PNEUMOVAS
« Multicenter randomized controlled trial comparing the immunogenicity and safety of two innovative anti-pneumococcal vaccine strategies to the standard vaccination regimen in patients with ANCA-associated vasculitides receiving rituximab therapy»

BIOMEDICAL RESEARCH PROTOCOL RELATING TO A MEDICINAL PRODUCT FOR HUMAN USE

Version N°4.0 of 14/08/2018
Project Code: P150964 / EUDRACT N°2016-002888-33:

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SIGNATURE page for a biomedical research PROTOCOL

Research Research Code: **PNEUMOVAS**
Title: **« Multicenter randomized controlled trial comparing the immunogenicity and safety of two innovative anti-pneumococcal vaccine strategies to the standard vaccination regimen in patients with ANCA-associated vasculitides receiving rituximab therapy»**

Version N° 4.0 of 14/08/2018

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

Coordinating Investigator:
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The research received a favourable opinion from the CCP Ile de France I on 11/01/2017 and authorisation from the ANSM on 20/12/2016.

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SUMMARY

Full title	Multicenter randomized controlled trial comparing the immunogenicity and safety of two innovative anti-pneumococcal vaccine strategies to the standard vaccination regimen in patients with ANCA-associated vasculitides receiving rituximab therapy
Acronym	PNEUMOVAS
Coordinating Investigator	Dr Benjamin Terrier Service de Médecine Interne, Centre de référence « Maladies systémiques et autoimmunes rares, en particulier Vascularites nécrosantes et Sclérodermies systémiques » Hôpital Cochin, Paris
Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	Studies in patients treated with immunosuppressive agents, and in particular anti-CD20 monoclonal antibody (rituximab), showed an increased risk of infection, especially invasive pneumococcal infections. Previous studies comparing vaccine responses following treatment with rituximab versus placebo showed that responses are strongly reduced under rituximab therapy. However, most of these studies were performed for influenza vaccination or with unconjugated anti-pneumococcal polysaccharide vaccine. It is thus unclear which anti-pneumococcal vaccine strategy provides the best immune response to reduce the risk of invasive infections. Systemic vasculitides are rare inflammatory diseases of blood vessels, among which anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are the more severe disease with life-threatening manifestations or complications. AAV include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis, and are classified as AAV because most patients have antibodies against proteinase 3 or myeloperoxidase. AAV affect small-to-medium-size blood vessels, with a predilection for the respiratory tract and kidneys. Rituximab was demonstrated to be an effective therapeutic agent to induce and maintain remission in these patients. Because these patients often justify immunosuppressive or immunomodulatory agents in emergency, the development of new anti-pneumococcal vaccine strategies with improved immunogenicity despite simultaneous administration of rituximab is critical. The current standard vaccination schedule is based on a combined strategy using the 13-valent anti-pneumococcal conjugate vaccine (PCV13) followed at least two months later by the 23-valent unconjugated vaccine (PPV23), to obtain a T-dependent B cell response against 13 serotypes of the conjugate vaccine, secondarily extended to 23 serotypes of the unconjugated vaccine, given that 12 serotypes are common to both vaccines. We hypothesize that a “reinforced” anti-pneumococcal combined vaccine strategy during rituximab therapy will allow to induce a better immune response than the current standard regimen in these patients, with an acceptable safety.
Primary objective and assessment criterion	The primary objective of this trial is to compare immunogenicity at month 6 (M6) of two “reinforced” innovative pneumococcal vaccine regimens (two double doses (one double dose at D0 and one double dose at D7) or one quadruple dose of PCV13 followed by

	one dose of PPV23 at month 5), to the standard regimen (one dose of PCV13 followed by one dose of PPV23 at month 5), in patients with ANCA-associated vasculitides receiving rituximab therapy. The primary assessment criterion of this trial is immune response at M6 against 12 pneumococcal serotypes, according to four ordered categories of response: positive response to 0-3, 4-6, 7-9, or 10-12 serotypes common to the PCV13 and PPV23 vaccines. This endpoint will be analyzed as the number and proportion of participants in each of the four response categories According to international criteria, a participant will be considered as responder to given serotype if s/he has, at M6, i.e.one month after the PPV23 injection, a titer of specific IgG ≥1 µg/mL using ELISA, and a two-fold increase in antibody titer at M6 compared to the titer at Day 0.
Secondary objectives and assessment criteria	The secondary objectives of this trial are the following: - To evaluate clinical and biological safety of the vaccine strategies. - To evaluate and compare immune response: o Functional immune response of the different vaccine strategies at M6 using opsonophagocytosis (OPA), o Extension of serotype coverage after PPV23 injection at M6, assessed on 3 PPV23 specific serotypes : 10A, 12F and 15B serotypes, o Sustainability and evolution of immune response over time after the beginning of each vaccine strategy and an eventual prime-boost effect. - To assess determinants of immune response to pneumococcal vaccine strategies at M6 (including vaccine strategy, age, gender, previous immunosuppressive or immunomodulatory agents, time from previous unconjugated vaccination, previous PPV23 injections). - To describe the frequency of occurrence of invasive pneumococcal infections in the different vaccine strategies. The secondary assessment criteria of this trial are: - Safety: o Local and/or systemic solicited reactions 7 days following each vaccination: proportion of participants with an event; number, nature, grade and time of occurrence. o Any adverse event during the trial related or possibly related to vaccine immunization: proportion of participants with an event; number, nature, grade and time of occurrence. o Any adverse event during the trial related to vaccine immunization and leading to discontinuation of the immunization regimen: proportion of participant with an event; number, nature, grade and time of occurrence; o Any serious adverse event during the study, regardless of the relationship to vaccine immunisation: proportion, number, nature, grade and time of occurrence. o Proportion of patients with vasculitis flare according to EULAR criteria during the study period, and time to disease relapse. - Immune response: o Titer of specific IgG against the 12 serotypes common to both

	conjugate and unconjugated vaccines (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19 A, 19F and 23F) measured by OPA at Day 0,M6, M12 and M18 and proportion of responding participants (according to the four predefined categories of numbers of positive responses used in the primary endpoint), with a positive response per serotype (defined by antibody titer ≥ LLOQ (Lower Limit Of Quantification) and a four-fold increase of antibody titer compared to level at Day 0). o Titer of specific IgG against the 12 serotypes common to both conjugate and unconjugated vaccines (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19 A, 19F and 23F) measured by OPA at Day 0, M6, M12 and M18 and proportion of responding participants (according to the four predefined categories of numbers of positive responses used in the primary endpoint), with a positive response per serotype (defined by antibody titer ≥ LLOQ). o Titer of specific IgG against the 12 serotypes common to both conjugate and unconjugated vaccines (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19 A, 19F and 23F) measured by OPA at Day 0, M6, M12 and M18 and proportion of responding participants (according to the four predefined categories of numbers of positive responses used in the primary endpoint), with a positive response per serotype (defined by a four-fold increase of antibody titer compared to level at Day 0). o Titer of specific IgG against the 3 specific serotypes of PPV23 (10A, 12F et 15B) at Day 0 and M6, and proportion of responding participants per individual serotype and per number of responses to these three serotypes at M6 (with a positive response per serotype defined by a titer of specific IgG ≥1 µg/mL using ELISA and antibody titer doubling compared to level at Day 0). o Titer of specific IgG against the 3 specific serotypes of PPV23 (10A, 12F et 15B) at Day 0 and M6, and proportion of responding participants per individual serotype and per number of responses to these three serotypes at M6 (with a positive response per serotype defined by a titer of specific IgG ≥1 µg/mL using ELISA). o Titer of specific IgG against the 3 specific serotypes of PPV23 (10A, 12F et 15B) at Day 0 and M6, and proportion of responding participants per individual serotype and per number of responses to these three serotypes at M6 (with a positive response per serotype defined by antibody titer doubling compared to level at Day 0). o Titer of specific IgG against the 12 serotypes common to both conjugate and unconjugated vaccines (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19 A, 19F and 23F) measured by ELISA at M1 and M5, M12 and M18 (titers and proportion of responding participants, (according to the four predefined categories of numbers of positive responses used in the primary endpoint)with a positive response per serotype (defined by a titer of specific IgG ≥1 µg/mL using ELISA, and a two-fold increase in antibody titer at M6 compared to the titer at Day 0. Proportion of patients with specific IgG ≥1 µg/mL against the 12 serotypes (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19 A, 19F and 23F) measured by ELISA at M1, M5, M6, M12 and M18.

