgia, arthralgia, and weight loss. This vasculitis commonly involves the lung that exhibits multiple, bilateral and cavitary nodules or infiltrates in 80-90% of patients. The upper airway lesions typically revealed the disease and encompass chronic sinusitis, otitis, subglottic and oral lesions [6]. Ear, nose, and throat (ENT) manifestations occur in 90% of GPA patients during the course of the disease [6]. Renal manifestations generally dominate the clinical picture. Pauci-immune glomerulonephritis are present in 20% of patients at presentation but subsequently develop in 80% of patients, usually within the first two years of disease onset [6, 7]. Other manifestations evocative of GPA include corneal ulceration, retro-orbital pseudotumor, and pyoderma grangrenosum. Approximately 90% of patients with active GPA have a positive antiproteinase-3 ANCA [8]. However, in the absence of active disease or in the granulomatosis subtypes without overt vasculitis, sensitivity drops to approximately 60 to 70%. A small percentage of GPA patients may have MPO rather than anti-PR3 autoantibodies. ANCA are detectable in nearly all patients with active severe GPA [9].
The diagnosis of GPA will be based on the revised Chapel Hill nomenclature [1] or on American College of Rheumatology criteria requiring in patients with an evidence of vasculitis the presence of 2 out of the 4 following criteria [10] (Table 1 – Page 14):

Table 1. American College of Rheumatology criteria for GPA

- Nasal or oral inflammation (painful or painless oral ulcers, or purulent or bloody nasal discharge)
- Abnormal chest radiograph showing nodules, fixed infiltrates, or cavities
- Abnormal urinary sediment (microscopic hematuria with or without red cell casts)
- Granulomatous inflammation on biopsy of an artery or perivascular area

Microscopic polyarteritis was introduced into the literature in 1948 in recognition of the presence of glomerulonephritis in patients with periarteritis nodosa [11]. In 1994 the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis adopted the term MPA to connote a necrotizing pauci-immune vasculitis of small vessels without granulomatous inflammation [12]. The estimated annual incidence of MPA ranges from 4 to 10 per million [3, 4]. Because of its predilection to involve veinules, capillaries, and arterioles, MPA shares similar clinical feature with GPA [12]. Glomerulonephritis is as frequent as seen in GPA with a prevalence of 80% and may lead to renal failure [8]. Lung capillaritis is responsible of alveolar hemorrhage in 10% of patients [8]. Upper airway involvement and pulmonary nodules are not usually found in MPA, and, if present, strongly suggest GPA [1]. ANCA are present in 70-80%

of patients, with anti-MPO being the predominant ANCA associated with this vasculitis [8]. Diagnosis of MPA relies on the revised Chapel Hill nomenclature [1].

EGPA was first described in 1951 by Jacob Churg and Lotte Strauss [13] and was initially called allergic angiitis and granulomatosis. Thus, histological findings included necrotizing vasculitis, eosinophilic infiltrates in tissues and granulomas [1, 5]. Since it is rare to identify the three lesions in the same patient, the diagnosis of EGPA mainly relies on clinical parameters. A clinical definition of EGPA, established in 1984 by Lanham et al. [14], has allowed clinicians to diagnose EGPA with good specificity and sensitivity without relying on histological findings. The three diagnostic criteria are asthma, blood eosinophilia exceeding 1,500/mm^3 and evidence of vasculitis involving two or more organs.
Other criteria have been proposed, especially for classification purposes, notably the American College of Rheumatology criteria in which 4 out of 6 criteria should be present [15] (Table 2 – Page 15**)**.

Table 2. American College of Rheumatology criteria for EGPA

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

2.2.3. Treatment of Granulomatosis with Polyangiitis and Microscopic Polyangiitis

Initial immunosuppressive therapies are similar for severe GPA and MPA and consist of induction by glucocorticoids combined with either cyclophosphamide or rituximab and maintenance by immunosuppressive drugs encompassing azathioprine, methotrexate, mycophenolate mofetil, or rituximab [16]. The use of aggressive initial immunosuppression is justified because the mortality rate in untreated severe MPA or generalized GPA is as high as 90 percent at two years, usually due to respiratory or renal failure [6, 7].
Mortality has markedly diminished with the introduction of initial therapy with oral cyclophosphamide and glucocorticoids. Since the 1970s treatment consisting of a combination of glucocorticoids (prednisone 1 mg/kg/day—maximum daily dose 80 mg) with cyclophosphamide (2 mg/kg/day—maximum 200 mg/day) has been used for remission induction in AAV [16, 17]. Due to concern about the long-term side effects of cumulative cyclophosphamide exposition, pulsed intravenous regimens were tested in the CYCLOPS trial [18]. The rate of relapsing patients may be higher in those individuals treated with pulsed

cyclophosphamide and there were no differences in all-cause mortality, rate of transplantation or renal function. However, pulsed regimens are favoured due to the reduced total dose of cyclophosphamide overall and reduced risk of bladder-related complications.

In 2010, two randomized trials, RAVE and RITUXVAS showed that rituximab, a monoclonal antibody against anti-CD20 targeting B lymphocytes, is an effective alternative to cyclophosphamide for the induction of newly diagnosed or relapsing disease [19, 20], although in RITUXVAS, those assigned to rituximab also received initially cyclophosphamide. In both studies patients initially received high-dose glucocorticoids with subsequent dose tapering. The rituximab dose in both studies was 375 mg/m^2 of body surface area, once a week for four infusions. All patients received one to three pulses of methylprednisolone (1000 mg) followed by prednisone (1 mg/kg per day). In the RAVE trial, patients who received induction therapy with 4 rituximab infusions did not receive other immunosuppressive drug until endpoint whereas patients who were treated with cyclophosphamide as induction therapy were switched for azathioprine for 18 months. In both trials, rituximab was non-inferior to cyclophosphamide in terms of efficacy and safety and appeared more effective for the subgroup of relapsing patients in the RAVE trial. Of the 197 GPA and MPA patients initially enrolled in the RAVE trial, the proportion of patients remaining in complete remission was similar comparing rituximab- with cyclophosphamide-based induction (39 versus 33%) at 18 months of follow-up. In the 44 patients of the RITUXVAS trial, there was no difference in the sustained remission rate (defined as the absence of disease activity for at least six months) between the rituximab- and cyclophosphamide-only groups (76 versus 82%). There was also no difference between groups in the rate of AE. The factors predictive of relapse after complete remission induced by rituximab infusions was the positivity of anti-PR3 at diagnosis, the increase of PR3-ANCA at follow-up and a relapsing vasculitis compared to newly diagnosed disease [21, 22]. These studies led to registration of rituximab by the FDA and EMA as induction therapy in severe MPA and GPA, in addition with glucocorticoids. In regards of these results, for remission-induction of new-onset organ-threatening or life-threatening AAV, the 2016 EUropean League Against Rheumatism (EULAR)/European Renal Association (ERA) - European Dialysis and Transplantation Association (EDTA) Guidelines recommend treatment with a combination of glucocorticoids and either cyclophosphamide or rituximab [16]. Methotrexate (20-25 mg/week orally or parentally) may be an option in GPA patients with less severe disease, typically those presenting with ENT involvement, non-ulcerative cutaneous involvement, myositis or pulmonary nodules [16].

For remission maintenance of GPA or MPA, a combination of low-dose of glucocorticoids and either rituximab, azathioprine, mycophenolate mofetil or methotrexate is recommended by the

2016 EULAR/ERA-EDTA guidelines [16]. However, published trials reported discrepancies between the treatment effects of these drugs. After the publication of the IMPROVE trial [23], azathioprine is preferred over mycophenolate mofetil for remission maintenance. Azathioprine has been shown to be as effective and safe than methotrexate (20-25 mg/week) for maintenance after remission achievement with cyclophosphamide in the WEGENT trial [24].
Conventional immunosuppressive drugs were challenged by the MAINRITSAN trial that compared low-dose rituximab in severe GPA-MPA patients at a fixed 500 mg dose at months 6, 6,5,12, and 18 after induction to tapering dose of azathioprine for remission maintenance after induction with pulsed cyclophosphamide [25]. At month 28, rituximab maintenance treatment was superior to azathioprine to prevent relapse. Indeed major relapses occurred in 29% of patients receiving azathioprine group and in 5% of the rituximab group.

2.2.4. Use of Glucocorticoids

Although the glucocorticoids are view as the cornerstone of the induction of MPA and GPA, no consensus exists concerning the initial dose, the tapering and the withdrawal, reflecting the lack of published randomized trial dedicated to address this question [16].
When initiating glucocorticoid therapy, there is disagreement among the experts as to whether therapy should begin with pulse methylprednisolone (7 to 15 mg/kg to a maximum dose of 500 to 1000 mg/day for three days) in all patients or only in those with severe renal or pulmonary involvement [16]. Oral glucocorticoid therapy, either from day 1 or from day 4 if pulse methylprednisolone is given, typically consists of 1 mg/kg per day (maximum of 60 to 80 mg/day) of oral prednisone (or its equivalent) [16]. The 2016 EULAR/ERA-EDTA considered appropriate a target of between 7.5 mg and 10 mg of prednisolone (or equivalent) after 3 months (12 weeks) of treatment [16].
However, a review of the prednisolone protocol reduction regimens published for the key trials by the experts of the 2016 EULAR/ERA-EDTA guidelines illustrated that on average a dose of 10 mg was achieved after 19 weeks, and a dose of 7.5 mg after 21 weeks [16, 18, 20, 23, 25-27]. Therefore, although a target prednisolone dose of 7.5–10 mg is desirable by 3 months, in practice it may be 5 months before this is achieved (Figure 1 – Page 17), reflecting the lack of consensus about the optimal schedule of glucocorticoid administration and withdrawal, with significant difference between USA and Europe (Table 3 – Page 18). The withdrawal of glucocorticoids was not addressed in these guidelines.

Figure 1. Protocol target prednisone dosages in the key induction trials of ANCA associated vasculitides [16].

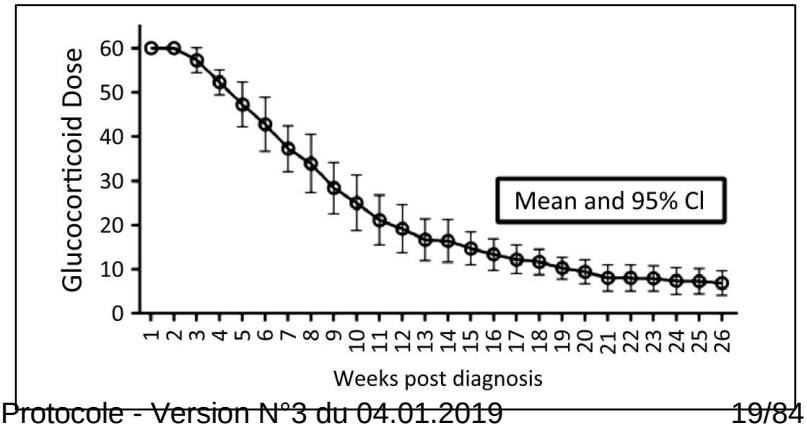
Table 3. Schedules of prednisone tapering in trials conducted in Europe and USA

	CYCAZAREM (Europe)	**WGET** (USA)	**EUVAS IMPROVE** (Europe)	**RAVE** (USA)
Trial duration	Daily dose of prednisone (mg/kg)			Daily dose (mg)
0 weeks	1	1	1	60
1 weeks	0.75	1	0.75	
2 weeks	0.5	1	0.5	
3 weeks	0.4	1	0.5	
4 weeks	0.4	1	0.4	40
6 weeks	0.33	0.66	0.4	30
8 weeks	0.25	0.33	0.3	20
3 months	15	15	15	10
4 months	12.5	8	12.5	5
6 months	10	0	7.5	0
12-15 months	7.5	0	5-2.5	0
15-18 months	5	0	0	0

2.3. Summary of Relevant Pre-clinical Experiments and Clinical Trials

Conventional immunosuppressive therapy and glucocorticoids have been the standard of care for remission induction and maintenance of GPA and MPA for four decades. This regimen has transformed the outcome from death to a strong likelihood of disease control and temporary remission. However, most patients have recurrent relapses that lead to damage and require repeated treatment. Cumulative side effects of immunosuppressive agents and glucocorticoids thus remain major causes of long-term morbidity, damage and death.

Rituximab, an anti-CD20 monoclonal antibody, has been shown to be as effective as cyclophosphamide to induce remission in severe GPA and MPA patients, with an acceptable safety profile, leading to its registration by the EMA and FDA as drug remission-induction therapy in



these patients [19, 20]. Moreover, the recent MAINRITSAN randomized trial showed that rituximab is superior to azathioprine for maintenance of remission with a high percentage of rituximab-treated patients achieving this goal at 30 months (PHRC 2008) [25].

However, although rituximab is becoming the standard of care for maintenance therapy in these patients, relapse still occurs and the optimal duration of prednisone therapy is still debated.

The high relapse rates observed in protocols with very early glucocorticoids withdrawal, such as in the RAVE trial where the objective was glucocorticoids cessation at 6 months [19], has challenged short-term duration of maintenance glucocorticoids.

This question remains a question of high importance because a systematic review and meta-analysis has shown that glucocorticoids regimen was the most significant variable explaining the variability between the proportions of ANCA-associated vasculitis patients with relapses [28]. One the one hand, most US studies use early withdrawal (6-12 months) because of feared side effects [28]. On the other hand, most European trials propose late withdrawal (18-24 months) given a lower observed relapse rate observed on long-term low dose glucocorticoids treatment.

The duration of prednisone is still debated with protocols using early withdrawal (~12 months) and late withdrawal (18-24 months). Because of the lack of randomized trial, the relapse rate according to the length of prednisone administration is indirectly estimated by observational studies or non-dedicated trials [28].
The relapse rate in patients with early glucocorticoids withdrawal (10-12 months) was provided in two studies and was of 37 and 34%, respectively [29, 30]. The relapse rate (severe or non-severe) in patients with late prednisone withdrawal (>18 months) after rituximab maintenance treatment was 16% at 28 months (10 months after last rituximab maintenance infusion) in the MAINRISTAN trial [25]. Of note, the decision to withdraw glucocorticoids after 18 months was left to physician's discretion and two thirds of the non-severe relapses occurred when patients were off prednisone.

Similar results were retrieved from the systematic review and meta-analysis pooling all trials and observational studies according to the length of glucocorticoid treatment. This meta-analysis concluded that combined longer-term (i.e. >12 months) use of low dose prednisone or nonzero glucocorticoids target is associated with a 20% reduction of relapse compared to early withdrawal (i.e. ≤12 months) [28]. The meta-analysis concluded that long-term use of

glucocorticoids after the induction of remission in ANCA-associated vasculitis may significantly alter disease activity and that a randomized controlled trial is now needed to address this question [28].

It has also been shown that sustained remission reduces cumulative damage, morbidity and cumulative drug toxicity, in patients with ANCA-associated vasculitis who otherwise exhibit frequent relapses.

However, long-term administration of glucocorticoid is still debated in regards of the well-known burden of this therapy. A post-hoc analysis of randomized trials reported a relation between longer duration of glucocorticoid and Vasculitis Damage Index, questioning the safety of regimen with long administration of prednisone [31].

Hence the determination of the risks and benefits — especially with regard to infection, osteoporosis, and insulin resistance — of long-term, low-dose prednisone treatment requires further examination in a prospective, controlled study.

2.4. Studied Population Description and Justification for the Choice of Participants

Uncontrolled series and pooled trial arms according length of prednisone administration have suggested that the glucocorticoid duration was the most significant variable explaining the variability of relapse rate in AAV. However, to date, no prospective randomized trial has been designed to confirm this assumption in MPA or GPA patients after achievement of remission.

The administration of rituximab as maintenance therapy strongly modifies the course of AAV. Several trials are ongoing to best administrate rituximab in those patients (MAINRITSAN 2, PHRC 2011 and its extension, MAINRITSAN 3). But no data are available concerning the length of glucocorticoid use in this setting, which may play a major role.

Because of the requirement of the long-term administration of glucocorticoids to control asthma, EGPA patients will be excluded of the scope of this study [32].

Therefore, given the absence of any prospective trial evaluating the optimal length of glucocorticoid administration in maintenance remission of GPA and MPA, conducting such study evaluating the efficacy and safety of extended administration seems necessary to improve the management of these patients.

2.5. Identification and Description of the Experimental Medication or Medications

Experimental medication will be the use of the extended administration of prednisone at the daily dose of 5 mg. Prednisone is a synthetic glucocorticoid drug that is used as immunosuppressive drug. This drug is view as the cornerstone of treatment of auto-immune diseases.

2.6. Dosage Description and Justification, Administration Design and Treatment Period.

Patients with newly diagnosed or relapsing MPA and GPA will be randomized at Day 1, after remission achievement at 12 months after vasculitis onset or flare while being treated with rituximab (500-mg fixed low-dose) maintenance therapy every 6 months, in a 1:1 ratio to receive two regimens of long or short prednisone duration. Eligible patients are those in remission and receiving a prednisone dose of 5-10 mg/day at 12 months during the second maintenance rituximab infusion (= Day 1). The patients will have to decrease prednisone daily dose to reach 5 mg daily at Day 1, this tapering ranging from 2 days to 4 weeks before Day 1 for an initial dose to 5 to 10 mg/d, respectively (*Table 10, page 52*). The randomization will be performed in patients still in remission (BVAS = 0) at Day 1, all receiving prednisone daily dose of 5 mg with two arms:

- **Control regimen:** Prednisone will be tapered of 1 mg/week within 4 first weeks until drug cessation.
- **Experimental regimen:** All patients will receive 5 mg daily prednisone administration for 52 weeks. At Week 52, prednisone will be tapered of 1 mg/week within 4 weeks until drug cessation obtained.

2.7. Foreseeable Benefits and Risks Summary for the Research Participants

Foreseeable benefits are a superior efficacy of extended administration of low-dose prednisone compared to the conventional therapeutic strategy to maintain remission of vasculitis, and an improved outcome with higher rates of complete remission and lower cumulative morbidity in the experimental group.

Foreseeable risks are those associated with toxicity of treatments. The rate of side effects related to low dose prednisone is expected to be low in regards low dose used (<7.5mg/day). In the control group, foreseeable risk linked with prednisone is lower. The rate of major relapse would correspond to at maximum 50% of all the relapses, i.e.an absolute theoretical difference of 10% between both arms.

Risks associated with Prednisone

The glucocorticoids AE are dose-dependent and uncommon with low doses <7.5 mg/day. The most commonly observed AE of prednisone are:

- Immunosuppression: increase of secondary infection (including fungal infection), exacerbation of viral infection, limitation of response to inactivated vaccines, reactivation of latent tuberculosis, dissemination of amebiasis;
- Cardiovascular system: congestive heart failure (in susceptible patients), hypertension;
- Central nervous system: emotional instability, headache, intracranial pressure increased (with papilledema), and psychic derangements (including euphoria, insomnia, mood swings, personality changes, severe depression)
- Skin: bruising, facial erythema, petechiae, thin fragile skin, wound healing impaired;
- Endocrine & metabolic system: adrenal suppression and adrenal crisis, adrenocortical and pituitary unresponsiveness in times of stress, carbohydrate intolerance, Cushing's syndrome, diabetes mellitus, fluid retention, menstrual irregularities, negative nitrogen balance due to protein catabolism, potassium loss, sodium retention;
- Gastrointestinal tract: peptic ulcer (with possible perforation and hemorrhage), ulcerative esophagitis, abdominal distension, pancreatitis, hepatitis;
- Neuromuscular & skeletal system: aseptic necrosis of femoral and humeral heads, muscle mass loss, muscle weakness, osteoporosis, pathologic fracture of long bones, steroid myopathy, tendon rupture (particularly Achilles tendon), vertebral fractures;
- Ocular: glaucoma, intraocular pressure increased, posterior subcapsular cataracts.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of this trial is to compare relapse rate of patients continuing low-dose prednisone treatment until Month 13 versus those who will have prednisone treatment cessation at Month 1, on remission maintenance with rituximab therapy, after achievement of remission of GPA or MPA, defined as patients maintaining a BVAS=0 at Month 30, in patients with newly-diagnosed or relapsing GPA or MPA and who will all have received glucocorticoids for 12 months after diagnosis or last flare before Day 1.

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

Remission will be defined as the absence of disease activity attributable to MPA and GPA vasculitis manifestations (e.g. ENT manifestations, renal involvement, parenchymal lung disease, skin, cardiac, gastrointestinal signs, and peripheral nerve involvement), corresponding to BVAS=0.

Clinical flares attributable to vasculitis activity will be defined as the reoccurrence or new onset of disease attributable to active MPA or GPA. According to EULAR recommendations for conducting clinical studies on systemic vasculitis, relapse will be defined as the re-occurrence or new onset of disease activity attributable to active inflammation. A major relapse will be defined as the re-occurrence or new onset of potentially organ- or life-threatening disease activity that cannot be treated with an increase of glucocorticoids alone and requires further escalation of treatment. All the other relapses will be qualified as minor relapses.

3.2. Secondary Objectives

The secondary objectives of this trial are the following:

- To compare the rate of AE and SAE between Day 1 and Month 30,
- To compare the rate of predefined severe events related to glucocorticoids including osteoporotic fracture and weight gain between Day 1 and Month 30,
- To compare the duration of complete remission, defined as the total accrued duration in week with BVAS=0 between Day 1 and Month 30,
- To compare the rate of minor or major vasculitis relapse between Day 1 and Month 30,
- To compare the side effects related to low dose prednisone by GTI toxicity score between Day 1 and Month 30,
- To compare the prednisone use between Day 1 and Month 30,
- To compare the number of deaths between Day 1 and Month 30,
- To compare variation of the bone mineral density and markers between Day 1 and Month 30,
- To compare weight gain between Day 1 and Month 30,
- To compare sequelae assessed by the Vasculitis Damage Index (VDI), the Combined Damage Assessment (CDA) Index and the vasculitis activity (BVAS score) between Day 1 and Month 30,
- To compare functional disability (HAQ score) and quality of life (SF36) and healthcare resource utilization between Day 1 and Month 30.

For secondary endpoints, AE rate will be assessed, expressed as AE according to the CTCAE toxicity grading system per participant-year.

The duration of complete remission, defined as the total accrued duration in weeks with BVAS=0 will be also assessed using the same parameters as previously described.
The area under the curve for glucocorticoids in the two treatment groups will be analyzed.
Finally, damage, functional disability and quality of life will be assessed using VDI, CDA, HAQ and SF-36 questionnaires during follow-up, respectively.

This trial will be the first prospective, randomized and controlled study evaluating efficacy and safety of extended administration of prednisone to maintain remission in MPA and GPA patients. This study, if it demonstrated a benefit of extended treatment of prednisone compared to conventional therapeutic strategy, would improve the management of patients with MPA and GPA.

4. STUDY ENDPOINTS

4.1. Primary Assessment Criterion

The primary assessment criterion of this trial is to compare relapse rate at Month 30 of patients continuing low-dose prednisone treatment until Month 13 versus those who will have prednisone treatment cessation at Month 1, in GPA and MPA on remission maintenance with low-dose pre-emptive rituximab therapy, after achievement of remission, in relapsing or newly-diagnosed vasculitis.

The maintenance will be defined as GPA and MPA patients maintaining a Birmingham Vasculitis Activity Score (BVAS) = 0 at Month 30.

4.2. Secondary Assessment Criteria

The secondary assessment criteria of this trial are:

- Percentage of patients with at least one AE between Day 1 and Month 30,
- Percentage of patients with at least one minor or major vasculitis flare (BVAS>0) or one predefined severe event corresponding to AE of grade 3 to 5 of the Common Terminology Criteria, including severe side effect related to glucocorticoids (infection requiring hospitalization or intravenous antibiotics, osteoporotic fracture, diabetes requiring medication, cardiovascular event, osteonecrosis, psychiatric or mood disorder requiring drug administration, weight gain >10 kg), between inclusion Day 1 and Month 30
- Percentage of patients with at least one SAE between Day 1 and Month 30 corresponding to any AE that results in death, is life-threatening, requires inpatient hospitalisation or

prolongation of existing hospitalisation, results in persistent or significant disability/incapacity or congenital anomaly/birth defect or any other AE considered "medically significant",

- Percentage of patients with minor (reappearance or worsening of disease with a BVAS >0, not corresponding to a major relapse but requiring mild treatment intensification) or major vasculitis (occurrence or new onset of potentially organ- or life-threatening disease activity that cannot be treated with an increase of glucocorticoids alone and requires further escalation of treatment) between Day 1 and Month 30 (BVAS >0) and time to first vasculitis relapse,
- Variation of GTI toxicity score between Day 1 and Month 30,
- Prednisone area under the curve of administrated dose between Day 1 and Month 30,
- Number of deaths, whatever the cause at Month 30,
- Variation of the bone mineral density between Day 1 and Month 30,
- Weight gain between Day 1 and Month 30,
- Variation of BVAS (vasculitis activity), VDI and CDA (damage), HAQ (disability), SF-36 (quality of life) between Day 1 and Month 30,
- Healthcare resource utilization during the study between Day 1 and Month 30 being defined as the percentage of patients being hospitalized at least once except only for rituximab infusions.

A clinical diagnosis of osteoporosis will be made in the presence of a [33]:

- Fragility fracture, particularly at the spine, hip, wrist, humerus, rib, and pelvis

OR

- T-score ≤-2.5 standard deviations (SD) at any site based upon bone mineral density measurement by dual-energy x-ray absorptiometry

Fragility fractures are those occurring from a fall from a standing height or less, without major trauma such as a motor vehicle accident. Certain skeletal locations, including the skull, cervical spine, hands, feet, and ankles, are not associated with fragility fractures and will not be count as osteoporosis fractures.

Cardiovascular events will included (i) stroke defined as defined as a sudden focal neurologic deficit of presumed cerebrovascular etiology that persisted beyond 24 hours and not due to another identifiable cause and (ii) myocardial infarction defined by percutaneous coronary intervention or coronary artery bypass graft surgery or clinical symptoms and elevated biomarker elevation, Q waves (2 of 3) [34].

5. STUDY POPULATION

Eligibility will be reviewed and documented by an appropriately qualified member of the investigator's team before subjects are enrolled.

The diagnosis of GPA will be based on the revised Chapel Hill nomenclature [1] or the American College of Rheumatology criteria requiring in a patient with an evidence of vasculitis the presence of 2 out of the 4 following criteria:

- Nasal or oral inflammation (painful or painless oral ulcers, or purulent or bloody nasal discharge)
- Abnormal chest radiograph showing nodules, fixed infiltrates, or cavities
- Abnormal urinary sediment (microscopic hematuria with or without red cell casts)
- Granulomatous inflammation on biopsy of an artery or perivascular area

The diagnosis of MPA will be based on the revised Chapel Hill nomenclature corresponding to a necrotizing vasculitis with pauci-immune deposits with the absence of granuloma formation [1]**.**

The patients included in the protocol will have not to fulfill the ACR criteria for EGPA in which 4 out of 6 criteria should be present [15].

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

5.1. Inclusion Criteria

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

- Patients who has been informed about the study and has given his/her written informed consent prior to participation in the study,
- Patients with newly-diagnosed or relapsing MPA or GPA according to the ACR 1990 criteria and/or revised Chapel Hill Consensus Conference definition, independently of ANCA status,
- Patients aged of 18 years or older,
- Patients in remission (BVAS=0) for MPA or GPA achieved with rituximab, cyclophosphamide, or methotrexate,

- Patients who will all have already received glucocorticoids for 12 months ± 2 weeksafter diagnosis or last flare before Day 1.
- Patients having received 500 mg low-dose rituximab maintenance infusion at remission achievement (4 to 6 months after initiation of induction therapy and possibly 15 days after, according to the MAINRITSAN study, so 6 month ± 2 weeks before Day 1,
- Patients receiving from 5 to 10 mg/day prednisone dose within 35 days[1] before Day 1 (=before the third rituximab maintenance infusion).

5.2. Non-Inclusion Criteria

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

- Patients with EGPA, or other vasculitides, defined by the ACR criteria and/or the Chapel Hill Consensus Conference [1],
- Patients with vasculitis with active disease defined as a BVAS >0,
- Patients with acute infections or chronic active infections (including HIV, HBV or HCV),
- Patients with active cancer or recent cancer (<5 years) or myelodysplasia, except basocellular carcinoma and low activity prostatic cancer controlled by hormonal treatment, Pregnant women and lactation. Patients with childbearing potential should have reliable contraception for the total duration of the study,
- Patients with contraindication to use rituximab,
- Patients with other uncontrolled diseases, including drug or alcohol abuse, severe psychiatric diseases, that could interfere with participation in the trial according to the protocol,
- Patients included in other investigational therapeutic study within the previous 3 months excepted for the PNEUMOVAS trial.
- Patients suspected not to be observant to the proposed treatments,
- Patients who have neutrophils cell count ≤1.500 /mm^3,
- Patients who have platelet count ≤100,000/mm^3,
- Patients with severe hypogammaglobulinemia (invasive bacterial or fungal infection with IgG < 5 g/L or IgG < 3 g/L in patients without infection)
- Patients who have ALT or AST level greater than 3 times the upper limit of normal that cannot be attributed to underlying MPA-GPA disease,
- Patients unable to give written informed consent prior to study participation.
- Patients under judicial protection,
- Patient not affiliated to a social security scheme or other social protection scheme.