	○ Proportion of patients with a two-fold increase of specific IgG against the 12 serotypes (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19 A, 19F and 23F) measured by ELISA at M1, M5, M6, M12 and M18. - Modelling of the determinants of immunogenicity: vaccine strategy, age, sex, previous immunosuppressive or immunomodulatory agents, time from previous unconjugated vaccination, previous PPV23 injections - Number and time to severe invasive pneumococcal infections during the study period. The description of any invasive pneumococcal infections and community acquired pneumonia occurring during the time course of the study will be evaluated by the documentation of invasive bacterial infections with biological +/- radiological examinations in case of suspected invasive infection.
Experimental design	This is a comparative, multicenter, prospective, randomized, open label, phase 2 trial in France, comparing two innovative “reinforced” anti-pneumococcal vaccine strategies to standard vaccination regimen in patients with ANCA-associated vasculitides receiving rituximab therapy. Participants will be randomized 1:1:1 to three parallel arms (two arms receiving two different re-inforced vaccine strategies, one common control arm receiving the standard vaccination regimen).
Population involved	Patients with ANCA-associated vasculitides treated with rituximab therapy
Inclusion criteria	1. Participants with a diagnosis of ANCA-associated vasculitis, either granulomatosis with polyangiitis (GPA, Wegener) or microscopic polyangiitis (MPA), according to ACR 1990 criteria and/or revised Chapel Hill Consensus Conference definitions and/or European Medical Agency algorithm, 2. Participants (males and females) aged of 18 years or older, 3. Participants with childbearing potential having reliable contraception for all the duration of the study such as established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device (IUD) or intrauterine system (IUS); barrier methods: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; male partner sterilization (the vasectomized partner should be the sole partner for that subject); surgical sterilization (hysterectomy, bilateral oophorectomy, tubal ligation) or true abstinence (when this is in line with the preferred and usual lifestyle of the subject) prior to enrollment at D0 4. Participants with newly-diagnosed disease at the time of inclusion or presenting with a relapse of the disease. For relapsing patients, maintenance therapy at stable dose during the last 3 months will be admitted: prednisone dose ≤10 mg/day, azathioprine dose ≤3 mg/kg/day, methotrexate dose ≤25 mg/week, or mycophenolate mofetil dose ≤3 g/j. 5. Participants with an active disease defined as a BVAS ≥ 3, 6. Participants planned to receive rituximab as induction therapy using the recommended regimen (i.e. 375 mg/m2/week for 4 consecutive weeks), 7. Participants able to give written informed consent prior to participation in the study,

	8. Participants covered by social security regimen or equivalent.
Exclusion criteria	1. Participants with eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss) or other vasculitis, 2. Participants with acute infections or chronic active infections at inclusion visit. 3. Documented positive serology result for HIV, HBV (Ag Hbs), HCV at inclusion. 4. Participants with disease associated with decreased immune response (splenectomy, hematopoietic stem cell transplantation, primary immune deficiency such as common variable immunodeficiency, cancer within the previous 5 years, drepanocytosis), 5. Participants treated with rituximab within the previous 12 months, 6. Participants who have received blood, blood products, and/or plasma derivatives including parenteral immunoglobulin preparations in the past 3 months before enrolment, 7. Participants treated with new other immunosuppressive or immunomodulatory agents within the previous 3 months (including cyclophopshamide, anti-TNF-alpha, intravenous immunoglobulins, abatacept), 8. Participants treated with prednisone dose >10 mg/day for a duration greater than 21 days before inclusion, 9. Participants with vaccination with a conjugate anti-pneumoccocal vaccine at any time, 10. Participants with vaccination with PPV23 within the previous 3 years, 11. Participants who have received any another vaccines within 4 weeks prior to enrolment or who are planning to receive any vaccine within the first 6 months of the study (except annual influenza vaccination and hepatitis B virus vaccination which are permitted before and after each vaccination visit of the study and then allowed at any time during the study follow up) 12. Pregnant women and lactation, 13. Participants with contraindication to use rituximab, 14. Participants with contraindication to intramuscular injections (hemophilia, anticoagulant therapy (excepted if subcutaneously), thrombocytopenia < 50 000/mm^3) 15. Participants with hypersensitivity to previous vaccination 16. Participants with hypersensitivity to aluminium phosphate, phenol or protein CRM_{197} protein from Corynebacterium diphtheria. 17. Participants included in another investigational therapeutic study in the month prior D0. Participation to an observational research is allowed. 18. Participants under legal guardianship or mental incapacity
Benchmark treatment	Arm A : Prime-boost strategy combining a single dose of 13-valent pneumococcal conjugate vaccine (Prevenar, PCV13) at Day 0 (lying within a window of ± 2 days of the first infusion of rituximab), followed by a single dose of 23-valent unconjugated vaccine (Pneumovax®PPV23) at month 5 (M5)
Treatment being tested	Two reinforced innovative vaccine strategy : - Arm B (innovative vaccine strategy 1): prime-boost strategy combining 2 doses of PCV13 at Day 0 and 2 doses of PCV13 at Day 7, followed by a single dose of PPV23 at M5

	- Arm C (innovative vaccine strategy 2): prime-boost strategy combining 4 doses of PCV13 at Day 0, followed by a single dose of PPV23 at M5
Other procedures added by the research	Assessment of immunogenicity using ELISA and opsonophagocytosis on serum samples
Risks added by the research	Risk C
Number of participants chosen	120 participants (40 per arm) The sample size per arm has been calculated to allow for a comparison of each reinforced strategy to the standard strategy with 90% power and a 2.5% two-sided type I error (adjusted for two comparisons) assuming the following response proportions for the ordered categorical endpoint: a) standard strategy: 30%, 40%, 20%, 10%, and b) reinforced strategy: 10%, 20%, 45%, 25% in response categories 0-3, 4-6, 7-9, and 10-12 serotypes, respectively
Number of centres	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 ANCA-associated vasculitides. As previous trials conducting by the FVSG on this topic, around 50 centers will participate in the PNEUMOVAS research.
Research period	Duration of inclusion : 24 months Duration of participation : 18 months Total duration : 42 months
Number of inclusions expected per centre and per month	0,1 patient expected per centre and per month
Statistical analysis	Participants' characteristics will be described per randomized arm. The primary endpoint analysis will be conducted in the modified intention-to-treat population (i.e. all randomized participants who are eligible and have received at least one vaccine injection will be analyzed in their randomized arm), with imputation of missing endpoint data as failure in the main analysis (i.e. imputation of the lowest response category of the primary endpoint). The comparison between Arm B and Arm A, and between Arm C and Arm A, respectively, of the participants' distribution according to four categories of response will be performed using a proportional odds model (POM; McCullagh, Journal of the Royal Statistical Society: Series B, 1980), as previously recommended (Pedrono, J Clin Epidemiol 2009). An odds-ratio (OR) for each comparison will be estimated in the model and reported with its 97.5% confidence interval. Using a Bonferonni correction for two comparisons, a statistical test will be conducted at the 2.5% level for each comparison to assess whether the OR is statistically different from 1 (null effect). The OR provides a measure of the benefit in terms of immunogenicity of being treated with the given "Innovative vaccine strategy" (Arm B or C, respectively) compared to "Arm A: Standard vaccination strategy". Additional sensitivity analyses will be performed. Analyses of secondary endpoints will be performed with a type I error rate of 5% (2-sided). Safety endpoints will be analyzed per arm. Antibody titers will be described using geometric means.

Funding source	PHRC-N 2015
Independent Data Safety Monitoring Board anticipated (iDSMB)	Yes – meetings at least on an annual basis

1 STUDY PLAN

Arm A	Inclusion		Vaccination and Post vaccination Phase						
Visit type	Clinic	Clinic	Clinic	Clinic	Clinic	By phone	Clinic	Clinic	Clinic
Study day	D0	D7	D7+7days	M1-D30	M5-D150	M5+7days	M6-D180	M12-D360	M18-D540
Time window	Rituximab +/- 2days	+/- 1 day	+/- 1 day	+/- 10 days	+/- 7 days	+/- 1 day	+/- 7 days	+/- 15 days	+/- 15 days
Informed consent	x								
Assign participant code	x								
Randomization	x								
Medical History	x								
Concomitant therapy	x	x		x	X	x	x	x	x
Clinical exam	x	x	x	x	X		x	x	x
Review of inclusion and exclusion criteria	x								
Blood Draw for ELISA (12 serotypes: 1,3,4,5,6B,7F,9V,14,18C,19A,19F,23F)	x			x	X		x	x	x
Blood Draw for ELISA (3 serotypes: 10A, 12F, 15B)	x						x		
Blood Draw for OPA (12 serotypes: 1,3,4,5,6B,7F,9V,14,18C,19A,19F,23F)	x						x	x	x
Blood draw to perform a serum bank (7mL)	x			x	X		x	x	x
Safety blood draw	x*	x*	x*		x*		x		
Collect data from other routine follow-up of vasculitis assessment	x	x	x	x	X		x	x	x
Pregnancy Test (dipstick)	x				X				
Vaccine administered PCV13 (Prévenar13)	x								
Vaccine administered PPV23 (Pneumovax®)					X				
30 minutes follow up	x				X				
Participant card	x								
Diary card (DiCa) provided	1	2**	3**	4	5 and 6		7	8	
Diary card reviewed and collected		1	2	3	4		5 and 6	7	8
Assess adverse events	x	x	x	x	X	x	x	x	x
Study Termination									x
Volume of blood (ml)/visit ***	25.5	0	0	17	17	0	25.5	25.5	25.5

*Blood draw and safety analysis performed during routine follow up of vasculitis
** Different diary card exist for each randomisation arm. Be careful to use the diary card corresponding to volunteer's arm.
***In accordance with local laboratory procedures, an additional blood draw of 3mL will be asked before each blood draw in order to purge the needle. Variation in amount of the blood draw can happen in accordance with local laboratory procedures. These variations will not exceed 5ml for a visit (applicable only for analysis performed by local laboratory).