[1] A Run-in period will be performed to decrease prednisone dose to reach 5mg daily at randomization

5.3. Randomization Criteria

Randomizations criteria have to be validated at Day 1 Visit at the same time as the inclusion and non-inclusion criteria. Will be randomized in the trial patients with the following criteria:

- Patients who have all inclusion criteria;
- Patients without non-inclusion criteria;
- Patient in remission (BVAS = 0) and receiving a Prednisone Dose of 5 mg/day on Day 1;
- Second rituximab maintenance infusion scheduled at Day 1;
- White Blood cells ≥ 4,000/mm3 at Screening;
- Platelets ≥ 100,000/mm3 at Screening;
- Normal hepatic function with;
    - ≤ 3 x ULN ASAT at Screening
    - ≤ 3 x ULN ALAT at Screening
    - ≤ 3 x ULN GGT at Screening
    - ≤ 3 x ULN PAL at Screening
    - ≤ 2 x ULN Total Bilirubin at Screening
- Normal serological results:
    - HIV Negative
    - HBV Negative
    - HCV Positive

6. STUDY DESIGN AND STUDY DRUG REGIMENS

This is a prospective, comparative, randomized, double-blind, placebo controlled, in parallel groups multicenter study in subject ≥ 18 years of age with MPA or GPA comparing 5 mg daily prednisone cessation at Month 1 and at Month 13 during rituximab remission maintenance.
146 subjects will be randomized to 1 of 2 treatment arms as described in Table 4 (page 29).

6.1. Maintenance of Stable Medication Regimen for MPA or GPA:

146 Patients with newly diagnosed or relapsing MPA and GPA will be randomized after remission achievement at 12 months after vasculitis onset or flare while receiving rituximab (500-mg fixed low-dose) maintenance therapy every 6 months in a 1:1 ratio to receive two regimens of long (52 weeks) or short (4 weeks) prednisone duration. Eligible patients are those in remission and receiving a prednisone dose of 5-10 mg/day within 5 weeks before Day 1 which is the visit where the second rituximab maintenance infusion will be performed.
All patient received a standard maintenance treatment with rituximab preemptive low-dose (500 mg) infusions given every 6 month within 18 months. The first rituximab infusion of 500

mg has been given 6 months prior to Day 1, when remission is obtained. One additional 500 mg rituximab infusion may have been given, 15 days after the first maintenance rituximab infusion according to the MAINRITSAN's study, when cyclophosphamide or methotrexate was used as induction therapy. The first rituximab maintenance infusion(s) is(are) followed by 3-low-dose additional rituximab infusions of 500 mg, each administered every 6 months at Day 1, Month 6 and Month 12.

All patients will decrease prednisone daily dose within 5 weeks during a run-in period to reach 5 mg at Day 1 (Table 10 page 52). The randomization Day 1 will be performed in patients still in remission all receiving prednisone daily dose of 5 mg (*BVAS = 0*), within two arms:

- **Conventional arm – Short treatment duration:** Patients will carry out a progressive stop of prednisone (decrease of 1 mg / week during the first 4 weeks of treatment) until stop of the prednisone obtained in M1. Then, they will receive a placebo of prednisone 5 mg up to the end of the 13th month of treatment (M13 visit).
- **Experimental Arm – Long treatment duration:** Patients will receive a daily dose of 5 mg of prednisone for 12 months and then perform a gradual discontinuation of prednisone therapy (decrease of 1 mg per week) for 4 weeks until the end of the 13th month of treatment (M13 visit).

The experimental plan is summarized in **Figure 2** (p31).

6.2. Randomization Method:

Subjects will be randomized to 1 of 2 treatment arms when all inclusion/non-inclusion criteria are met. Subjects will be randomized in 1:1 ratio (prednisone 5mg/day vs 0mg [Placebo]).

6.3. Participation Expected Length, Chronology and Duration Research Description

The duration of participation for each patient will be 30 months (Day 1 to Month 30), whereas the duration of recruitment will be 24 months. Overall, the total duration of the study will be 54 months.

The maximum duration between inclusion and Day 1 will be 35 days. Patients will be randomized at Day 1, and blindness will be effective from Day 1 to the end of the research.

Table 4. Study Duration

Maximum period between inclusion and randomization	35 days
Inclusion period	24 months
The included subject's length of participation, of which :	30 months
- Run-in period	Between 0 to 35 days
- Treatment period	13 months

- Follow-up period	17 months
Total research period	54 months

Start of inclusions: September 2018

As explained in Figure 2 (page 31), this study includes the following periods:

- **Screening Period:** Day -35 to Day -1.
- **Treatment Period:** Day 1 (first IP dose administered) through Month 13.
- **End of Study Visit:** Month 30.
- Early Termination Visit for a subject who discontinues from study drug treatment(s) and who does not complete the remaining assessments in the treatment period.

As soon as the first inclusion, the sponsor must inform the EC and the ANSM without delay, of the effective start date of the study (effective start date = date of the signature of consent by the first person participating in study).

The end date of the study will be sent by the sponsor to the EC and the ANSM within a delay of 90 days. The end date of the study corresponds to the end of the participation of the last person participating in the study.

6.4. Number of Centers Participating

This multicenter research will involve the participation of the French Vasculitis Study Group (FVSG) network, which includes more than 100 clinical departments involved in the management of MPA and GPA.

As previous trials conducting by the FVSG on this topic, 38 centers will participate in the research. Each of the previous trials of the FVSG network have included all patients planned by the protocol and have been published.

6.5. Identification of the Subjects

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

Centre No. (3 numerical positions) - Selection order No. of the person in the centre (3 numerical positions) - surname initial - first name initial.

This reference is unique and will be retained for the entire research period.

A randomization number will be assigned during randomization and a treatment number will be assigned when treatment is allocated.

7. SCHEDULE OF ASSESSMENTS

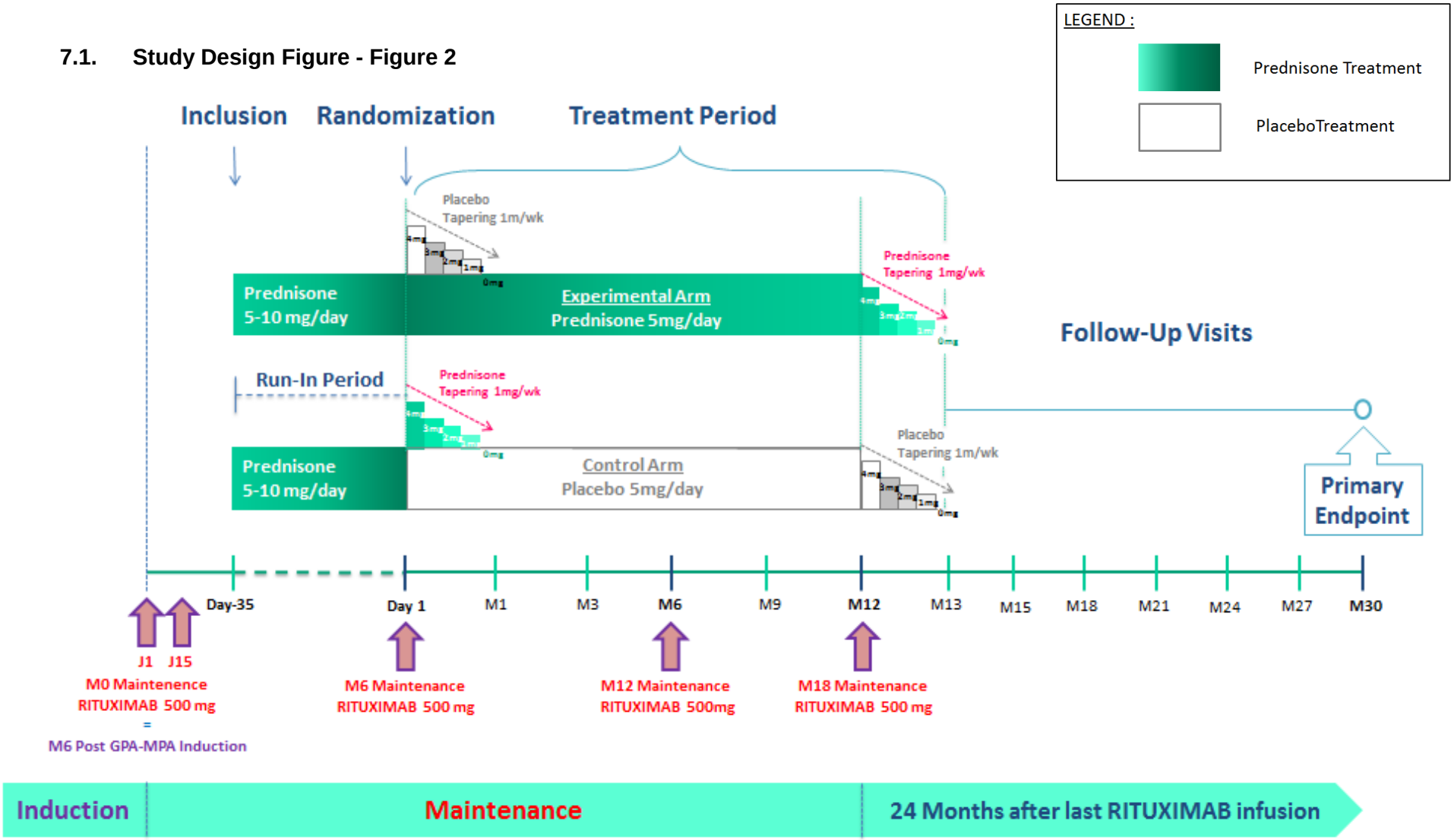
Before any inclusion or acts related to the research, the investigator will collect the informed consent from the patient.

All visits will be performed by physicians involved in the management of MPA and GPA patients, including practitioners from Internal Medicine, Nephrology, Pulmonology or Rheumatology. Visits will take place in hospitalization or consultation according to disease severity and good clinical practices. Experimental plan summarized in **Figure 2** (page 31) indicates where each visit will take place. Please to note that visit Month “x” means at the end of month “x”.

One month of treatment or follow-up lasts 30 days

During the first month after Day 1, visits should be performed +/- 5 days For Month 1, and +/- 10 days for Month 3 and +/- 15 days from Month 6 to Month 30.

7.1. Study Design Figure - Figure 2



7.2. Schedule of Assessments – FlowChart - Table 5

Event/Assessment	Inclusion Screening	Baseline Random.	Follow-Up Visits												Relapse Visit	ETV[2] Visit	SFU Visit
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	**Relapse**	**ETV**	**SFU**
Day / Week	**D-35 to Day-1**	**D1**	**M1**	**M3**	**M6**	**M9**	**M12**	**M13**	**M15**	**M18**	**M21**	**M24**	**M27**	**M30**			28 days after ETV Visit[3]
Window (*in days*)		±3	±5	±10	±15	±15	±15	±15	±15	±15	±15	±15	±15	±15			±7
Consultation Visit	X		X	X		X		X	X	X	X	X	X	X	X	X	X
Hospitalization Visit[4]		X			X		X								X		
Inclusion/Exclusion criteria review	X	X															
Written Informed Consent/assent	X																
Randomization Criteria Review & Randomization[5]		X															
Demographics and disease characteristics	X																
HAQ and SF36 Questionnaires[6]		X				X	X		X			X		X	X	X	
Medical History	X																
Concomitant Medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Osteodensitometry[7]		X					X							X		X	

[2] If the subject prematurely discontinues study treatment, an Early Termination Visit (*ETV*) should be scheduled as soon as possible after the subject decides to terminate study treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 28 days (±*7 days*) after their last dose of study drug. If the ETV occurs following the last dose of study drug, then the ETV will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required.

[3] The SFU visit scheduling is only required if ETV occurs between Day 1 and Month 13.

[4] At Day 1, Month 6 and Month 12, the patient will be hospitalized to receive rituximab infusion maintenance.

[5] Randomization must occur after all inclusion and non-inclusion criteria are met and before the first dose of study drug. Randomization will be done through CLINSIGHT and may occur on Day -1.

[6] The HAQ and SF-36 must be completed before the start of any other assessments scheduled for that visit.

[7] Osteodensitometry is performed to assess bone mineral density assessed at D1, Month 12, Month 30 and if needed at ETV Visits. Bone mineral density is assessed through this exam.

Event/Assessment	Inclusion Screening	Baseline Random.	Follow-Up Visites												Relapse Visit	ETV[8] Visit	SFU Visit
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14			
Day / Week	D-35 to Day-1	D1	M1	M3	M6	M9	M12	M13	M15	M18	M21	M24	M27	W120	Relapse	ETV	SFU
Window (*in days*)		±3	±5	±15	±15	±15	±15	±15	±15	±15	±15	±15	±15	±15			± 7
Imaging tests[9]	Continuous from signing of ICF (*and assent form if applicable*) through Safety Follow-up Visit																
Height and weight[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Standard 12-lead ECG[11]	X														X	X	X
Complete Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BVAS, CDA, VDI & GTI Questionnaires[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum β-hCG[13] & Serum FSH[14]	X																
Serology (HIV, BHV, CHV)	X																
Blood samples[15]	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Bank Collection[16]		X					X					X		X	X	X	
Urinalysis	X	X		X	X	X	X		X	X	X	X	X	X	X	X	X
Dispense prednisone handset		X	X	X	X	X	X										
Prednisone Drug Count			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Notebook Delivery		X	X	X	X	X	X										
AE and SAE review		Continuous from signing of ICF (*and assent form if applicable*) through Safety Follow-up Visit															

[8] If the subject prematurely discontinues study treatment/or the study, an Early Termination Visit (*ETV*) should be scheduled as soon as possible after the subject terminate study treatment/or study. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 28 days (±*7*) days after their last dose of study drug. If the ETV occurs following after the last dose of study drug, then the ETV will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required.

[9] Imaging tests (*Chest X-ray, Thoracic CT-Scan and Echocardiography*) performed less than 1 month before Inclusion must be recorded in e-CRF (*if applicable*).

[10] Weight and height will be measured with shoes off. The height is only measured at Inclusion

[11] A standard 12-lead ECG will be performed after the subject has been supine for at least 5 minutes.

[12] Every questionnaires will be perform at each visit except CDA, VDI and GTI which not be perform at Inclusion Visit.

[13] All female of childbearing potential must have a serum pregnancy test.

[14] FSH will be measured for any suspected postmenopausal female with at least 12 months of continuous spontaneous amenorrhea. Serum FSH levels must be ≥40 mIU/mL to be considered postmenopausal.

[15] Blood samples contain Hematology, Serum chemistry, Serum Protein Electrophoresis & Immunology tests. Every samples detail is notified in Table 8. Safety Laboratory Test Panel.

[16] Serum Bank and Plasma Bank will be collected at Day 1, Month 12, Month 24, Month 30 and if needed at ETV and Relapse visits. DNA Bank will only be collected at Day 1.