Arm B	Inclusion		Vaccination and Post vaccination Phase						
Visit type	Clinic	Clinic	Clinic	Clinic	Clinic	By phone	Clinic	Clinic	Clinic
Study day	D0	D7	D7+7days	M1-D30	M5-D150	M5+7days	M6-D180	M12-D360	M18-D540
Time window	Rituximab +/-2days	+/- 1 day	+/- 1 day	+/- 10 days	+/- 7 days	+/- 1 day	+/- 7 days	+/- 15 days	+/- 15 days
Informed consent	x								
Assign participant code	x								
Randomization	x								
Medical History	x								
Concomitant therapy	x	x		x	X		x	x	x
Clinical exam	x	x	x	x	X		x	x	x
Review of inclusion and exclusion criteria	x								
Blood Draw for ELISA (12 serotypes: 1,3,4,5,6B,7F,9V,14,18C,19A,19F,23F)	x			x	X		x	x	x
Blood Draw for ELISA (3 serotypes: 10A, 12F, 15B)	x						x		
Blood Draw for OPA (12 serotypes: 1,3,4,5,6B,7F,9V,14,18C,19A,19F,23F)	x						x	x	x
Blood draw to perform a serum bank (7mL)	x			x	X		x	x	x
Safety blood draw	X *	X *	X *		X *		x		
Collect data from other routine follow-up of vasculitis assessment	x	x	x	x	X		x	x	x
Pregnancy Test (dipstick)	x	x			X				
Vaccine administered PCV13 (Prévenar13)	x (dose x 2)	x (dose x 2)							
Vaccine administered PPV23 (Pneumovax®)					X				
30 minutes follow up	x	x			X				
Participant card	x								
Diary card (DiCa) provided	1	2**	3**	4	5 and 6		7	8	
Diary card reviewed and collected		1	2	3	4		5 and 6	7	8
Assess adverse events	x	x	x	x	X	x	x	x	x
Study Termination									x
Volume of blood (ml)/visit***	25.5	0	0	17	17	0	25.5	25.5	25.5

* Blood draw and safety analysis performed during routine follow up of vasculitis
** Different diary card exist for each randomisation arm. Be careful to use the diary card corresponding to volunteer's arm.
***In accordance with local laboratory procedures, an additional blood draw of 3mL will be asked before each blood draw in order to purge the needle. Variation in amount of the blood draw can happen in accordance with local laboratory procedures. These variations will not exceed 5ml for a visit (applicable only for analysis performed by local laboratory).

Arm C	Inclusion		Vaccination and Post vaccination Phase						
Visit type	Clinic	Clinic	Clinic	Clinic	Clinic	By phone	Clinic	Clinic	Clinic
Study day	D0	D7	D7+7days	M1-D30	M5-D150	M5+7days	M6-D180	M12-D360	M18-D540
Time window	Rituximab +/-2days	+/- 1 day	+/- 1 day	+/- 10 days	+/- 7 days	+/- 1 day	+/- 7 days	+/- 15 days	+/- 15 days
Informed consent	x								
Assign participant code	x								
Randomization	x								
Medical History	x								
Concomitant therapy	x	x		x	x	X	x	x	x
Clinical exam	x	x	x	x	x		x	x	x
Review of inclusion and exclusion criteria	x								
Blood Draw for ELISA (12 serotypes: 1,3,4,5,6B,7F,9V,14,18C,19A,19F,23F)	x			x	x		x	x	x
Blood Draw for ELISA (3 serotypes: 10A, 12F, 15B)	x						x		
Blood Draw for OPA (12 serotypes: 1,3,4,5,6B,7F,9V,14,18C,19A,19F,23F)	x						x	x	x
Blood draw to perform a serum bank (7mL)	x			x	x		x	x	x
Safety blood draw	X *	X *	X *		X *		x		
Collect data from other routine follow-up of vasculitis assessment	x	x	x	x	x		x	x	x
Pregnancy Test (dipstick)	x				x				
Vaccine administered PCV13 (Prévenar13)	x (dose x 4)								
Vaccine administered PPV23 (Pneumovax®)					x				
30 minutes follow up	x				x				
Participant card	x								
Diary card (DiCa) provided	1	2**	3**	4	5 and 6		7	8	
Diary card reviewed and collected		1	2	3	4		5 and 6	7	8
Assess adverse events	x	x	x	x	x	x	x	x	x
Study Termination									x
Volume of blood (ml)/visit***	25.5	0	0	17	17	0	25.5	25.5	25.5

* Blood draw and safety analysis performed during routine follow up of vasculitis
** Different diary card exist for each randomisation arm. Be careful to use the diary card corresponding to volunteer's arm.
***In accordance with local laboratory procedures, an additional blood draw of 3mL will be asked before each blood draw in order to purge the needle. Variation in amount of the blood draw can happen in accordance with local laboratory procedures. These variations will not exceed 5ml for a visit (applicable only for analysis performed by local laboratory).

2 SCIENTIFIC JUSTIFICATION FOR THE RESEARCH

2.1 Hypothesis for the research

The study hypothesis is that a “reinforced” pneumococcal combined vaccine strategy in patients with ANCA-associated vasculitides treated with rituximab will induce a better immunogenicity than the current standard regimen, with an acceptable safety profile.

This study therefore aims at evaluating the immunogenicity and safety of two “reinforced” innovative pneumococcal vaccine regimen [two double doses (one double at D0 and one double at D7) or a quadruple dose of 13-valent anti-pneumococcal conjugate vaccine (PCV13) followed by one dose of 23-valent unconjugated vaccine (PPV23) at month 5], compared to the standard regimen (one dose of PCV13 followed by one dose of PPV23 at month 5), in patients with ANCA-associated vasculitides receiving rituximab therapy.

2.2 Description of knowledge relating to ANCA-associated vasculitides and pneumococcal vaccination

2.2.1 ANCA-associated vasculitides

Autoimmune disorders are frequent in the general population and are responsible for an increased morbidity and mortality (1).

Of the many autoimmune diseases, systemic vasculitides are inflammatory diseases of blood vessels, among which anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are the most severe diseases with life-threatening manifestations or complications. AAV include granulomatosis with polyangiitis (GPA, formerly Wegener’s granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome), the latter being usually considered separately from the others because of distinct pathophysiology. They are classified as AAV because most patients with generalized disease have antibodies against neutrophil enzymes, i.e. proteinase 3 (PR3) or myeloperoxidase (MPO). AAV affect small-to-medium-size blood vessels, with a predilection for the respiratory tract and kidneys (2).

2.2.2 Infections in ANCA-associated vasculitides

Patients with systemic vasculitides treated with corticosteroids associated with immunosuppressive or immunomodulatory agents are prone to develop severe infections, in particular bronchopneumonia, and half of these major infections occurs within 3 years after AAV diagnosis (3). In this setting, corticosteroids and immunosuppressive agents are independently associated with significantly higher risk of major infection (3). In a recent large study, cumulative incidence of infection at 1, 2 and 5 years was 51, 58 and 65% and severe infection was 22, 23 and 26%, and pulmonary and upper respiratory infections were most common, highest in the first 3 months (4).
Such infections represent the leading cause of death during the first year of follow-up, with frequent pneumonia (5)(6). After 5 years of follow-up, infections still account for 20% of causes of death (5).
Preventing pulmonary and upper respiratory infections in such conditions is thus mandatory to improve short-term and long-term prognosis. The development of anti-pneumococcal vaccine strategies with improved immunogenicity despite simultaneous administration of immunosuppressive or immunomodulatory agents could help to decrease this risk.

2.2.3 Rituximab in ANCA-associated vasculitides

Rituximab, an anti-CD20 monoclonal antibody, depletes B cells from the peripheral blood, lymph nodes and bonne marrow. B-cell depletion with rituximab has proved effective in hematological diseases and autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosis, and more recently ANCA-associated vasculitides.
Rituximab was shown to be non inferior to cyclophosphamide to induce remission with an acceptable safety profile in patients with systemic AAV in prospective controlled trials, by the administration of 375 mg/m^2/week for 4 consecutive weeks (7)(8). In addition, the prospective, randomized, controlled MAINRITSAN trial conducted by our group compared rituximab to azathioprine to maintain remission of AAV, and demonstrated that 500 mg-fixed dose of rituximab every 6 months was superior to azathioprine to maintain remission long-term follow-up (9). Rituximab has now become a standard of care in patients with AAV, as well in induction phase as in maintenance phase.

Regarding the risk of infections under rituximab therapy, no data is available during AAV. In contrast, in other vasculitides such as cryoglobulinemia vasculitis, even if rituximab plus corticosteroids showed a greater therapeutic efficacy compared to other therapeutic

regimens, it was significantly associated with a higher risk of severe infections, mainly bronchopneumonia, fatal in half of cases (10).
In addition, in the setting of autoimmune diseases, the rate of serious bacterial infectious events after rituximab treatment was high at 18.7 per 100 patient-years. Risk factors for serious bacterial infectious events at the initiation of rituximab included lower immunoglobulins G (IgG) levels, lower B-cell count and creatinine clearance ≤45 ml/min. Conversely history of pneumococcal vaccination significantly decreased the risk of serious bacterial infectious events (11).
In another study in AAV, risks factors for infections were also low IgG level during rituximab therapy and possibly the cumulative rituximab dose (12).

2.2.4 Pneumococcal vaccination

The most effective strategy to limit the risk of pneumococcal infection is anti-pneumococcal vaccination. Currently, two types of vaccines are available in adults in France to prevent pneumococcal infections, i.e. 13-valent anti-pneumococcal conjugate vaccine (PCV13) and polysaccharide 23-valent unconjugated vaccine (PPV23). They induce both the synthesis of anticapsular IgG, which have both neutralizing and opsonizing activities.
PPV23 vaccine has been on the market since 1982 for children older than 5 years and adults who present risk factors for invasive pneumococcal disease, including conditions associated with immunosuppression. One dose of PPV23 vaccine contains 25 µg of each of the 23 serotypes. The PPV23 covers 78% of invasive infections <2 years and 74.4% to 80.5% of bacteremia and 67.3 to 71.1% of pneumococcal meningitis in adults> 16 years.
In addition, vaccination of children aged from 2 months to 5 years by pneumococcal conjugate vaccine was introduced in France in 2001 to reduce invasive pneumococcal infections. PCV13 obtained an extension of European Marketing Authorization for the adults over 50 years at risk of pneumococcal disease in October 2011. It recently also obtained an extension of marketing authorization in France (HAS, Commission de la transparence, avis 18 décembre 2013 modifié le 04/02/2014) for adults from 18 to 50 years to prevent invasive pneumococcal disease.

Although reduced, the immunogenicity of pneumococcal vaccine persists in patients treated with immunosuppressive agents. In rheumatoid arthritis, rituximab-treated patients have decreased responses to pneumococcal polysaccharide vaccine (57% of patients had a 2-fold rise in titer in response to ≥1 serotype, compared with 82% of patients treated with methorexate alone) (13). A recent meta-analysis was conducted to summarize the impact of

rheumatoid arthritis treatments on the humoral response to pneumococcal and influenza vaccines. Influenza vaccination response was reduced in patients treated by rituximab compared to methotrexate (OR 0.44 [95% CI (0.17-1.12] for H1N1, OR 0.11 [95% CI (0.04-0.31] for H3N2, and OR 0.29 [95% CI (0.10-0.81] for B) but not by anti-TNFα. Pneumococcal vaccination response was also reduced with rituximab (OR 0.25 [95% CI 0.11-0.58] for 6B and OR 0.21 [95% CI 0.04-1.05] for 23F) compared to methotrexate, but not with anti-TNFα therapy (14). In contrast, in patients with ANCA-associated vasculitides, no data are available emphasizing the importance of the present trial.
Therefore, in patients treated with immunosuppressive agents, a combined vaccine strategy by one dose of PCV13 followed by one dose of PPV23 at least 8 weeks later is now recommended by the Haut Conseil de Santé Publique in France in adult patients who have never received pneumococcal vaccines or in whom the last vaccination was more than 3 years ago. This strategy allows to combine the immunogenicity of PCV13 with the larger serotype coverage of PPV23.

According to World Health Organization (WHO) recommendations published in 2003, the assessment of immunogenicity induced by these vaccines is based on the measurement of specific IgG against the different serotypes 4 weeks after vaccination using Enzyme Linked Sorbent Assay (ELISA) (15). Recently, the importance of evaluating the functional activity of these anti-pneumococcal antibodies using opsonophagocytosis (in combination with ELISA) was emphasized in a consensus conference held in Ottawa in 2008 (16).

2.3 Summary of relevant pre-clinical experiments and clinical trials

2.3.1 Studies on efficacy

Previous studies comparing vaccine responses following treatment with rituximab versus placebo showed that responses are strongly reduced under rituximab therapy. However, most of these studies were performed for influenza vaccination or with unconjugated anti-pneumococcal polysaccharide vaccine. It is thus unclear which anti-pneumococcal vaccine strategy provides the best immune response to reduce the risk of invasive infections.

In a pilot study on 20 smoldering multiple myeloma, immunogenicity of PCV13 in untreated patients was assessed after 1 dose of PCV13. Quantitative antibody titers were measured by ELISA for 7 vaccine serotypes at baseline, 1 and 6 months after vaccination. Patients were defined as responders if they were responding to at least 4 serotypes. Twelve patients (60%)

were responders in ELISA, among whom 10 were also responders in OPA. Seventeen patients (85%) were at least responding to one serotype, but only 2 (10%) were responding to the 7 serotypes in ELISA. At 6 months, only 6 of the 10 tested responders had persistent immunity. This study showed that one dose of PCV13 was immunogenic in patients with untreated smoldering multiple myeloma, but only 60% were responding to at least 4 serotypes. This study concluded that a more immunogenic schedule using a double or quadruple dose of PCV13 was needed to induce sufficient immune memory before injection of PPV23 and obtained an extended protection.

A study was performed to examine the ability of patients undergoing autologous hematopoietic stem cell transplantation to respond to a pneumococcal conjugate vaccine given after transplantation and to determine whether there was a potential benefit of immunizing these patients before stem cell collection. Sixty-one patients scheduled for autologous hematopoietic stem cell transplantation were randomized to receive either PCV or no vaccine before stem cell collection. After stem cell reinfusion, all study patients were immunized with PCV at 3, 6, and 12 months. Serotype-specific pneumococcal antibody concentrations were significantly higher in patients immunized with PCV before stem cell collection compared with patients not immunized before their stem cells were collected. In addition, after the 3-dose series of PCV after autologous hematopoietic stem cell transplantation, >60% of study patients had protective concentrations of antibody to **all** vaccine serotypes regardless of immunization before stem cell collection (17).

Lode et al. conducted in 2011 a randomised, open-label study evaluating pneumococcal protein conjugate vaccine in healthy adults aged ≥70 years with no history of pneumococcal vaccination. Patients were randomized to receive 7- or 9-valent pneumococcal conjugate vaccine (PCV7 or PCV9) at 1 × (PCV7 only), 2 × (PCV7+PCV9), or 4 × (2 × PCV7+2 × PCV9) dosage. Controls received PPV23. Both geometric mean concentration enzyme-linked immunosorbent assay and opsonophagocytic activity antibody titers assessed 1 month after vaccination were significantly increased over baseline titers for all PCV7 serotypes, with a trend toward a **dose-dependent immune response** (18).

In a dose-ranging study conducted in seniors who had received PPV23 at least 5 years prior to enrollment, patients were assigned to receive 1/5, 1, 2 or 4 doses of 7-valent pneumococcal conjugate (PCV7) vaccine or a dose of PPV23. There was evidence of a **dose response to PCV7 vaccine** showing that increased dose of vaccine was more immunogenic in elderly adults previously vaccinated with PPV23 vaccine (19).

2.3.2 Studies on safety

In the study by Lode et al. conducted in patients over 70 years receiving 1, 2 or 4 doses of 7- or 9- valent pneumococcal conjugate vaccine, local reactions for the quadruple dose, but not for the double dose, were significantly more frequent than for one dose. The most frequently reported local reactions within 7 days after vaccination were injection site pain, followed by redness and swelling. Differences in percentages among treatment groups were statistically significant for most types of reactions, with the highest percentages noted in the quadruple dose group. Pain that interfered with limb movement occurred statistically significantly more often in the quadruple dose group (13%) than in any of the other three groups (≤4%). The majority of local reactions were reported within the first 3 days after vaccination. The mean duration ranged from 1 to 2.7 days, with the highest mean duration in the quadruple dose group. However, no significant differences between groups in systemic events such as fatigue, headache, chills, rash, muscle pain, or joint pain were noted, and less than 3% of participants reported mild fever with no difference in incidence between groups. No vaccine-related serious adverse events were reported in any arm (18).

In the study by Jackson et al., signs or symptoms of local reactions tended to be reported by a significantly lower proportion of participants in the lower dose PCV groups compared with the PPV23 group, but reaction rates were comparable between the quadruple dose PCV group and the PPV23 group. Across the PCV groups, there was a significant trend toward a higher frequency of localized swelling in the vaccinated arm, pain in the vaccinated arm, and limitation of movement of the vaccinated arm with increasing vaccine volume (19).

2.4 Justification of the research

This multicenter, prospective, randomized, controlled trial will compare two innovative anti-pneumococcal vaccine strategies to standard vaccination regimen in patients with ANCA-associated vasculitides receiving rituximab therapy. This trial will be the first prospective randomized trial evaluating different anti-pneumococcal vaccine strategies in patients receiving rituximab in order to improve vaccine immunogenicity. Preventing pulmonary and upper respiratory infections in patients with ANCA-associated vasculitides is mandatory to improve short-term and long-term prognosis of these patients, and the development of anti-pneumococcal vaccine strategies with improved immunogenicity could help to decrease this risk.

3 OBJECTIVES

3.1 Primary objective

The primary objective of this trial is:

- To compare the immunogenicity at month 6 (M6) of two “reinforced” innovative pneumococcal vaccine regimens (two double doses or a quadruple dose of PCV13 followed by one dose of PPV23 at month 5), to the standard regimen (one dose of PCV13 followed by one dose of PPV23 at month 5), in patients with ANCA-associated vasculitides receiving rituximab therapy.