7.3. Screening Visit

Screening will occur before inclusion to confirm that subjects meet the selection criteria for the study. The subject will be granted a reflection period of one day between the time when the subject receives the information and the time when he or she signs the consent form. During the Screening Visit, it should be determined whether the subject will be included and will have a Run-in Period.

The Screening Visit will include:

- Inclusion/Non-Inclusion criteria review;
- Written Informed consent and assent (*where applicable*) obtained by the investigator (*or an appropriate authorized designee at the study* site) from each subject;
- Demographics and disease characteristics;
- Medical history, including medication use;
- Complete physical exam;
- Imaging tests recording (*Chest X-ray, Thoracic CT-Scan, Echocardiography*) performed in the previous month as appropriate according to clinical assessment and patient history;
- BVAS questionnaires;
- Height, weight;
- Standard 12-lead ECG;
- Blood sample collection (30 mL will be taken) with:
    - Serum β-HCG for any female of childbearing potential;
    - Serum FSH for any suspected postmenopausal female with at least 12 months of continuous spontaneous amenorrhea. Serum FSH levels must be ≥40 mIU/mL;
    - Hematology with hemogram;
    - Chemistry:

Complete serum ionogram	Phosphoremia	C-Reactive Protein (CRP)
Glycaemia	LDH	Liver enzymes (ASAT, ALAT, PAL, BIL)
Calcemia	Creatinine	CPK

    - Coagulation with Prothrombine Time (PT) and Partial Thromboplastin Time (PTT);
    - Immunochemistery with serum protein electrophoresis;
    - Serology (HIV, HBV and HCV serological tests);
    - Immunology with CD4+, CD8+, CD19+ and ANCA (IF and ELISA tests)
- Urinalysis: urine test strip (for the search of microscopic blood microscopic haematuria, Glucose, Leukocytes esterase, Nitrites, and Proteins), , and glucose, proteinuria/creatinuria index in case of abnormality of strip;

- Blood tests to check for inclusion and non-inclusion criteria and to determine disease severity assessed by the ANCA status at 12 months after vasculitis onset or flare;
- Concomitant medication review.

At Inclusion, all patients should have a prednisone dose between 5 and 10 mg/day to be decreased to 5 mg/day at Day 1 (*see Table 10, page 52*). Patients receiving prednisolone before the Run-in period must be switched for prednisone with a 1:1 ratio.

7.3.1. Repetition of Screening Assessment(s)

Repetition of individual screening assessment(s) that did not meet eligibility criteria is not permitted with the following exception:

- If there is a clear evidence of a laboratory error (e.g hemolyzed sample) or equipment malfunction, collection of a repeat sample for the appropriate laboratory test or assessment may be permitted with the approval of the coordinating investigator.
- If repeat values of the individual assessment(s) are within the eligibility criteria and completed within the screening window, then the subject is eligible for the study.

7.3.2. Rescreening Visit

Subject may be rescreened after discussion with, and approval from the coordinating investigator. If a subject is rescreened, all Screening Visit assessment will be repeated except for Follicle-stimulating hormone (FSH) level if serum FSH level was ≥40 mIU/mL during prior screening.

Subject may only be rescreened once. If a subject is rescreened, the screening window will begin once the first rescreening assessment has been initiated.

7.4. Inclusion Visit and Run-in Period Visit

The Run-in Period will start after the screening and will occur between Day-35 to Day-1 for subject with a prednisone dose between 5 and 10 mg/day

The Run-in period is the period between Screening and Day 1. During this period, every patient will be treated with commercially available prednisone (5-10 mg/day) as usually prescribed and must follow a tapering within 5 weeks to reach a baseline dose of 5 mg/day at Day 1. Prednisone treatment used during Run-in period visit will not be provided by the sponsor.

Table 6 Run-in Period Subject Assignment

Prednisone treatment dosing at Screening Visit	Run-in Period needed?
5 mg/day	No, a Randomization visit can directly be plannified soon as possible after Screening Visit.
6 mg/day	Yes, subjects will take their own commercial prednisone from screening to Day 1 respecting dose mentioned in Table 10 – Schedule of prednisone administration and tapering according to arms of randomization (page 52).
7 mg/day	
8 mg/day	
9 mg/day	
10 mg/day	

The last dose of commercially available prednisone will be the morning day before the Day 1.

7.5. Day 1 - Randomization Visit (±3 jours)

At Day 1, subjects will take the sponsor provided prednisone Handset obtained after randomization on CLINSIGHT software.

Day 1 will include:

- Inclusion / Non-Inclusion criteria review;
- Randomization criteria review;
- SF36 and HAQ patient questionnaires;
- Complete physical exam to collect manifestations related to active MPA or GPA;
- Bone mineral density assessed by osteodensitometry;
- BVAS, CDA, VDI and GTI Questionnaires;
- Concomitant medication review;
- Weight;
- Blood sample test (46 mL will be taken) with:
  - Hematology with hemogram;
  - Chemistry:

Complete serum ionogram	Phosphoremia	C-Reactive Protein (CRP)	LDH
Glycaemia	Liver enzymes (ASAT, ALAT, PAL, BIL)		NT-pro-BNP
Calcemia	Creatinine	CPK	Troponin

  - Coagulation with Prothrombine Time (PT) and Partial Thromboplastin Time (PTT);
  - Immunochemistry with serum protein electrophoresis;
  - Immunology:

CD4+cells	CD19+ cells
CD8+ cells	ANCA using immunofluorescence and ELISA

- Serum (6 mL), Plasma (6 mL) and DNA bank (12 mL)

- Urinalysis: urine test strip (for the search of search of microscopic blood microscopic haematuria, Glucose, Leukocytes esterase, Nitrites, and Proteins), , and glucose, proteinuria/creatinuria index in case of abnormality of strip;
- Prednisone handset dispensation;
- Patient notebook delivery
- The second rituximab 500 mg infusion maintenance, i.e. 12 months after MPA or GPA remission.

7.6. Follow-up visits (FU)

Follow-up visits will take place at Month 1, Month 3, Month 6, Month 9, Month 12, Month 13, Month 15, Month 18, Month 21, Month 24, Month 27 and Month 30. Dates of each visit will be planned by the protocol, with a margin of +/- 5 days for Month 1+/- 10 days for Month 3 and ± 15 days from Month 6 to Month 30. The third and the fourth rituximab 500mg infusion maintenance will be performed at Month 6 and Month 12 visits, i.e 18 and 24 months after MPA or GPA remission.

Follow-up visits will include:

- SF36 and HAQ patient questionnaires only must be completed at Month 9, Month 12, Month 15, Month 24 and Month 30;
- Osteodensitometry only must be performed at Month 12 and Month 30;
- Weight at each follow-up visits;
- Complete physical examination to collect manifestations related to active GPA or MPA activity or remission at each follow-up visit;
- BVAS, CDA, VDI and GTI questionnaires only must be completed at each follow-up visits;
- Blood sample test[17] at each follow-up visits except Month 13 with:
  - Hematology with hemogram,
  - Chemistry with simple ionogram (sodium, potassium), C-reactive protein (CRP), Creatinine, Glycaemia, Liver enzyme (ASAT,ALAT) :
  - Immunochemistry with serum protein electrophoresis,
  - Immunology with CD4+, CD8+, CD19+ cells and ANCA using immunofluorescence and ELISA.
- Serum and Plasma bank will be collected at Month 12, Month 24 and Month 30.
- Urinalysis: urine test strip (for the search of search of microscopic blood microscopic haematuria, Glucose, Leukocytes esterase, Nitrites, and Proteins), and glucose,

[17] 14 mL of blood will be taken at each follow up visit with the exception of Week 48, Week 96 and Week 120 where 26mL will be taken with Serum and Plasma Bank collection.

proteinuria/creatinuria index in case of abnormality of strip. This analysis will be made at Month 1, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, Month 21, Month 24, Month 27 and Month 30;

- Concomitants medication review at each follow-up visits;
- Prednisone Handset Dispensation at Month 1, Month 3, Month 6, Month 9 and Month 12;
- Patient notebook delivery at Month 1, Month 3, Month 6, Month 9 and Month 12
- Prednisone Drug count at Month 1, Month 3, Month 6, Month 9, Month 12 and Month 13;
- AEs and SAEs review et each follow-up visits;
- e-CRF data completion at each follow-up visits.

Visit 14 (Month 30) is the last scheduled visit except in the case of early termination

7.7. Relapse Visit

A subject for whom a GPA or MPA relapse occurs is required to complete a Relapse Visit, which is to be scheduled as soon as possible.

The Relapse Visit will include:

- SF36 and HAQ patient questionnaires;
- Weight;
- Standard 12-lead ECG;
- Complete physical exam that notices how is treated the relapse;
- Imaging tests recording (*Chest X-ray, Thoracic CT-Scan, Echocardiography*);
- BVAS, CDA and VDI and GTI questionnaires;
- Blood tests (34mL will be taken) with:
    - Hematology with hemogram;
    - Chemistry:

Complete serum ionogram	Phosphoremia	C-Reactive Protein (CRP)	LDH
Glycaemia	Liver enzymes (ASAT, ALAT, PAL, BIL)		NT-pro-BNP
Calcemia	Creatinine	CPK	Troponin

    - Coagulation with Prothrombine Time (PT) and Partial Thromboplastin Time (PTT);
    - Immunochemistry with serum protein electrophoresis;
    - Immunology:

CD4+cells	CD19+ cells
CD8+ cells	ANCA using immunofluorescence and ELISA

- Serum and Plasma bank;

- Urinalysis: urine test strip (for the search of search of microscopic blood microscopic haematuria, Glucose, Leukocytes esterase, Nitrites, and Proteins), , and glucose, proteinuria/creatinuria index in case of abnormality of strip;
- Concomitants medication review;
- Prednisone Drug counts if applicable.
- AEs and SAEs review;
- e-CRF data completion;

7.8. Early Termination Visit (ETV)

A subject who discontinues from study drug treatment/study is required to complete an ETV Visit, which is to be scheduled as soon as possible after it is confirmed that the subject does not intend to complete the remaining assessment.

If the subject withdraws consent for the study, no further evaluations should be performed and no additional data should be collected.

The Early termination of Treatment visit will include:

- SF36 and HAQ patient questionnaires;
- Bone mineral density assessed by osteodensitometry;
- Weight;
- Standard 12-lead ECG;
- Complete physical exam;
- BVAS, CDA and VDI and GTI questionnaires, GTI toxicity score;
- Blood tests (34 mL will be taken) with:
    - Hematology with hemogram;
    - Chemistry:

Complete serum ionogram	Phosphoremia	C-Reactive Protein (CRP)	LDH
Glycaemia	Liver enzymes (ASAT, ALAT, PAL, BIL)		NT-pro-BNP
Calcemia	Creatinine	CPK	Troponin

    - Coagulation with Prothrombine Time (PT) and Partial Thromboplastin Time (PTT);
    - Immunochemistry with serum protein electrophoresis;
    - Immunology:

CD4+cells	CD19+ cells
CD8+ cells	ANCA using immunofluorescence and ELISA

- Serum and Plasma bank;

- Urinalysis: urine test strip (for the search of search of microscopic blood microscopic haematuria, Glucose, Leukocytes esterase, Nitrites, and Proteins), , and glucose, proteinuria/creatinuria index in case of abnormality of strip;
- Concomitants medication review;
- Prednisone Drug count if applicable;
- AEs and SAEs review;
- e-CRF data completion.

If the subject prematurely discontinues study treatment/or the study, an Early Termination Visit (ETV) should be scheduled as soon as possible after the subject terminates study treatment/or study. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 28 days (±7) days after their last dose of study drug. If the ETV occurs following after last dose of study drug, then the ETV will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required.

7.9. Safety Follow-Up Visit (28 ± 7 days after ETV Visit)

The SFU visit scheduling is only required if ETV occurs between Day 1 and Month 30. The Safety Follow-up visit will take place 28 days ± 7 days after Early Treatment Visit (ETV) and will include:

- Complete physical examination to collect manifestations related to active GPA or MPA activity or remission;
- Weight;
- Standard 12-lead ECG;
- BVAS CDA, VDI and GTI questionnaires;
- Blood tests (22 mL will be taken) with:
    - Hematology with hemogram;
    - Chemistry:

Complete serum ionogram	Phosphoremia	C-Reactive Protein (CRP)	LDH
Glycaemia	Liver enzymes (ASAT, ALAT, PAL, BIL)		NT-pro-BNP
Calcemia	Creatinine	CPK	Troponin

    - Coagulation with Prothrombine Time (PT) and Partial Thromboplastin Time (PTT),
    - Immunochemistry with serum protein electrophoresis;
    - Immunology:

CD4+cells	CD19+ cells
CD8+ cells	ANCA using immunofluorescence and ELISA

- Urinalysis: urine test strip for the search of microscopic blood, glucose, leukocytes esterase, nitrites, and proteins, microscopic hematuria, and proteinuria/creatinuria index.
- Concomitants medication review;
- AEs and SAEs review;
- e-CRF data completion.

7.10. Distinction between care and research

Table 7. Distinction between procedures associated with "care" and procedures added because of the "research"

Procedures and treatments carried out as part of the research	Procedures and treatments associated with <u>care</u>	Procedures and treatments added because of <u>the research</u>
Treatments	Glucocorticoids Rituximab	Placebo according to randomization Placebo tapering schedule
Consultations	Every 3 month during maintenance treatment	None
Blood samples	Hemogram, renal function, liver tests, glycaemia proteinuria, hematuria, ANCA,	β-HCG, FSH, calcemia, phosphoremia, , troponin, NT-pro-BNP, HIV, HBV and HCV serology DNA samples (12mL of blood) Serum and plasma bank
Imaging	Osteodensitometry Chest X-ray Thoracic CT-scan Echocardiography Electrocardiogram Cardiac MRI according to clinical presentation	None
Others		SF-36 and HAQ Questionnaires

8. GUIDELINES FOR STUDY PROCEDURES

8.1. Administration of Questionnaires HAQ and SF-36

HAQ and SF-36 questionnaire must be performed before any other assessment (blood collection, urine samples, etc…). HAQ and SF-36 will be administered by the site staff.

8.2. Imagery

8.2.1. Bone Mineral Density assessed by Osteodensitometry

An osteodensitometry exam will be performed at Day 1, Month 12, Month 30 and at ETV. In addition, every effort should be made to have the Month 12 and Month 30 osteodensitometry performed at the same time of day as the D1 ±3 hours. The radiation dose per osteodensitometry is estimated to be on the order of 0.5 to 4 microsieverts (µSv).

8.2.3. Imaging tests (chest X-ray, thoracic CT-Scan, echocardiography)

Imaging tests (Chest X-ray, Thoracic CT-Scan, Echocardiography) performed after randomization must be recorded (if applicable) in e-CRF. These tests will be prescribed according to the physician judgment.