3.2 Secondary objectives

The secondary objectives of this trial are the following:

- To evaluate clinical and biological safety of the vaccine strategies.
- To evaluate and compare:
    - Functional immune response of the different vaccine strategies at M6 using opsonophagocytosis (OPA),
    - Extension of serotype coverage after PPV23 injection at M6, assessed on 3 PPV23 specific serotypes : 10A, 12F and 15B serotypes,
    - Sustainability and evolution of immune response over time after the beginning of each vaccine strategy and an eventual prime-boost effect.
- To assess determinants of immune response to pneumococcal vaccine strategies at M6 (including vaccine strategy, age, gender, previous immunosuppressive or immunomodulatory agents, time from previous unconjugated vaccination, previous PPV23 injections).
- To describe the frequency of occurrence of invasive pneumococcal infections in the different vaccine strategies.

The record of any specific local and systemic adverse events will use a specific question for each of the following symptoms and the diary cards as support : local pain, cutaneous reactions (erythema, induration, itching, blistering), temperature, headache, asthenia, myalgia, and arthralgia. The grade and relatedness to vaccine administration will be assessed by the investigator.

4 PLAN FOR THE RESEARCH

4.1 Concise description of the primary and secondary assessment criteria

4.1.1 Primary assessment criterion

- The primary assessment criterion of this trial is immune response at M6 against 12 pneumococcal serotypes, according to four ordered categories of response (20): positive response to 0-3, 4-6, 7-9, or 10-12 serotypes common to the PCV13 and PPV23 vaccines. This endpoint will be analyzed as the number and proportion of participants in each of the four response categories
- According to international criteria, a participant will be considered as responder to given serotype if he has, at M6, i.e.one month after the PPV23 injection, a titer of specific IgG ≥1 µg/mL using ELISA, and two-fold increase in antibody titer at M6 compared to the titer at Day 0.

The methodological rational for this endpoint is detailed in chapter 5.2.

4.1.2 Secondary assessment criteria

The secondary assessment criteria of this trial are:

- Safety will be assessed according to the following endpoints:
    - Local and/or systemic solicited reactions 7 days following each vaccination: proportion of participants with an event; number, nature, grade and time of occurrence.
    - Any adverse event during the trial related or possibly related to vaccine immunization: proportion of participants with an event; number, nature, grade and time of occurrence.
    - Any adverse event during the trial related to vaccine immunization and leading to discontinuation of the immunization regimen: proportion of participants with an event; number, nature, grade and time of occurrence;
    - Any serious adverse event during the trial, regardless of the relationship to vaccine immunisation: proportion, number, nature, grade and time of occurrence.
    - Proportion of patients with vasculitis flare according to EULAR (21) criteria during the study period, and time to disease relapse.

- In case of discordance with regards to the nature and grade (≥3) of the AE, between the site investigator and the Endpoint Adjudication Committee (chapter 11.2), the committee's opinion will be taken into account for the statistical analysis of the endpoints.

- Immune response will be assessed according to the following endpoints :
  - Titer of specific IgG against the 12 serotypes common to both conjugate and unconjugated vaccines (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19 A, 19F and 23F) measured by OPA at Day 0,M6, M12 and M18 and proportion of responding participants (according to the four predefined categories of numbers of positive responses used in the primary endpoint), with a positive response per serotype (defined by antibody titer ≥ LLOQ (Lower Limit Of Quantification) and a four-fold increase of antibody titer compared to level at Day 0).
  - Titer of specific IgG against the 12 serotypes common to both conjugate and unconjugated vaccines (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19 A, 19F and 23F) measured by OPA at Day 0, M6, M12 and M18 and proportion of responding participants (according to the four predefined categories of numbers of positive responses used in the primary endpoint), with a positive response per serotype (defined by antibody titer ≥ LLOQ).
  - Titer of specific IgG against the 12 serotypes common to both conjugate and unconjugated vaccines (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19 A, 19F and 23F) measured by OPA at Day 0, M6, M12 and M18 and proportion of responding participants (according to the four predefined categories of numbers of positive responses used in the primary endpoint), with a positive response per serotype (defined by a four-fold increase of antibody titer compared to level at Day 0).
  - Titer of specific IgG against the 3 specific serotypes of PPV23 (10A, 12F et 15B) at Day 0 and M6, and proportion of responding participants per individual serotype and per number of responses to these three serotypes at M6 (with a positive response per serotype defined by a titer of specific IgG ≥1 µg/mL using ELISA and antibody titer doubling compared to level at Day 0).
  - Titer of specific IgG against the 3 specific serotypes of PPV23 (10A, 12F et 15B) at Day 0 and M6, and proportion of responding participants per individual serotype and per number of responses to these three serotypes at M6 (with a positive response per serotype defined by a titer of specific IgG ≥1 µg/mL using ELISA).
  - Titer of specific IgG against the 3 specific serotypes of PPV23 (10A, 12F et 15B) at Day 0 and M6, and proportion of responding participants per individual serotype and per number of responses to these three serotypes at M6 (with a positive response per serotype defined by antibody titer doubling compared to level at Day 0).
  - Titer of specific IgG against the 12 serotypes common to both conjugate and unconjugated vaccines (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19 A, 19F and 23F) measured by ELISA at M1 and M5, M12 and M18 (titers and proportion of responding participants, (according to the four predefined categories of numbers of positive responses used in the primary endpoint)with a positive response per serotype (defined by a titer of specific IgG ≥1 µg/mL using ELISA, and a two-fold increase in antibody titer at M6 compared to the titer at Day 0. Proportion of patients with specific IgG ≥1 µg/mL against the 12 serotypes (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19 A, 19F and 23F) measured by

ELISA at M1, M5, M6, M12 and M18.
  - Proportion of patients with a two-fold increase of specific IgG against the 12 serotypes (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19 A, 19F and 23F) measured by ELISA at M1, M5, M6, M12 and M18.

- Modelling of the determinants of immunogenicity. Immunogenicity will be defined as in the primary endpoint. The following determinants will be investigated : vaccine strategy, age, sex, previous immunosuppressive or immunomodulatory agents, time from previous unconjugated vaccination, previous PPV23 injections
- Number and time to severe infections during the study period, in particular invasive pneumococcal infections. The description of any invasive pneumococcal infections and community acquired pneumonia occurring during the time course of the study will be evaluated by the documentation of invasive bacterial infections with biological analysis in case of suspected invasive infection. In case of discordance with regards to the nature and grade of the adverse events, between the local investigator and the Endpoint Adjudication Committee (chapter 11.2), the committee's opinion will be taken into account for the analysis of the endpoints.

4.2 Description of research methodology

4.2.1 Experimental plan

This is a comparative, multicenter, prospective, randomized, open label, phase 2 trial in France, comparing two innovative "reinforced" anti-pneumococcal vaccine strategies to standard vaccination regimen in patients with ANCA-associated vasculitides receiving rituximab therapy.

Participants will be randomized 1:1:1 to three parallel arms to receive:

- **Arm A** (standard vaccination regimen): prime-boost strategy combining a single dose of 13-valent pneumococcal conjugate vaccine (Prevenar, PCV13) at Day 0 (lying within a window of ± 2 days of the first infusion of rituximab), followed by a single dose of 23-valent unconjugated vaccine (Pneumovax® PPV23) at month 5 (M5)
- **Arm B** (innovative vaccine strategy 1): prime-boost strategy combining 2 doses of PCV13 at Day 0 and 2 doses of PCV13 at Day 7, followed by a single dose of PPV23 at M5
- **Arm C** (innovative vaccine strategy 2): prime-boost strategy combining 4 doses of PCV13 at Day 0, followed by a single dose of PPV23 at M5

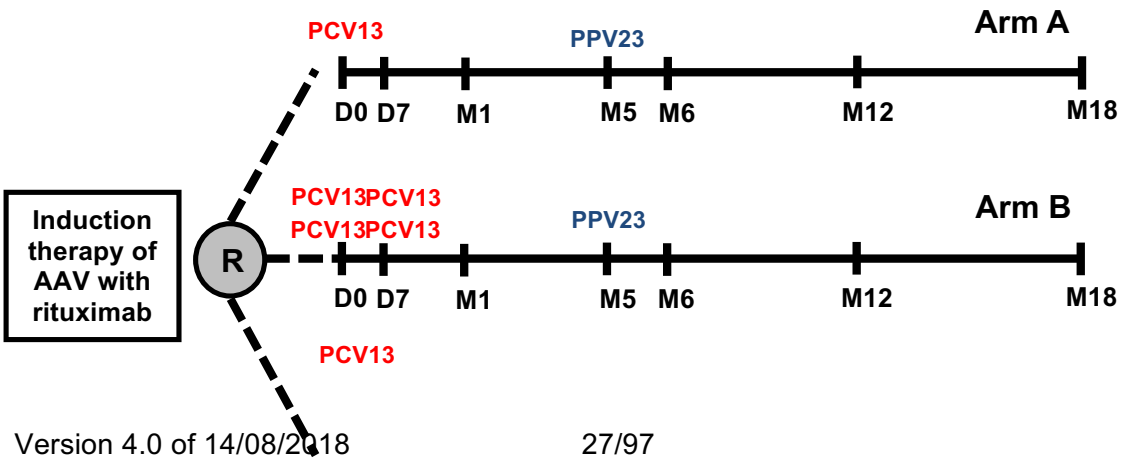
The choice of PCV13 dosages in the experimental arms (Arms B and C) relies on the assumption that given the initial strong immunosuppression in this patient population, a better antibody induction could either be obtained by giving a high (i.e. quadruple) initial single dose (Arm C) or by giving to 2 intermediate dose injections close in time (Arm B). The choice of 7 days between the 2 injections in Arm B is empirical, as published studies lack on this subject.