8.3. Adverse Events

See Section 12 (page 58).

8.4. Subject and Disease Characteristics

Subject and disease characteristics include the following: demographics, medical history, height, weight. For information, Body Mass Index is calculated as follows: Weight (kg)/ Height $(m)^2$.

Medical history will be elicited from each subject during screening. Based on the medical history, the subject will be assessed for any disqualifying medical conditions as specified in the inclusion and exclusion criteria. The medical history shall include a complete review of systems, past medical and surgical histories, and any allergies.

8.5. Standard 12-lead ECG

Standard 12-lead ECGs will be performed using a machine with printout at Screening visit, Relapse visit, ETV and SFU if applicable. Additional standard 12-lead ECGs will be performed at any other time if clinically indicated.

8.6. Complete Physical Examination

Complete physical examination will be performed by a licensed health care provider of, at a minimum, the following systems: Skin, head, ears, eyes, nose and throat, respiratory, cardiovascular, gastrointestinal, neurological, musculoskeletal, and lymphatic systems. Breast, anorectal and genital examinations will be performed when medically indicated. After screening, any clinically significant abnormal findings in physical examinations will be reported as AEs.

8.7. Clinical Questionnaires

8.7.1. BVAS Questionnaires

BVAS Questionnaires must be performed by the investigator or a licensed health care provider at each visit.

8.7.2. CDA Questionnaires

CDA Questionnaires must be performed by the investigator at each visit except Screening.

8.7.3. VDI Questionnaires

VDI Questionnaires must be performed by the investigator at each visit except Screening.

8.7.4. GTI toxicity score

GTI Questionnaires must be performed by the investigator at each visit except Screening.

8.8. Clinical Laboratory Assessment - Blood and Urine Samples

Blood and urine samples will be analyzed in each participating center's laboratories.
Blood and urine samples for clinical laboratory assessments will be collected as shown in Flow Chart (Table 5 p.32). Laboratory test results that are abnormal and considered clinically significant will be reported as AEs. The safety laboratory test panels are shown in Table 8 below.

Table 8. Safety Laboratory Test Panels

Serum chemistry	Complete serum ionogram	CPK
	Calcemia	CRP
	Phosphoremia	Troponin
	Glycemia	LDH
	Liver Enzymes (ASAT, ALAT, PAL, BIL)	NT-pro BNP
	Creatinin Renal Function	
Hematology	Hemogram	
Coagulation	PT, PTT	
Immunochemistry	Serum Protein Electrophoresis	
Immunology	CD4+, CD8+, CD19+ and ANCA using immunofluorescence and ELISA	
Urinalysis	Urine test strip for the search of microscopic blood, glucose, leukocytes esterase, nitrites, and proteins, microscopic hematuria, and proteinuria/creatinuria index.	

Additional clinical laboratory evaluation will be performed at other times if judged to be clinically appropriate.

8.8.1. Serum Pregnancy Test (β-human Chorionic Gonadotropin) for Female Childbearing Potential

A serum pregnancy test (β-hCG dosing) will be obtained at Screening and analyzed in each participating centers. If the serum pregnancy test is positive, rituximab administration will be stopped, the pregnancy will be reported and the subject will be permanently withdrawn from the study.

Participation in this study requires a commitment from the subject to use at least 1 acceptable method of contraception, which must be used correctly with every act of sexual intercourse.

Subjects will be counseled to inform the investigator of any pregnancy that occurs during study. If a subject becomes pregnant while participating in the study, study drug must be permanently discontinued immediately. This investigator must notify the sponsor within 24 hours of the site's knowledge of the subject's pregnancy using the Pregnancy Information Collection Form.

8.8.2. FSH Test for Post-menopausal Female

Blood sample for FSH will be measured at Screening only for any potentially postmenopausal female with at least 12 months of continuous spontaneous amenorrhea. Serum FSH levels must be ≥ 40 mIU/mL to be considered post-menopausal.

8.8.3. Hematology

Hematology must contain Hemogram and will be performed at Screening, Day 1, Month 1, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, Month 21, Month 24, Month 27, Month 30, Relapse, ETV, and SFU visits.

8.8.4. Serum Chemistry

Serum Chemistry must contain complete serum ionogram, calcemia, glycaemia, phosphoremia, liver enzymes tests (Alkaline Phosphatase, ALT, AST, GGT, Bilirubin total), CPK, Troponin, Renal Function Tests (Creatinine), CRP, LDH, NT-pro-BNP. Every serum chemistry will be performed at Screening, Day 1, Month 1, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, Month 21, Month 24, Month 27, Month 30, Relapse, ETV, and SFU visits.

8.8.5. Coagulation

Coagulation tests must contain Prothrombin Time (PT) and Partial Thromboplastin Time (PTT) and will be realized at Screening, Day 1, Month 1, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, Month 21, Month 24, Month 27, Month 30, Relapse, ETV, and SFU visits.

8.8.6. Immunochemistry

Immunochemistry consists to make a serum protein electrophoresis. This sample will be collected at Screening, Day 1, Month 1, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, Month 21, Month 24, Month 27, Month 30, Relapse, ETV, and SFU visits.

8.8.7. Immunology

Immunology tests must contains CD19+, CD4+, CD8+, ANCA using immunofluorescence and ELISA. This sample will be collected at Screening, Day 1, Month 1, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, Month 21, Month 24, Month 27, Month 30, Relapse, ETV, and SFU visits.

8.8.8. Serology

Serology consists to make HIV, HBV and HCV tests. This sample will be collected only at Screening.

8.9. Bank Collections

Samples (*serum bank, plasma bank and DNA bank*) taken as part of the research will be included in a biological collection. Each tube will be labeled with study number, patient initials, patient's study number, and date and time of sample collection.
The collections will be stored at Cellular Biotechnology Laboratory (Groupe Hospitalier Est, HCL) under the supervision of Dr Isabelle Rouvet for an unlimited duration.

8.9.1. Serum Bank

6 ml of blood will be collected (at Day1, Month 12, Month 24, Month 30, Relapse and ETV) and centrifuged, with serum extraction that will be aliquoted into 2 ml cryotubes and stored at -80°C by the investigator center. Transportation and delivery of serum banks will be conducted

in dry ice to the Cellular Biotechnology Laboratory (Groupe Hospitalier Est), at the end of patients Follow-up in each participating centers.

8.9.2. Plasma Bank

6 ml of blood will be collected (at Day1, Month 12, Month 24, Month 30, Relapse and ETV) and centrifuged, with plasma extraction that will be aliquoted into 2 ml cryotubes and stored at -80°C by the investigator center. Transportation and delivery of plasma banks will be conducted in dry ice to the Cellular Biotechnology Laboratory (Groupe Hospitalier Est), at the end of patients follow-up in each participating centers.

8.9.3. DNA bank

12 ml of blood will be collected at Day 1 only, stored at room temperature and immediately transported at room temperature to the Cellular Biotechnology Laboratory (Groupe Hospitalier Est). At this laboratory patients DNA will be extracted.

The biobank samples will be used with the explicit agreement of the subject on the consent form for further analyses not included in the protocol but that could be beneficial for the scientific knowledge and the management of the disease.
At the end of the research, the samples will be preserved for an unlimited duration. The collection will be declared to the minister responsible for research and to the director of the regional health authority with local jurisdiction (Article L.1243-3 of the CSP (French Public Health Code)).

Table 9 – Biobank Management (Laboratory)

Type of sample	Quantity	Storage location	Collection supervisor	Purpose of the collection	Storage conditions	Storage period	Outcome (destruction, etc.)
DNA	12 ml at D1	Groupe Hospitalier Est (HCL)	Dr Isabelle Rouvet	Scientific knowledge	-80°C	Unlimited	Storage
Serum	6 ml at D1, M12, M24, M30, Relapse and ETV	Groupe Hospitalier Est (HCL)	Dr Isabelle Rouvet	Scientific knowledge	-80°C	Unlimited	Storage
Plasma	6 ml at D1, 12, 24, M30, Relapse and ETV	Groupe Hospitalier Est (HCL)	Dr Isabelle Rouvet	Scientific knowledge	-80°C	Unlimited	Storage

8.10. Urinalysis

Urines samples will be collected at Screening, D1, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, Month 21, Month 24, Month 27, Month 30, Relapse, ETV and SFU if needed. Urinalysis will be made by urine test strip (for the search of microscopic blood,

glucose, leukocytes esterase, nitrites, and proteins), microscopic hematuria, and proteinuria/creatinuria index.

9. TERMINATION RULES

9.1. Subjects Removal: Prematurely Treatment Termination Criteria and Methods

Different situations for the removal of a subject in the study are listed below:

- If temporary termination of treatment, the investigator must document the reason for stopping and restarting the treatment in the subject's source file and the electronic case report form (CRF)
- If premature termination of treatment, but the subject is still included in the research, until the end of the subject's participation, the investigator must document the reason in the subject's source file and the electronic case report form (CRF). An unplanned dose decrease may be organized at the clinician's discretion if he/she considers it appropriate. The reason of the unplanned dose decrease must be documented in the subject source file and the electronic case report form (CRF). Double blind could be interrupt upon request of investigator to aid corticosteroids management.
- If premature termination of treatment and end of participation in the research.

The investigator must:

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

- Il premature termination of study once treatment completed, the investigator must :
  - Document the reason(s);
  - Collect the assessment criteria when participation in the research ends, if the subject agrees.

9.2. Criteria and Methods for Temporary or Permanent Discontinuation

Criteria for the premature termination of the research are listed below:

- Any subject may be withdrawn from the study at any time at their own request and for any reason. In case of premature termination, the investigator must document the reasons as thoroughly as possible.
- If a subject has been withdrawn from study drug treatment, the subject will continue to be followed, provided the subject has not withdrawn consent.

If a subject is lost to follow-up, the investigator will make every effort to contact the subject to at least know if the subject is alive or dead. If a subject does not return for a scheduled visit, every effort will be made to contact the subject. In any circumstance, every effort will be made to document subject outcome. The investigator will inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a SFU visit, if applicable, and follow-up with the subject regarding any unresolved AEs.

In the event of a withdrawal of consent, the data collected up to the date of withdrawal will be analyzed.

A subject will be withdrawn from study treatment for any of the following reasons:

- Regulatory Authorities, or the site's institutional review board (IRB) or independent ethics committee (IEC) close the study.
- Development of a life-threatening AE or a SAE that places him/her at immediate risk, and discontinuation of study treatment deemed necessary.

A subject may be withdrawn from study treatment after a discussion between the Investigator and Investigator Coordinator for any of the following reasons:

- Development of a medical condition that requires prolonged concomitant therapy with a prohibited medication or prolonged interruption of the study drug.
- Noncompliance with study requirements.

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

- ☐ Ineffective (vasculitis relapse)
- ☐ Adverse reaction
- ☐ Other medical problem
- ☐ Subject's personal reasons
- ☐ Explicit withdrawal of consent
- ☐ Lost to follow-up

9.3. Follow-up of the Subjects after the Premature Termination of Treatment

Ending a subject's participation does not affect the normal management of the subject's illness in any way.

9.4. Subject Replacement

Subjects who withdraw or are withdrawn during the Screening periods will be replaced by another subject. Subject who withdraw or are withdrawn during the study drug Treatment Period will not be replaced.

9.5. Terminating part or all of the Research

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

- First of all, in the event of unexpected serious adverse reactions requiring a review of the characteristics of the strategy.
- Likewise, unexpected facts, new information about the product, or the method of investigation in light of which the objectives of the research or of the clinical program are unlikely to be achieved, can lead the HCL as sponsor or the Competent Authority (ANSM) to prematurely halt the research the HCL as sponsor reserves the right to permanently suspend inclusions at any time if it appears that the inclusion objectives are not met.

If the research is terminated prematurely, the sponsor (HCL) will give the decision and justification to the Competent Authority (ANSM) and to the CPP within 15 days, along with recommendations from the Data and Safety Monitoring Board.

10. STUDY DRUG ADMINISTRATION AND MANAGEMENT

10.1. Description of the Non Experimental Medications

10.1.1. Identification: prednisone (commercial)

Administration*:*

The patients in remission and receiving a prednisone dose of 5-10 mg/day within 5 weeks before Day 1 will have to decrease prednisone daily dose to reach 5 mg daily at Day 1. Day 1 is the visit where the second 500 mg rituximab maintenance infusion will be performed. During this period between Screening and Day 1, every patient will be treated with commercially available prednisone.

Predefined prednisone tapering schedule will be done according to initial dose of prednisone at screening (5-10mg/day) in order to achieve a daily dose of 5 mg/d at randomization within a maximum period of 5 weeks (**Table 10 Page 50**).
The last dose of commercially available prednisone will be the morning day before Day 1. Study drug will start administered at Day 1.

10.1.2. Identification : rituximab/ MabThera®

Administration:

Patients in experimental and non-experimental arms will receive 4 low-dose 500 mg pre-emptive maintenance rituximab infusions at 6, 12, 18, and 24 months after the diagnosis or flare as standard maintenance treatment, which correspond to M-6 before Day1, to Day 1, Month 6 and Month 12, according to the 2016 EULAR/ERA-EDTA guidelines and the MAINRISTAN study.
Premedication protocol using 100 mg methylprednisolone, paracetamol (acetaminophen) and dexchlorpheniramine will be administered at Day 1 and at Month 6 and Month 12.
Contra-indications, route of administration, side effects and restrictions to use are described in Summary of Product Characteristics (Annexe 10).
Rituximab (non-experimental drug) is not provided by Sponsor.

10.2. Description of the experimental drug

10.2.1. Product

Identification: prednisone 5 mg, 4 mg, 3 mg, 2 mg, 1 mg (for clinical trial) or placebo

Form: capsule

Composition: Prednisone capsules are prepared from prednisone micronised powder (provided by INRESA, France) and microcrystalline cellulose (provided by COOPERATION PHARMACEUTIQUE FRANCAISE, France). Placebo capsules are only composed of microcrystalline cellulose.

VERUM		
Prednisone 5 mg capsule	*Prednisone micronized 5 mg*	*5 mg*
	Excipient: microcrystalline cellulose	*s.q.f one capsule*
Prednisone 4 mg capsule	*Prednisone micronized 4 mg*	*4 mg*
	Excipient: microcrystalline cellulose	*s.q.f one capsule*
Prednisone 3 mg capsule	*Prednisone micronized 3 mg*	*3 mg*
	Excipient: microcrystalline cellulose	*s.q.f one capsule*
Prednisone 2 mg capsule	*Prednisone micronized 3 mg*	*2 mg*
	Excipient: microcrystalline cellulose	*s.q.f one capsule*
Prednisone 1 mg capsule	*Prednisone micronized 3 mg*	*1 mg*
	Excipient: microcrystalline cellulose	*s.q.f one capsule*

PLACEBO		
Placebo of prednisone 5 mg capsule	*Excipient: microcrystalline cellulose*	*s.q.f one capsule*
Placebo of prednisone 4 mg capsule	*Excipient: microcrystalline cellulose*	*s.q.f one capsule*
Placebo of prednisone 3 mg capsule	*Excipient: microcrystalline cellulose*	*s.q.f one capsule*
Placebo of prednisone 2 mg capsule	*Excipient: microcrystalline cellulose*	*s.q.f one capsule*
Placebo of prednisone 1 mg capsule	*Excipient: microcrystalline cellulose*	*s.q.f one capsule*

The experimental drug will be prednisone 5 mg, 4 mg, 3 mg, 2 mg, 1 mg capsules, and its placebo, in a specific conditioning for patient treatment box:

- **Prednisone 4 mg, 3mg, 2 mg, 1 mg or placebo weekly decreasing kit:**

Weekly decreasing kit is a numbered treatment kit consisting of 4 brown pillboxes (75 mL) of 7 prednisone / placebo capsules:

- Pill box A: 1 pillbox of 7 white-red prednisone 4 mg or placebo capsules
- Pillbox B: 1 pillbox of 7 white-blue prednisone 3 mg or placebo capsules
- Pill box C: 1 pillbox of 7 white-green prednisone 2 mg or placebo capsules
- Pill box D: 1 pillbox of 7 white-yellow prednisone 1 mg or placebo capsules

Weekly decreasing kit will be dispensed at Day 1 and Month 12 to achieve decrease of corticosteroid therapy in double blind according to the treatment arm (conventional or experimental arm).

- **Prednisone 5mg or placebo monthly pill box:**

Prednisone monthly treatment is a numbered pillbox consisting of 42 prednisone 5 mg or placebo ivory capsules in brown pillbox (75 mL).
Prednisone 5 mg/placebo pillboxes will be dispensed at Day 1 (1 pillbox), Month 1 (2 pillboxes), Month 3 (3 pillboxes), Month 6 (3 pillboxes), and Month 9 (3 pillboxes) to achieve corticosteroid therapy in double blind according to the treatment arm (conventional or experimental arm).

At each visit during the maintenance period, additional pills are provided to ensure a security in case of lost, damage, or other problems which can occur.

10.2.2. Dosage form, labelling and packaging

Experimental drugs are provided by the sponsor.
Prednisone capsules and placebo capsules are prepared, blinded and packaged by the Pharmacy of the Edouard Herriot Hospital (Groupement Hospitalier Centre, Hospices Civils Lyon (HCL), France) according to European Union's Good Manufacturing Practice.
Experimental drug will be presented in a numbered pill box and labeled according to the decree of 24 May 2006 fixing the content of the experimental drugs labeling.
Each dosage of prednisone and its placebo capsules are provided in the same appearance (color, size).
Procedures concerning manufacturing and control of the investigational medicinal (prednisone capsule and placebo capsule) product are presented in the dossier of the experimental medicinal product folder.

10.2.3. Administration

Every prednisone/placebo administration scheduled and decreasing according to arms of randomization is listed in the **Table 10.** (p.54).

Table 10. Schedule of prednisone administration and tapering according to arms of randomization

Time point								
Screening		**Starting dose at screening : between 5 to 10mg/day**						
Inclusion (D-35 to D-1)		**Starting dose mg/day at inclusion :**						
		10	9	8	7	6	5	
D-35 to D-29	**Run In period[18]**	9	8	7	6	5	5	
D-28 to D-22		8	7	6	5	5	5	
D-21 to D-15		7	6	5	5	5	5	
D-14 to D-8		6	5	5	5	5	5	
D-7 to D-1		5	5	5	5	5	5	
Schedule according to Randomization								
Time point		**Experimental Arm**			**Control Arm**			
Day 1		**Week 1**	Prednisone Placebo 4 mg/day		**Week 1**	Prednisone 4 mg/day		Decreasing of 1mg/week until stop
		Week 2	Prednisone Placebo 3 mg/day		**Week 2**	Prednisone 3 mg/day		
		Week 3	Prednisone Placebo 2 mg/day		**Week 3**	Prednisone 2 mg/day		
		Week 4	Prednisone Placebo 1 mg/day		**Week 4**	Prednisone 1 mg/day		
Day 1 to Visit M1		Prednisone 5 mg/day			Prednisone Placebo 5 mg/day			
Visit M1 to Visit M12		Prednisone 5 mg/day			Prednisone Placebo de 5 mg			
Visit M12 to Visit M13		**Week 53**	Prednisone 4 mg/day		**Week 53**	Prednisone Placebo 4 mg/day		Corticotherapy decreasing of 1mg/week until stop
		Week 54	Prednisone 3 mg/day		**Week 54**	Prednisone Placebo 3 mg/day		
		Week 55	Prednisone 2 mg/day		**Week 55**	Prednisone Placebo 2 mg/day		
		Week 56	Prednisone 1 mg/day		**Week 56**	Prednisone Placebo 1 mg/day		
Visit M13 to Visit M30		**Discontinuation of drug treatments**						

[18] During the Run-in Period, all subjects who are receiving commercial prednisone between 5 and 10 mg must follow a tapering within 5 weeks to reach a dose of 5mg/day on randomization day.

Patients will take:

- From Day 1 to Visit Month 1: Two capsules per day in the morning during meal and fixed time in both groups:
    - One capsule per day of weekly pillboxes from the “prednisone 4 mg, 3 mg, 2 mg, 1 mg or placebo decreasing kit” according to the instructions during 4 weeks.
    - One capsule per day from the “Prednisone 5 mg or placebo monthly pillbox”
- From Visit M 1 to Visit M 12: One capsule per day in the morning during meal and fixed time in both groups, from the “Prednisone 5 mg or placebo monthly pillbox”.
- From Visit M 12 to Visit M 13: - One capsule per day of weekly pillboxes from the “prednisone 4 mg, 3 mg, 2 mg, 1 mg or placebo decreasing kit” according to the instructions during 4 weeks.

10.2.4. Precautions for use and contraindications

The precaution of use and the contraindication for prednisone are described in the Summary of Product Characteristics (SPC); see public base on medication http://base-donnees-publiques.medicaments.gouv.fr

10.2.5. Accountability procedures for experimental drugs

Edouard Herriot Hospital Pharmacy (Hospices Civils Lyon, Lyon, France) is the pharmacy coordinator of this clinical trial and is responsible for:

- Preparing the experimental drug (prednisone/placebo)
- Packaging, blinding and labeling capsules in numbered pillboxes
- Storing of experimental drugs and ensuring their traceability
- Dispatching of the investigational drug to the pharmacies of the investigating centers.

10.2.6. Storage conditions

Treatments will be stored in each investigating center pharmacies, at ambient temperature (15°C-25°C) in a place dedicated to clinical trials, locked with temperature controlled.

10.2.7. Distribution

Pharmacy of the Edouard Herriot Hospital (main pharmacy) will supply and resupply pharmacies of according to inclusions rhythm, by transport at controlled temperature. After verification of the shipment conformity, an acknowledgment of receipt will have to be transmitted back by local pharmacy.

10.2.8. Dispensation

Dispensing of the study treatment will be made by local pharmacy, according to local regulations. Pharmacy should keep dispensing records.

Experimental drugs are dispensed on the study drug prescription completed by the investigator. The practical arrangements for dispensing are left to the discretion of the pharmacists responsible for the clinical trials of each center. Subject will be instructed by the investigator and the pharmacy to return at each visit all used bottles (empty or not) and unused bottles associated with the study drugs to the site

Depending of visits, a numbered weekly decreasing kit and/or prednisone 5 mg/placebo monthly pill box(es) are assigned to the patient by an IWRS system. The experimental drug is dispensed by investigating center pharmacy.

10.2.9. Traceability, Return and Destruction of Experimental Drug

Each investigating center pharmacy is responsible for traceability of experimental drugs as soon as it is received at the center. Pharmacy should keep all dispensing records.

After dispensing, all treatment units have to be returned at each visit to the investigator for accounting to assess compliance and then to local pharmacy for accounting. They will be destroyed on site after monitoring and authorization of Sponsor. The investigator will record in the CRF the number of capsules returned by the patient. The study monitor will review study drug records and inventory through the study at the pharmacy. He/she will check consistency between data on CRF and the actual number of capsules returned at the pharmacy.

At the end of the study, the study monitor will provide instructions as to the disposition of any unused investigational product and used bottles. If the study monitor authorizes destruction at the study site, the study site staff or pharmacy personnel will ensure that the materials are destroyed in compliance with applicable environmental regulation, institutional policy, and any special instructions provided by the Monitor. Destruction will be adequately documented.

Monitors designated by Sponsor will ensure for both prednisone and placebo that:

- Storage times and conditions are acceptable, and that supplies are sufficient throughout the trial;
- Investigational products have been supplied only to subjects who are eligible to receive it and at the protocol specified dose;
- Medical and paramedical staff are provided with necessary instruction on properly using, handling, storing, and returning the investigational products;
- The receipt, use and return of the investigational products at the trial sites are controlled and documented adequately;

- The disposition of unused investigational products at the trial sites complies with applicable regulatory requirements and is in accordance with the Sponsor.

10.3. Method of Assigning Subjects to Treatment Groups

Approximately 146 subjects will be randomized to 1 of 2 treatment arms when all inclusion/non-inclusion criteria are met. Subjects will be randomized in 1:1 ratio (prednisone 5mg/day vs 0mg [Placebo]).

The randomization list will be generated by IWRS with CLINSIGHT e-CRF according to a randomization list prepared by the Biostatistician; treatment assignments will be generated in permuted blocks.

10.4. Study drug Missed Doses

On Non-Study Visit Day:

- If a subject misses a dose of study drug and remembers the missed dose within 12 hours, the subject should take the dose of study drug.
- If more than 12 hours elapsed after the usual dosing time, the subject should skip that dose of study drug and resume the normal schedule for the following dose. A double dose should not be taken to make up for the forgotten dose.

10.5. Compliance

To maximize treatment compliance during the study, the investigator or designee will supervise study drug dosing at each visit. A compliance notebook will be given to the patient. The investigator will remind the patients to bring back this book at each visit together with the unused and used bottles.

To maximize treatment compliance during the study, the investigator or designee will supervise study drug dosing at each visit. At each visit, site personnel will review subject compliance with study drug dosing comparing the compliance notebook data and the remaining tablets in the bottle; site personnel will remind the subject of study drug dosing requirements. Compliance will be assessed by ongoing study drug count which will be recorded on CRF.

10.6. Blinding

This trial will be comparative, randomized, double-blind and placebo controlled in order to limit confusion and evaluation bias.

Sites will be provided a set of blinded medication kits. Therefore, neither patients nor physicians will know the treatments allocated to their patients.

The subject and all site personnel, including the investigator, the site monitor, and the study team, will be blinded with the exception of the following:

- Any site personnel for whom this information is important to ensure the safety of the subject in the event of a life–threatening medical emergency;
- Any site personnel for whom this information is important to ensure the safety of the subject and the fetus in the event of a pregnancy;
- Investigator coordinator;
- External vendor (unblinded) statistician preparing the final (production) randomization list who is not part of the study team;
- The medical monitor may, for matters relating to safety concerns, unblinded individual subjects at any time.

10.7. Unblinding

At the initiation of the study, the study site will be instructed on the method for breaking the blind.

Unblinding of an individual subject's treatment by the investigator will be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. In such cases, investigators will use their best judgment as to whether to unblind, based on the nature and urgency of the clinical situation, and may proceed with unblinding without having successfully reached and discussed the situation with the medical monitor. An individual subject unblinding can be performed in case of adrenal insufficiency suspicion.

Contact information is provided below:

- Groupement Hospitalier Est Poison Center (CAP, HCL, Lyon). The telephone number to contact is +33 (4) 72.11 69 11.

If a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the Sponsor will be notified soon as possible of the unblinding event. The reason and the date of the unblinding will be documented clearly in the subject's study file. Information about the treatment assigned obtained from the unblinding will be maintained in a secure location with controlled access and will not be shared with any site personnel (other than the physician treating the subject). In addition, the investigator will consider whether the clinical event that prompted will be considered an SAE, according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report to the Sponsor.

The safety department of the sponsor can unblind to satisfy SAE processing and SUSAR reporting to competent authorities.

10.8. Hydrocortisone for Secondary Adrenal Insufficiency

The diagnosis of adrenal insufficiency will be done according to the 2016 Clinical Guidelines Subcommittee of the Endocrine Society [35]. Because of its paucity, this test will be left at the physician's discretion and may be performed on clinical judgment in case of evocative signs of adrenal insufficiency. It will be systematically realized in occurrence of signs evocative of secondary adrenal insufficiency encompassing chronic malaise, lassitude, anorexia, weight loss, vomiting, abdominal pain, musculoskeletal symptoms, hypotension, hyperkaliemia, and hypoglycemia. The diagnosis of secondary adrenal insufficiency will be established by administration of the standard dose (250 µg for adults) of intravenous corticotropin stimulation (30 or 60 min). Peak cortisol levels below 500 nmol/L (18 µg/dL) (assay dependent) at 30 or 60 minutes indicate adrenal insufficiency. If a corticotropin stimulation test is not feasible, a morning cortisol 140 nmol/L (5 g/dL) will be performed in combination with ACTH as a preliminary test suggestive of adrenal insufficiency (until confirmatory testing with corticotropin stimulation is available) as stated in the Guidelines of the Endocrine Society.

In case of adrenal insufficiency, we will use a short-acting glucocorticoid, hydrocortisone, in two or three divided doses as the glucocorticoid of choice for the management of chronic primary adrenal insufficiency [35]. The lowest glucocorticoid dose that relieves symptoms of glucocorticoid deficiency will administrated to avoid confusion bias related to the potential immunosuppressive effects of higher doses of hydrocortisone.

The protocols will allow a maximal replacement dose of 15 mg/m^2; most patients will require 15 to 20 mg daily given in two or three doses (for example 10 mg morning and 5 mg in afternoon). For the patients with severe adrenal insufficiency symptoms or adrenal crisis, intravenous hydrocortisone (100 mg) will be administrated at an appropriate stress dose prior to the availability of the results of diagnostic tests [35].

The monitoring glucocorticoid replacement will use clinical assessment including body weight, postural blood pressure, energy levels, and signs of frank glucocorticoid excess [35].

The occurrence of adrenal insufficiency will be registered as an AE.

10.9. Study Authorised and Prohibited Treatments (Medicinal, Non-Medicinal, Surgical), including Rescue Medications

Authorized treatments will include (non-exhaustive list):

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

Patients with past fracture related to osteoporosis will be systematically referred to rheumatologist for assessment and cares including treatment preventing bone demineralization.