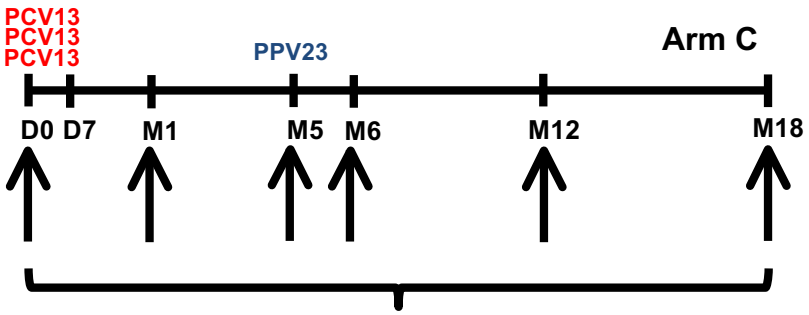
We decided to inject PPV23 vaccine at month 5 in order to be far away from the last rituximab infusion used as induction therapy, and to be one month before next rituximab infusion used in the maintenance phase.

All participants will receive rituximab at 375 mg/m2/week for 4 consecutive weeks, at Days 0 ± 2 days, Day 7 ± 2 days, Day 14 ± 2 days and Day 21 ± 2 days, as induction therapy of vasculitis flare, followed by 500 mg-rituximab infusion every 6 months as maintenance therapy, i.e. at Month 6, Month 12 and Month 18 (Stone, NEJM, 2010, Jones, NEJM, 2010; Guillevin, NEJM, 2014), as recommended.
Day 0 will be defined as the first vaccine injection (within ± 2 days of the first infusion of rituximab).
PCV13 vaccine injections will be performed at Day 0, and at Day 7 ± 1 day in the Arm B.
PPV23 injections will be performed at M5 ± 7 days in all arms.

Analysis of immune responses will be performed in a centralized laboratory blinded for the trial arm, by ELISA at Day 0 (pre-vaccination sample), M1, M5, M6, M12, and M18 for the 12 serotypes common to both conjugate and unconjugated vaccines, by OPA at Day 0, M6, M12, and M18 for the 12 serotypes common to both conjugate and unconjugated vaccines, and by ELISA at Day 0 and M6 for the 3 specific serotypes of PPV23.

The experimental plan is summarized in **Figure 1**.





4.2.2 Methodological rationale

ANCA-associated vasculitis are a rare disease, the study population for this trial is thus limited in size. The following methodological choices have been made in order to optimize statistical power for this comparative trial with a limited sample size (rare disease context).

Design

Participants will be randomized 1:1:1 to three parallel arms (two arms receiving two different re-inforced vaccine strategies, one common control arm receiving the standard vaccination regimen). A three-arm trial with a common control arm allows for an efficient use of the sample size allocated to the standard regimen. A Bonferonni-correction will be used to control test multiplicity due to the double comparison (two reinforced arms), thus achieving a stringent type I error rate control.

Primary endpoint

The primary efficacy endpoint is based on the immunogenicity of the evaluated vaccine strategies and is defined as the proportion of responding participants against pneumococcal serotypes at M6, according to four categories of response:

- Participants with positive response against 0 to 3 serotypes.
- Participants with positive response against 4 to 6 serotypes.
- Participants with positive response against 7 to 9 serotypes.
- Participants with positive response against 10 to 12 serotypes.

The definition of a positive response to a given serotype is based on international criteria (i.e., a titer of specific IgG ≥1 µg/mL using ELISA one month after the PPV23 injection, and two-fold increase in antibody titer at M6 compared to the titer at Day 0.

An ordered categorical immunogenicity endpoint is clinically and biologically relevant in trials of vaccine interventions covering several serotypes and has been previously proposed for anti-pneumococcal vaccine trials (20) (21). Using a clinical endpoint (i.e. incidence of invasive pneumococcal disease) as a primary endpoint is not feasible in this trial as it would require very large sample sizes. IgG antibody titers induced by anti-pneumococcal vaccination are however considered a correlate of clinical protection in anti-pneumococcal vaccine research (22)(23). Incidence of pneumococcal disease will be explored as a secondary endpoint.

In order to optimize statistical power for this comparative, the primary statistical analysis of the ordered categorical immunogenicity endpoint will use a proportional odds model as previously recommended in the context of vaccine trials (21).

Analysis of immune responses to the 12 serotypes common to both conjugate and unconjugated vaccines will be performed by ELISA at day 0 prior to vaccine administration, M1, M5, M6, M12, and M18 in a centralized laboratory blinded for the trial arm. Blinding of trial participants and site staff is not considered reasonable given the different number of injections in the three arms (each dose requiring an injection). Use of a centralized laboratory for these assessments and analyses in batch at M6 only for the primary endpoint then at the end of the trial for the others endpoint allow to limit background variability of measurements and thus also contributes to optimizing statistical power.

Safety monitoring

Relevant adverse events related to vaccination will be continuously monitored throughout the trial, and pausing rules have been specified in the protocol that trigger an ad-hoc iDSMB meeting in case of any safety concern (see chapter 11.3).

4.2.3 Number of participating centres

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 ANCA-associated vasculitides.
As previous trials conducting by the FVSG on this topic, around 50 centers will participate in the PNEUMOVAS research.

4.2.4 Randomization

Participants who fulfill all eligibility criteria for the study will be enrolled and randomized in a ratio of 1:1:1 between the three different parallel arms.
Randomization will be stratified on: personal history of PPV23 injection and age (≥ or < 65 years). Given the large number of centers and limited sample size, no stratification on the center will be performed.
The randomization list will be established centrally by the statistician of the EUCLID/F-CRIN clinical trials platform prior to the first inclusion.
The document describing the randomization specifications and the randomization list are kept confidentially in a secured place at the EUCLID/F-CRIN clinical trials platform and at URC/CIC Paris Descartes Necker Cochin.
The randomization list will be implemented in a randomization tool of the e-CRF on Cleanweb software by DRCD.
Allocation of a trial participant will only be visible to the remaining trial staff once this participant is randomized. Randomization will be performed by the site staff using the centralized tool in the e-CRF (https://cleanweb.aphp.fr/Ctms-02/portal/login) just prior to the first vaccine injection on Day 0.

4.2.5 Blinding methods and provisions put in place to maintain blinding

Trial participants and site staff are not blinded to the vaccine arm. The central laboratory performing the immunogenicity assessment (ELISA and OPA) will be blinded for the trial arm in order to limit measurement bias.

5 PROCEDURE FOR THE RESEARCH

Before any inclusion or acts related to the research, the investigator will collect signed informed consent from the participant.
All visits will be performed by physicians involved in the management of patients and/or physicians from the Centres d'Investigation Clinique included in REIVAC network, trained in Good Clinical Practice for clinical trials.
Study days should be calculated based on the date of the first vaccination (Day 0). One month will be equal to 30 days in this protocol.
During the first month after randomization, visits should be performed ± 1 day compared to reference visit (first vaccination), and ± 7 days from Day 30 to M6 (not included), and ± 15 days from M6 to M18 of follow-up.

Administration of vaccines will be performed at:

- Arm A : PCV13 at Day 0 ; PPV23 at Month 5
- Arm B : PCV13 (x2) at Day 0 ; PCV13 (x2) at Day 7 and PPV23 at Month 5
- Arm C : PCV13 (x4) at Day 0 ; PPV23 at Month 5

Participants will receive diary card at each visit which are the source document for the follow-up monitoring.
The diary card will be collected by the investigator at each visit. The diary card will collect safety information during 7 days after vaccine administration of local (surveillance of the point of injection) and general solicited reactions (temperature taken, headache, muscular pain…) and also concomitant treatments and non-related events between study visits.
Information on the diary card will not be entered directly into the database but will serve as support for the safety review made by the investigator to determine whether an adverse event (AE) has occurred between the visits. Any newly described information known at the visit must not be written into the diary card and must be described in the medical file. AE will be graded by the investigator according to protocol gradation scale and will be entered in the eCRF. If after review of events by the investigator, there are changes in the information recorded by the patient on the diary card, then the investigator must note the correct information in the medical file and justify the correction. The completed diary card will be kept at the site.
Participants will be provided with a ruler for daily measurement of the size of local reactions at vaccination sites, and with a thermometer for daily measurement of temperature

5.1 Informed consent

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

Person whose consent is sought	Who informs the person and obtains their consent?	When will the person be informed?	When will the consent be obtained?
Patient willing to participate and presenting with active ANCA-associated vasculitides	• Investigator • Sub-investigator	• During a routine visit	• Inclusion visit

5.2 Site of the visit

Visits will take place in the service during hospitalization or consultation (routine follow-up visit) according to disease severity and good clinical practices. Vaccination may be performed in the service or at the corresponding CIC (if applicable, depending on the internal organization of each study site).

Visit	Site	Performed by
D0	Service or CIC or both	• Investigator • Sub-investigator
D7	Service or CIC or both	• Investigator • Sub-investigator
D7+7days	Service or CIC or both	• Sub-investigator
M1	Service	• Investigator • Sub-investigator
M5	Service or CIC or both	• Investigator • Sub-investigator
M5+7days	By phone	• Investigator • Sub-investigator
M6	Service	• Investigator • Sub-investigator
M12	Service	• Investigator • Sub-investigator
M18	Service	• Investigator • Sub-investigator

5.3 Inclusion visit : vaccination

During the screening period, eligibility will be determined based on the inclusion and non-inclusion criteria, medical records will be screened by study investigators, who will then propose to the patient to participate to the study during a phone call or a follow-up visit.
The investigator will explain the study to the patient. A copy of the information and consent forms will be given to him for reading and for having further information about the study (by email, by post, or personally).

After a patient has consented to participate to the study, the informed consent form (ICF) will be signed. The signed ICF **must be obtained prior to initiating any study specific assessments.** A unique 9-digit participant code is assigned sequentially by the site and is documented in the Screening Log and the medical file. Once assigned to a participant, the participant number cannot be reused.

The inclusion visit will represent Day 0. This visit takes place within a ± 2 days window of the first routine care rituximab administration.
Participants meeting all the inclusion criteria and none of the exclusion criteria and willing to participate in the study will be randomized.

During this visit, investigator or authorized study staff will:

□ Explain the study to the patient

□ Answer any questions about the purpose, process, constraints, risks and benefits of the study, depending of the participant's needs in order to properly understand the study.

□ Ask for their agreement to participate

□ Ensure that the patient has enough time to take freely his decision to read and understand the informed consent form.

□ Review all inclusion and non-inclusion criteria for eligibility of the patient

□ Obtain ICF signed by the patient and the investigator

□ Obtain demographic data from the patient, including age

□ Collect information about the medical history of the patient:

- Description of the previous relapses of the disease: Numbers of relapses, characteristics of treatments taken during outbreaks preceding that at inclusion
- documented history of pneumococcal vaccination (family doctor; vaccination certificate or medical record)
- Any medical history that may be relevant to participant eligibility for his participation to the study such as prior vaccinations, concomitant medications, and previous and ongoing illnesses or injuries or other chronic disease
- Any other significant medical conditions which may impair the assessment of the study.
- Results from routine assessment within the previous 12 months prior to Day 0: AbHBs - AgHBs –AbHBc- - AbHCV - AbHIV

□ Perform a clinical examination with measurement of vital signs (temperature, blood pressures and pulse) weight and height, inspection of the skin and check for the presence of respiratory, cardiovascular, neurological an abdominal disorders and psychiatric problems. An assessment of cervical and axillary lymph nodes will also be undertaken.

□ Perform clinical examination to collect manifestations related to active ANCA-associated vasculitis

□ Record prior (within one month) and dosage concomitant therapy, including recording of contraceptive methods in women

□ Record : BVAS, VDI at inclusion

□ Assign the participant identification code after verification of the eligibility criteria by entering the data collected into the eCRF:

|__|__|__| / |__|__|__|__| / |__|__|
Study site number Inclusion number Participant's initials

□ Perform a urine pregnancy test (dipstick) for women of childbearing age. The physician will ensure that urine beta-HCG test is negative.

□ Check all contraindications regarding the vaccination

□ Prescribe sampling before vaccination for:

- routine assessment (data will be collected for the research): hemogram, C-reactive protein, Glycemia, renal function (urea, creatinine, creatinine clearance,

glomerular filtration rate), serum protein electrophoresis, IgG, IgA and IgM, urine analysis, ANCA using immunofluorescence and ELISA, CD19+ cells, CD3+, CD4+ and CD8+ cells

- constitution of a serum bank
- performing ELISA
- performing OPA

□ Randomize by e-CRF

□ Perform injection(s) of PCV13 single, double or quadruple dose considering the randomization arm, as described in chapter 7.1.3

□ Perform follow-up of 30 minutes after vaccination: The investigator will inspect the site of vaccine administration for cutaneous reactions and ask specific questions regarding local (pain, erythema, induration, itching, blistering) and general symptoms (headache, asthenia, myalgia, arthralgia), and measure vital signs (temperature, blood pressure, pulse)

□ Record any significant medical events: local and systemic vaccine related events (any grade); any other grade ≥3 event

At the end of the visit, the investigator or authorized study staff will:

□ Explain to the patient how and how often he/she should filled the diary card (DiCa)

□ Give to the participant:

- a diary card (DiCa) that should be filled until the next visit.
- a ruler to measure any skin reactions
- a digital thermometer.
- a participant card, which must constantly be kept on the patient
- a new collection book to report prednisone tapering that should be filled during six months and brought back to every visit□ Enter data into the eCRF

In the event that the individual is determined ineligible for study participation, he/she will be considered as “screen failure”. The reason for screen failure must be documented on the Screening Log and into the eCRF.

5.4 Day 7 visit

This visit will take place at Day 7 +/- 1 day.
During this visit, investigator or authorized study staff will:

□ Verify medical history since last visit

□ Record new treatments taken and changes in treatment or dosage since the previous visit.

□ Record any significant medical events, hospitalizations, and serious adverse events (SAEs)

□ Perform a clinical examination with measurement of vital signs (temperature, blood pressures and pulse) weight, inspection of the skin and check for the presence of respiratory, cardiovascular, neurological an abdominal disorders and psychiatric problems. An assessment of cervical and axillary lymph nodes will also be undertaken. Examination of the vaccine injection site will also be performed.

□ Perform clinical examination to record manifestations related to active ANCA-associated vasculitis or remission.

□ Record any significant medical events: local and systemic vaccine related events (any grade); any other grade ≥3 event

□ Prescribe sampling (before vaccination, for group B) for routine assessment (data will be collected for the research): hemogram, C-reactive protein, Glycemia, renal function (urea, creatinine, creatinine clearance, glomerular filtration rate).

□ Review and collect DiCa data

□ Record any specific local and systemic adverse event since the last visit (using a specific question for each of the following symptoms and the diary card as support): local pain, cutaneous reactions (erythema, induration, itching, blistering), temperature, headache, asthenia, myalgia, and arthralgia. The grade and relatedness to vaccine administration will be assessed by the investigator.

Specifically for Arm B:

□ *Perform a urine pregnancy test (dipstick) for women of childbearing age. The physician will ensure that urine beta-HCG test is negative.*

□ *Check all contraindications regarding the vaccination*

□ *Perform injection of PCV13 double dose considering, as described in chapter 7.1.3*

□ *Perform follow-up of 30 minutes after vaccination: The investigator will inspect the site of vaccine administration for cutaneous reactions and ask specific questions regarding local (pain, erythema, induration, itching, blistering) and general symptoms (headache, asthenia, myalgia, arthralgia), and measure vital signs (temperature, blood pressure, pulse)*

At the end of the visit, the investigator or authorized study staff will:

□ Give to the participant a new diary card (DiCa) that should be filled until the next visit

□ Enter data into the eCRF

5.5 Day 7 + 7 days visit

This visit will take place at Day 7 + 7 days +/- 1 day.
During this visit, investigator or authorized study staff will:

□ Verify medical history since last visit

□ Record new treatments taken and changes in treatment or dosage since the previous visit (with diary card as support).

□ Record any significant medical events: local and systemic vaccine related events (any grade); any other grade ≥3 event

□ Perform a clinical examination with measurement of vital signs (temperature, blood pressures and pulse) weight, inspection of the skin and check for the presence of respiratory, cardiovascular, neurological an abdominal disorders and psychiatric problems. An assessment of cervical and axillary lymph nodes will also be undertaken. Examination of the vaccine injection site will also be performed.

□ Perform clinical examination to collect manifestations related to active ANCA-associated vasculitis

□ Prescribe sampling before vaccination for routine assessment (data will be collected for the research): hemogram, C-reactive protein, Glycemia, renal function (urea, creatinine, creatinine clearance, glomerular filtration rate),

□ Review and collect DiCa data

□ Record any specific local and systemic adverse events since the last visit (using a specific question for each of the following symptoms and the diary card as support): local pain, cutaneous reactions (erythema, induration, itching, blistering), temperature,

headache, asthenia, myalgia, and arthralgia. The grade and relatedness to vaccine administration will be assessed by the investigator.

At the end of the visit, the investigator or authorized study staff will:

□ Give to the participant a new diary card that should be filled until the next visit

□ Enter data into the eCRF

5.6 Month 1 (Day 30) follow-up visit

This visit will take place at Month 1 (Day 30) +/- 10 days.
During this visit, investigator or authorized study staff will:

□ Verify medical history since last visit

□ Record new treatments taken and changes in treatment or dosage since the previous visit (with diary card as support).

□ Record any significant medical events: local and systemic vaccine related events (any grade); any other grade ≥3 event

□ Perform a clinical examination with measurement of vital signs (temperature, blood pressures and pulse) weight, inspection of the skin and check for the presence of respiratory, cardiovascular, neurological an abdominal disorders and psychiatric problems. An assessment of cervical and axillary lymph nodes will also be undertaken. Examination of the vaccine injection site will also be performed.