In case of a physiological stress situation (influenza, acute fever or other situations considered physiologically stressful according to the investigator), a hydrocortisone prescription (10-30 mg/days according to physician judgment) is authorized for a maximum duration of 10 days in addition to prednisone 5 mg/placebo. At the end of this period, the patient will have to continue to take the trial treatment.

Prohibited medications are not allowed in this study (Screening Period though Safety Follow-Up Visit) as summarized in the non-exhaustive list of study prohibitions below:

- Any other immunosuppressive or immunomodulatory agent administered for the control of vasculitis or any other inflammatory disorders, except for rituximab as maintenance therapy

10.10. Prior and Concomitant Medications

Information regarding all prior and concomitant medications, including the subject's MPA or GPA medications, other medications, and herbal and naturopathic remedies administered from 30 days before the Screening Period through the Safety Follow-Up Visit will be recorded in each subject's source documents and electronic case report form (eCRF).

11. ADJUDICATION COMMITTEE

An Endpoint Adjudication Committee (Pr Loïc Guillevin, Dr Xavier Puéchal, and Dr Jean-Christophe Lega), blind to treatment allocation, will be created to review parameters of efficacy (major and minor relapse) for every patients included in the study.

12. SAFETY ASSESSMENTS - RISKS AND RESTRICTIONS ADDED BY THE RESEARCH

12.1. Definitions

According to article R1123-46 of public health code.

12.2. Adverse event (AE)

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

12.3. Adverse drug reaction

An adverse reaction implies at least a reasonable possibility of causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

12.4. Serious adverse event (SAE)

A serious adverse event (SAE) means any untoward medicinal occurrence that:

- Result in death; or
  Is life-threatening; or
- Requires in patient hospitalization or prolongation of existing hospitalization; or
- Results in persistent or significant disability / incapacity; or
- Results in a congenital anomaly / birth defect or;
- Is a medically significant event:
    - An event that may be considered as “potentially serious”, including certain biological abnormalities
    - A medically relevant event according to the investigator’s judgment
    - An event requiring medical intervention to prevent the evolution towards ont of the aforementioned condition

12.5. Unexpected adverse reaction

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

12.6. New safety issue

Any new information regarding safety:

- That could significantly alter the assessment of the benefit-risk ratio for the experimental medication, or for the trial;
- Or which could lead to the possibility of altering the administration of the experimental medication or altering the conduct of the trial.

12.3. The investigator's roles

All adverse events have to be investigated, reported and recorded, treated and evaluated from the first visit (inclusion D0) until the end of study and it resolution.

All adverse events will be noted on the Adverse Event Reporting Forms of the Case Report Form (CRF). Each observed adverse event will be recorded individually. **Adverse event be graded according to CTCAE scale. All adverse events of severe intensity, life-threatening grade, and death (grade 3 or above) shall be considered SERIOUS and must be notified to the sponsor without delay [unless they are described in the section "SAE that do not require the investigator to immediately notify the sponsor".**

The investigator evaluates each adverse event in terms of its severity. The investigator shall notify the sponsor, without delay and no later than 24 hours from the day of its knowledge, all serious adverse events and serious incidents in the trial, with the exception of those are identified in the protocol as not requiring notification without delay. This initial notification shall be the subject of a written report and shall be followed by one or more additional detailed written report(s) within 8 days of the first notification.

The investigator faxes at +33 (0)4 72 11 51 90 a SAE form dated and signed, since it has the 4 elements minimum to notify an SAE:

- A reporter
- A patient
- An experimental product
- An adverse event

The investigator must document the SAE as thoroughly as possible (by means of copies of laboratory results or reports of examinations or hospitalizations, including relevant negative results, without omitting to make these documents anonymous and enter the patient's number and code), and provide the medical diagnosis and establish a causal link between the serious adverse event and the drug(s).

The investigator must follow the patient who has submitted an SAE until resolution, stabilization at an acceptable threshold according to the investigator or return to the previous condition, even if the patient is out of the trial and inform the sponsor by fax on +33 (0)4 72 11 51 90 using the form (check the box: ☑ follow-up)

The investigator will assess the causal relationship between the SAE and the experimental medication. The investigator must evaluate the causal relationship of adverse events with the experimental drug(s) and with the procedures / acts added by the research. He must also assess the causal relationship of adverse events with the others concomitant treatments taken by the patient and forward the results of this evaluation to the sponsor. The causality assessment is binary (related / unrelated).

All serious and non-serious AE must be reported in the electronic CRF.

SAE that do not require the investigator to immediately notify the sponsor

The purpose of this section is to limit immediate notifications of SAE that are not relevant to the research and that do not imply a safety concern to the patient.

These SAE are only recorded in the "Adverse Event" section of the electronic case report form.

Normal and natural evolution of the pathology:

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

This normal and natural evolution without aggravation since the inclusion may also include clinical or biological manifestations related to disease relapse, including:

- Dyspnea, cough, hemoptysis
- Ear, nose of throat abnormalities
- Arthralgia or arthritis, myalgia
- Skin manifestations including purpura, nodules, ulcers, digital necrosis
- Renal involvement (nephritis)
- Other manifestations due to MPA/GPA (cf page 98 in annex)

Special circumstances

Special circumstances that will not require to immediately notify the sponsor include:

- Hospitalization predefined by the protocol
- Hospitalization for medical treatment or surgery planned before the research
- Hospitalization for social or administrative reasons
- Admission to day hospitalization
- Hospitalization in the Emergency Unit for less than 12 hours

SAE that require the investigator to immediately notify the sponsor

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

Adverse events of special interest (requiring immediate notification to the sponsor):

- **SAE grade ≥ 3 related to prednisone:**

The most commonly observed AE of prednisone are:

- Immunosuppression: increase of secondary infection (including fungal infection), exacerbation of viral infection, limitation of response to inactivated vaccines, reactivation of latent tuberculosis, dissemination of amebiasis;
- Cardiovascular system: congestive heart failure (in susceptible patients), hypertension;
- Central nervous system: emotional instability, headache, intracranial pressure increased (with papilledema), and psychic derangements (including euphoria, insomnia, mood swings, personality changes, severe depression)
- Skin: bruising, facial erythema, petechiae, thin fragile skin, wound healing impaired;
- Endocrine & metabolic system: adrenal suppression and adrenal crisis, adrenocortical and pituitary unresponsiveness in times of stress, carbohydrate intolerance, Cushing's syndrome, diabetes mellitus, fluid retention, menstrual irregularities, negative nitrogen balance due to protein catabolism, potassium loss, sodium retention;
- Gastrointestinal tract: peptic ulcer (with possible perforation and hemorrhage), ulcerative esophagitis, abdominal distension, pancreatitis, hepatitis;
- Neuromuscular & skeletal system: aseptic necrosis of femoral and humeral heads, muscle mass loss, muscle weakness, osteoporosis, pathologic fracture of long bones, steroid myopathy, tendon rupture (particularly Achilles tendon), vertebral fractures;
- Ocular: glaucoma, intraocular pressure increased, posterior subcapsular cataracts.

- ***Any premature and permanent discontinuation of the experimental drug due to an adverse event (any grade).***

- ***In case of serious adverse event due to a deviation in tapering schedule, precise on the SAE form.***

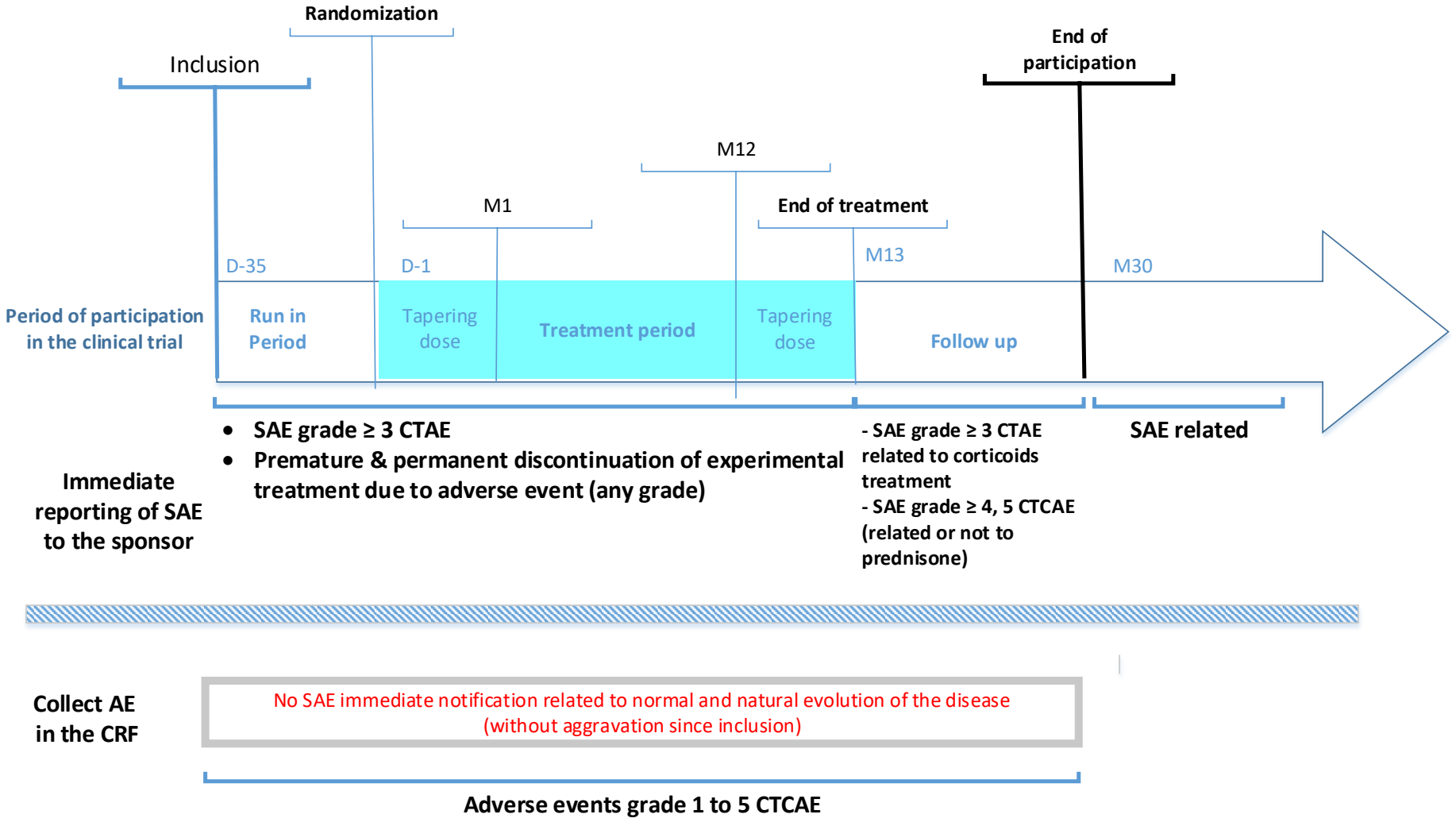
Period of notification of SAE without delay to the sponsor by the investigator

The investigator must notify the sponsor without delay all serious adverse events (except for events listed previously as not requiring notification):

- From INCLUSION OF THE PATIENT (date of signature of the 1st consent, screening) to the end of the treatment M13
- From M13 to the end of follow-up M30 :
    - only SAE grade ≥ 3 related to corticoids treatment,
    - and any SAE grade ≥ 4 according CTCAE (related or not to prednisone).

After the end of participation**: Without any time limit for serious adverse events related to the research**

Flow chart of adverse event reporting:



12.4. Sponsor Obligation

The sponsor will declare in accordance with article R1123-54 of the CSP (Public Health Code):

- to ANSM, any suspected serious unexpected adverse effect occurring in France and outside the national territory within the following time limits:
    - in case of life threatening or death of the subject: without delay as from the day on which the sponsor is aware of it and the relevant additional information to be submitted in the form of a follow-up report to ANSM within a period of 8 days from the initial declaration.
    - for all other unexpected serious adverse reactions: no later than 15 days from the date on which the promoter is aware of it and the relevant additional information to be submitted in the form of a follow-up report to ANSM Within a further period of 8 days from the initial declaration.
- to ANSM and to CPP, the recent safety news and, when appropriate, the measures taken without delay from the day on which the sponsor is aware of them and the relevant additional information to be submitted in the report form to ANSM within 8 days of the initial declaration.

The sponsor will also establish a Development Safety Update Report (DSUR) which will be forwarded to ANSM and CPP within 60 days after the anniversary date of the study (authorization's date of ANSM).

The expected or unexpectedness of a suspected serious adverse reaction related to prednisone is assessed from:

- Experimental Drug Reference Document: Summary of Product Characteristics (SmPC.) of Cortancyl®

The expected or unexpected of a suspected serious adverse event to rituximab is assessed from:

- Non Experimental Drug reference Document : SmPC of Mabthera®

12.5. Data Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) external to the trial investigators has been established specifically to monitor data throughout the life of a study to determine if is appropriate, from both the scientific and ethical standpoint, to continue the study as planned. The DSMB is mentioned in Article L. 1123-7 of the French Public Health Code.

The sponsor is responsible for justifying the creation or absence of a supervisory committee to the Competent Authority (ANSM) and to the CPP.

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

12.5.1. Composition of the DSMB:

This committee is composed of the following experts:

- Methodologist/Statistician
- Pharmacologist /Pharmacovigilant
- Internal Medicine specialist

12.5.2. General information about the DSMB

The DSMB makes recommendations to the sponsor about the continuation, modification or termination of the research. Their role is to protect the interest of patients in the study and of those still be entered by review of accumulating safety and tolerability data generated in the study. The recommendations that the DSMB can make are:

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

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

12.5.3. Definition of the DSMB's missions

- Validation of the research methodology:

The proposed methodology for the clinical trial will be validated by the DSMB so that it does not jeopardize the safety of subjects, in particular relating to the inclusion and randomization methods.

- Validation of tolerance monitoring methods:
    - nature of the evaluated parameters;

    - frequency of the evaluations, consultation schedule;
- Validation of termination criteria:
    - criteria for terminating a subject's participation for tolerance reasons;
    - criteria for the temporary or permanent termination of the research (leading to the establishment of certain recommendations ("stopping rules")).
- Modification of the protocol and recommendations:

In light of the analysis of tolerance data for the research, the DSMB can, when applicable propose substantial modifications in order to modify certain data, in particular relating to the protocol (inclusion and non-inclusion criteria, monitoring, additional exams, etc.). Likewise the DSMB can issue any recommendations it deems useful in order to best ensure the safety of the research subjects and to maintain a favorable benefit-risk balance throughout the research.

12.5.4. Definition of the DSMB's operating methods:

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

The DSMB appoints its chairman at the first meeting.

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

13. DATA MANAGEMENT

13.1. Data Collection Methods

Data will be collected in each center by the investigator or by a clinical research technician, supervised by the investigator. Most data will be collected on the e-CRF. At the end of the research, the study data will be used to implement the national GFEV database.

13.2. Identification of Data Collected Directly in the CRFs and that will be considered as Source Data

Data collected directly in the CRF will include:

- Age;
- Height, Weight;
- Clinical examination to collect manifestations related to active EGPA or remission;
- BVAS;
- VDI;
- CDA;

- GTI toxicity;
- SF36 and HAQ patient questionnaires.

13.3. Right to Access Source Data and Documents

13.3.1 Data Access

In accordance with Good Clinical Practices (GCPs):

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

13.3.2. Source Documents

Source documents are defined as any original document or object that can prove the existence or accuracy of data or a fact recorded during the clinical study. These documents will be kept for 25 years by the investigator or by the hospital in the case of a hospital medical file.

13.4. Data confidentiality

In accordance with provisions concerning the confidentiality of data to which persons responsible for the quality control of a study involving human individuals have access (article L.1121-3 of the public health code), and in accordance with the provisions regarding the confidentiality of information relating, in particular, to the trial, the persons who participate, and the results obtained (article R.5121-13 of the public health code), the persons having direct access to the data will take all necessary precautions to ensure the confidentiality of the information related to the trials, to the persons participating and, in particular, with regards to their identity as well as the results obtained.

These individuals, as well as the investigators themselves, are subject to professional confidentiality (in accordance with the conditions set out in Articles 226-13 and 226-14 of the Penal Code).

During or after the research involving human individuals, the data collected about the research subjects and sent to the sponsor by the investigators (or any other specialized parties) will be made non-identifying.

Under no circumstances should the names and addresses of the subjects involved be shown.

Only the first letter of the subject surname and the first letter of their first name shall be recorded, accompanied by a coded number specific to the study indicating the inclusion order of the subject.
The sponsor will ensure that each research subject has given permission in writing for access to personal information about him or her which is strictly necessary for the quality control of the research.

13.5. Data Processing and Storage of Documents and Data

13.5.1. Identification of the Manager and the Location(s) for Data Processing

The data management will be performed in the clinical research unit at the HCL, Lyon (Service de Pharmacologie Clinique, Pr François Gueyffier).

13.5.2. Data Entry

Study data for each enrolled subject are entered into a web-based electronic data capture (EDC) application (Clinsight solution). Data are stored on a web server owned by the sponsor. The coordination centre has view-only access to all data upon entry in the EDC application. Instances of missing, discrepant, or uninterpretable data are queried with the investigator for resolution. Any changes to study data are made to the eCRF and documented in an audit trail, which will be maintained within the clinical database.

13.6. CNIL

This research falls under the "Méthodologie de référence" (MR-001) according to the provisions of Article 54, paragraph 5 of modified Law No. 78-17 of 6 January 1978 relating to information technology, data files and privacy. This change was approved in a decision made on 5 January 2006 and modified on July 21-2016. The HCL, the research sponsor, has signed a commitment to comply with this "Méthodologie de référence".
This research falls under the “Réglement Européen sur la Protection des Données” n°2016/679 from European Parlement and Council dated 27 april 2016 concerning personal data protection and repealing the European Directive n°95/46/CE dated 24 october 1995

13.7. Archival

Specific documents for biomedical research relating to a medication for human use will be archived by the investigator and the sponsor for a period of 25 years after the end of the research.

The following documents will be archived under the name of the study and under the responsibility of the coordinating investigator or associated investigators in each site for 25 years:

- Protocol and annexes, possible amendments,

- Original signed copies of the information and consent form,
- Individual data (certified copies of raw data)
- Follow-up documents and letters relating to the study

The sponsor is also responsible for organizing the storage of the statistical analyses and the final study report for the required duration of archiving.

No moving or destruction can be carried out without the agreement of the sponsor. At the end of the 25 years, the sponsor will be consulted for the destruction. All data, documents, and reports may be the subject of an audit or inspection.

13.8. Ownership of the Data

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

14. STATISTICAL ASPECTS

Statistical analyses will be performed in the Clinical Research Unit Paris Descartes Cochin/Necker, and supervised by Pr Philippe Ravaud.

14.1. Number of Subjects Required

Patients will be included in the trial via the participation of the French Vasculitis Study Group (FVSG) network. This French network includes physicians and medical departments involved in the management of patients with AAV, in particular GPA and MPA.
Each of the previous trials conducted by the FVSG network have included all patients planned by the protocol and have been published in high ranked journals.

For the MAINEPSAN study, we plan to include 146 patients with MPA or GPA.
Based on the results of the previous MAINRISTAN controlled trial from the French Vasculitis Study Group, in MPA and GPA [2], the proportion of patients receiving at least 18 months of prednisone and experiencing vasculitis relapse (minor or major) after rituximab maintenance is expected to be 16% at 28 months in the late cessation group. Of note two thirds of minor relapses in this trial were observed in patients off prednisone. The same percentage (14%) of relapse was observed in the meta-analysis for the studies with no glucocorticoids withdrawal [3].

On the other hand, previous studies in ANCA-associated vasculitis reported a relapse rate of 34% and 37% in case of glucocorticoids cessation before 12 months, both after achievement of remission with cyclophosphamide [4,5].

The primary hypothesis of the trial is a relative decrease of about 60% of the relapse rate at 12 months (24 months post flare), i.e. 14% vs 34%. Based on this hypothesis, using a bilateral test, we calculated that 140 patients would be required for the study to have 80% power to detect an absolute 20% reduction with a two-sided alpha level of 5%, 70 patients in each arm. Given an expected loss of follow-up or withdrawal of consent of patients, 73 patients per arm will be necessary.

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

Table 12. Number of Subject Required / Center	Number of Subjects
Total number of subjects chosen	*146*
Number of centers	*38*
Inclusion period (months)	*24*
Number of subjects/year/center	*2*
Number of subjects/center/month	***0.16***

14.2. Description of Statistical Methods to be used including the Timetable for the Planned Interim Analyses

Statisticians will be blinded to treatment assignments. The primary analysis will be conducted on all randomized patients, except those who will have immediately withdrawn their consent and / or have been immediately found not to meet the study criteria post-enrolment and randomization, and have not taken study drug. However, an additional sensitivity analysis for the primary endpoint will include all enrolled patients.

Quantitative variables will be described as means (standard deviation, SD) and/or medians (range) and qualitative variables in absolute and relative percentages.

Relapse rate will be compared using a binomial GEE model with an identity link to estimate the risk difference for the correlated data (correlation will be due to a multicenter trial). Results will be presented as absolute risk difference with 95% confidence intervals (CIs). An offset term (Log follow-up duration) could be added to the model. As a sensitivity analysis, the Kaplan-Meier curves will be used to display the probability of remaining relapse-free according to treatment group and a marginal Cox model test will be used to compare overall survival (results will be presented as hazard ratio with 95% CIs).

Subgroup analyzes for the primary outcome will also be done separately for disease type (new diagnosis vs. relapsing disease), ANCA status at diagnosis (PR3 + vs other) induction treatment (rituximab or cyclophosphamide vs other).

Secondary quantitative endpoints with repeated measurements will be analyzed using constrained longitudinal analysis (mixed models for repeated measures that generated unbiased estimates for data missing at random, with fixed-effect parameters (treatment group), a random-intercept effect at the center level) to estimate the treatment effects. Results will be adjusted for the observed baseline difference and expressed as the mean change difference from baseline (95% CIs).

Linear mixed-effect models will be used to compare secondary quantitative endpoints without repeated measurements (F-test). Results will be expressed as mean difference (95% CIs).

The numbers of events (adjusted for Log follow-up duration as an offset variable) will be modelled with negative binomial regression, with results expressed as risk ratios (RRs) (95% CIs).

Patient rates will be analyzed with models used for the primary outcome (binomial GEE model with identity link). Survival rates will be compared to the log-rank test and results will be expressed with hazard ratios (95% CIs).

Adjustment for centre effect will be done for all secondary analysis.

Statistical analysis will be imputed with SAS v9.3 software (SAS Institute Inc, Cary, NC). All tests will be bilateral. P <0.05 will define significance. No interim analysis is scheduled in this research.

Depending on the missing data rate, the missing values for the main result will be imputed as a failure or with the multiple imputation method.

14.3. Management of Modifications made to the Analysis Plan for the Initial Strategy

An analysis plan will be developed and validated with the scientific committee before the database is frozen. It will take into account all protocol modifications or all unexpected events occurring throughout the study and having an impact on the analyses presented here. The planned analyses may be completed in line with the study objectives.

All modifications subsequently brought to the statistical analysis must be justified and will result in a new version of the document. These deviations in the analysis plan will be reported in the final study report. All the documents will be stored in the study folder.

15. QUALITY CONTROL AND ASSURANCE

15.1. General Organization

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

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

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

15.2. Quality Control

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

The investigator and the members of the investigator's team agree to be available during Quality Control visits carried out at regular intervals by the Clinical Research Associate. During these visits, the following elements will be reviewed depending on the level of monitoring appropriate for the study and determined in accordance with the SOPs of the sponsor:

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

- management of the experimental treatments used;
- Declaration if serious adverse events.

All visits will be the subject of a written monitoring report addressed to the investigator of the site visited and to the study coordinating structure.
Furthermore, the investigators agree to accept the quality control audits carried out by persons mandated by the sponsor as well as inspections by the competent authorities. All data and all documents and reports may be the subject of regulatory audits and inspections without the possibility of using medical secrecy as opposition.

15.3. Electronic Case Report Form

All information required according to the protocol must be entered in the electronic case report forms. Other patient data necessary for their follow-up outside of this study will be collated in their medical file. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Each missing data item must be coded.
This electronic case report form will be implemented in each of the centres thanks to a web-based data collection medium. Investigators will be given a document offering guidance in using this tool.
The completion of the case report form by the investigator through the internet allows the study coordination center to rapidly see the data at a distance. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. Thus, the investigator must validate any changes to the values in the electronic case report form. These modifications will be subject to an audit trail. A justification can be added when applicable, as a comment. A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the research. The investigator must archive a copy of the authenticated document that was delivered to the sponsor.

15.4. Management of Non-Compliances

Any events that occur as a result of non-compliance, by the investigator or any other individual involved in conducting the research, with the protocol, with the standard operating procedures, with the good clinical practices or with the legislative and regulatory provisions in force must be noted and justified in a deviation form provided by the sponsor. As a first step, minor, major or critical non-compliances will be reviewed and processed by the DRCI monitor and Project Manager in order to implement the necessary corrective or preventive actions. Next, the non-compliances could be reviewed by the Quality - Risk Management Division of the DRCI for

verification and analysis. These verifications could result in the investigator in charge of the research location in question being asked for information or could lead to compliance or audit visits.

15.5. Audits/Inspections

The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. Medical secrecy cannot be invoked in opposition to these audits and inspections.

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

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

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

15.6. Declaration of Conformity

The sponsor and the investigator undertake to ensure that the study is conduced:

- in conformity with the protocol;
- in conformity with both the French and international good clinical practices currently in force;
- in conformity with the current French and international legal and regulatory provisions.

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

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

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

16. ETHICAL AND LEGAL CONSIDERATIONS

16.1. Methods for obtaining Information and Consent from Research Participants

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

Patients will be fully and faithfully informed, in a comprehensive manner, of the objectives and restrictions of the study, of the potential risks, of the monitoring and security measurements required, of their right to decline participation in the study, or of the possibility to withdraw at any moment.
All this information will be presented in the information sheet and informed consent form given to the patient..
The subject will be granted a reflection period of one day between the time when the subject receives the information and the time when he or she signs the consent form.

The free and informed consent, in writing, of the subject is obtained by the investigator, or by a doctor representing the investigator, before the inclusion of the subject in the research. A copy of the information notice and the consent form signed by the two parties will be given to the patient; the investigator will keep the original.

The information sheet and a copy of the consent form signed and dated by the research subject and by the investigator or the doctor representing the investigator, are given to the individual prior to his or her participation in the research.

In addition, the investigator will specify in the research participant's medical file the methods used for obtaining his or her consent as well as the methods used for providing information with the goal of obtaining their consent.

16.2. Exclusion Period

From the beginning until the end of his/her participation, the patient cannot be participate simultaneously to another investigational study in the exception to the PNEUMOVAS trial.
The exclusion period after the trial participation is 3 months taking into account the duration of action of immunosuppressive agents used in this trial.

16.3. Competent Authorities

The protocol, the written information sheet and the consent form for the study will be submitted to ethics committee CPP Ouest IV Nantes for an opinion
The notification of the favorable opinion from the EC will be sent to the study sponsor and the ANSM. The sponsor will also send a study authorization request to the ANSM.
The sponsor undertakes to ensure that the start of the study only occurs after the favorable opinion of the EC and the study authorization from the ANSM has been obtained.

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

16.4. Substantial Modifications

In the event that a substantial modification is made to the protocol by the investigator, it will be approved by the sponsor. Before its implementation, the latter must obtain a favorable opinion from the EC and an authorization from the ANSM within the scope of their respective competencies. A new consent will be collected from the people already participating in the study, if necessary.

17. FUNDING AND INSURANCE

17.1. Funding Source

The present study is funded by the PHRC 2016.

17.2. Insurance

For the duration of the research, the Sponsor has subscribed an insurance policy covering the sponsor's own civil liability as well as the civil liability of all the doctors involved in carrying out the research. The sponsor will also provide full compensation for all harmful consequences of the research for the participating subjects and their beneficiaries, except with evidence, at their responsibility, that the damage is not attributable to their mistake or to that of all consultants,

without the possibility of being opposed to an act by a third party or the voluntary withdrawal of the person who had initially consented to participate in the research.

The insurance contract was signed before the start of the study with the Société Hospitalière d'Assurance Mutuelle, 18 rue Edouard Rochet, 69008 Lyon, under the number 153930

18. RULES RELATING TO THE PUBLICATION

Scientific communications and reports related to this study will be carried out under the responsibility of the study's principal investigator with the agreement of the associated investigators. The co-authors of the report and the publications will be the investigators and doctors involved, in proportion to their contribution to the study, as well as the biostatistician and the associated researchers.
The publications rules will follow international recommendations (N Engl J Med, 1997; 336:309-315).
The study will be registered on the freely accessible clinical trials register (clinicaltrials.gov) before the inclusion of the 1st patient.

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20. APPENDICES

20.1. Appendice 1 - Investigator List
20.2. Appendice 2 - BVAS Score 2003
20.3. Appendice 3 - Combined Damage Assessment Index (CDA)
20.4. Appendice 4 - VDI Score
20.5. Appendice 5 - GTI Score
20.6. Appendice 6- HAQ Questionnaire
20.7. Appendice 7 - SF36 Questionnaire
20.8. Appendice 8 Manifestation due to GPA / MPA (non-exhaustive liste)
20.9 Appendice 9 Patient Diary card