□ Perform clinical examination to collect manifestations related to active ANCA-associated vasculitis or remission

□ Perform routine BVAS, VDI evaluation

□ Prescribe sampling for:

- routine follow-up of vasculitis assessment (data will be collected for the research): Hemogram, C-reactive protein, , Glycemia, , renal function (urea, creatinine, creatinine clearance, glomerular filtration rate), serum protein electrophoresis, IgG, IgA and IgM, urine analysis, ANCA using immunofluorescence and ELISA,

- constitution of a serum bank

- performing ELISA

At the end of the visit, the investigator or authorized study staff will:

□ Enter data into the eCRF

□ Give to the participant a diary card that should be filled until the next visit

5.7 Month 5 follow-up visit

This visit will take place at Month 5 (Day 150) +/- 7 days.
During this visit, investigator or authorized study staff will:

□ Verify medical history since last visit

□ Record of new treatments taken and changes in treatment or dosage since the previous visit (with diary card as support).

□ Record any significant medical events: local and systemic vaccine related events (any grade); any other grade ≥3 event

□ Perform a clinical examination with measurement of vital signs (temperature, blood pressures and pulse) weight, inspection of the skin and check for the presence of respiratory, cardiovascular, neurological an abdominal disorders and psychiatric problems. An assessment of cervical and axillary lymph nodes will also be undertaken.

□ Perform clinical examination to record manifestations related to active ANCA-associated vasculitis or remission

□ Prescribe sampling before vaccination for:

- follow-up of vasculitis assessment (data will be collected for the research): Hemogram, C-reactive protein, , Glycemia, , renal function(urea, creatinine, creatinine clearance, glomerular filtration rate), serum protein electrophoresis, IgG, IgA and IgM, urine analysis, ANCA using immunofluorescence and ELISA,

- constitution of a serum bank

- performing ELISA

□ Perform BVAS, VDI evaluation

□ Perform a urine pregnancy test (dipstick) for women of childbearing age. The physician will ensure that urine beta-HCG test is negative.

□ Check all contraindications regarding the vaccination

□ Perform injection of PPV23 dose as described in chapter 7.1.3

□ Perform follow-up 30 minutes after vaccination. The investigator will inspect the site of vaccine administration for cutaneous reactions and ask specific questions regarding local (pain, erythema, induration, itching, blistering) and general symptoms (headache, asthenia, myalgia, arthralgia), and measure vital signs. (temperature, blood pressure, pulse)

At the end of the visit, the investigator or authorized study staff will:

□ Give to the participant 2 new diary cards (DiCa) (n°5 and n°6) that should be filled until the nexts visits.

□ Enter data into the eCRF

5.8 Month 5 + 7 days follow-up visit : by phone

This phone contact will take place at Month 5 (Day 150) + 7 days +/- 1 day.
During this phone contact, investigator or authorized study staff will:

□ Verify medical history since last visit

□ Record new treatments taken and changes in treatment or dosage since the previous visit (with diary card as support for the patient).

□ Record any significant medical events: local and systemic vaccine related events (any grade); any other grade ≥3 event

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□ Record any specific local and systemic adverse events since the last visit **At the end of the visit, the investigator or authorized study staff will:**

□ Enter data into the eCRF

5.9 Month 6 follow-up visit

This visit will take place at Month 6 (Day 180) +/- 7 days.
During this visit, investigator or authorized study staff will:

□ Verify medical history since last visit

□ Record of new treatments taken and changes in treatment or dosage since the previous visit (with diaries cards as support).

□ Record any significant medical events: local and systemic vaccine related events (any grade); any other grade ≥3 event

□ Perform a clinical examination with measurement of vital signs (temperature, blood pressures and pulse) weight, inspection of the skin and check for the presence of respiratory, cardiovascular, neurological an abdominal disorders and psychiatric problems. An assessment of cervical and axillary lymph nodes will also be undertaken. Examination of the M5 vaccine injection site will also be performed.

□ Perform clinical examination to record manifestations related to active ANCA-associated vasculitis or remission

□ Prescribe sampling for:

- routine follow-up of vasculitis assessment (data will be collected for the research) and safety assessment : Hemogram, C-reactive protein, Glycemia, renal function (urea, creatinine, creatinine clearance, glomerular filtration rate), serum protein electrophoresis, IgG, IgA and IgM, urine analysis, ANCA using immunofluorescence and ELISA, CD19+ cells, CD3+, CD4+ and CD8+ cells

- constitution of a serum bank

- performing ELISA

- performing OPA

□ Perform routine BVAS, VDI evaluation

□ Review and collect DiCa data

□ Record any specific local and systemic adverse events since the last visit

- Give a new collection book to report prednisone tapering that should be filled during six months and at each visit

<u>At the end of the visit, the investigator or authorized study staff will:</u>

□ Enter data into the eCRF

□ Give to the participant a diary card that should be filled until the next visit

5.10 Month 12 (D360) and 18 (D540) follow-up visits / End of study/ Premature and of study visit

This visit will take place at Month 12 +/- 15 days and Month 18 +/- 15 days. End of research visit will take place at month 18.

During this visit, investigator or authorized study staff will:

□ Verify medical history since last visit

□ Record of new treatments taken and changes in treatment or dosage since the previous visit (with diary card as support).

□ Record any significant medical events: local and systemic vaccine related events (any grade); any other grade ≥3 event

□ Perform a clinical examination with measurement of vital signs (temperature, blood pressures and pulse) weight, inspection of the skin and check for the presence of respiratory, cardiovascular, neurological an abdominal disorders and psychiatric problems. An assessment of cervical and axillary lymph nodes will also be undertaken.

□ Perform clinical examination to record manifestations related to active ANCA-associated vasculitis or remission

□ Prescribe sampling for:

- routine follow-up of vasculitis assessment (data will be collected for the research): Hemogram, C-reactive protein, , Glycemia, , renal function(urea, creatinine, creatinine clearance, glomerular filtration rate), serum protein electrophoresis, IgG, IgA and IgM, urine analysis, ANCA using immunofluorescence and ELISA, CD19+ cells, CD3+, CD4+ and CD8+ cells

- constitution of a serum bank

- performing ELISA

- performing OPA

□ Perform routine BVAS, VDI evaluation

- Give a new collection book to report prednisone tapering that should be filled during six months and at each visit

At the end of the visit, the investigator or authorized study staff will:

□ Enter data into the eCRF

□ Give to the participant a diary card that should be filled until the next visit (M12 only)

In case of early termination of trial follow-up (e.g. withdrawal from trial follow-up prior to M18), every efforts should be made to perform the procedures of the end of research visit at the time of withdrawal. Reasons for early termination of follow-up should be documented.

5.11 Supplementary visits

This visit will be performed only in case of invasive pneumococcal infection.

An unscheduled visit may be planned in case of an event of a suspected pneumococcal invasive infection (meningitis, bacteraemia), pneumonia, pleuro-pneumonia. Suspected sinusitis, acute otitis media, conjunctivitis, bronchial infections are not affected by the unscheduled visit but must be notified as an AE.
The care of the participant will be performed as a routine follow up. The participant will be taken care by a physician in this protocol, invasive pneumococcal infections are AESI.

During this visit, the investigator or authorized study staff will:

□ Record of new treatments taken and changes in treatment or dosage since the previous visit

□ Record any significant medical events: local and systemic vaccine related events (any grade); any other grade ≥3 event

□ Perform a clinical examination with measurement of vital signs (temperature, blood pressures and pulse) weight, inspection of the skin and check for the presence of respiratory, cardiovascular, neurological, abdominal disorders and psychiatric problems. An assessment of cervical and axillary lymph nodes will also be undertaken.

At the end of the visit, the investigator or authorized study staff will:

□ complete the eCRF

□ notify any SAEs (invasive pneumococcal infection) to the vigilance division of DRCD (fax 01 44 84 17 99), the sponsor, through the SAE form.

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

The duration of participation for each participant will be 18 months, whereas the duration of recruitment will be 24 months. Overall, the total duration of the study will be 42 months.
Participants will be randomized during the inclusion visit.
Participants will receive best available routine care for the duration of the study.

Inclusion period	24 months
The included participants' length of participation, of which:	
• Treatment period:	5 months
• Follow-up period:	18 months
Total research period:	42 months

5.13 Table or diagram summarising the chronology of the research

Tables indicating the chronology of the research are included in Chapter 2 and summarized in Figure 1.

5.14 Distinction between care and research

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

Procedures and treatments carried out as part of the research	**Procedures and treatments associated with care**	**Procedures and treatments added because of the research**
Treatments	Corticosteroids Rituximab	PCV13 PPV23
Consultations	Consultations or hospitalizations according to recommended management: D0, D7, D7+7days, M1, M6, M12 and M18	M5 and M5+7days
Blood samples	Blood draw at D0, D7, D7+7days, M1, M5, M6, M12 and M18	• At inclusion and M1 , M5, M6, M12 and M18 : Serum samples for ELISA and/or OPA •
Diary card	-	Inclusion, D7, D7+7days,

		M1, M5, M5+7days, M6 and M12
book of prednisone tapering	-	Inclusion, M6 and M12

All data obtained during the study for the routine assessment of the pathology described in this protocol will be collected for the research.

5.15 Pregnancy test

A urinary pregnancy test will be performed for women of childbearing age before each vaccination. They will be asked to continue or initiate contraception during the study.
The sponsor considers the following methods of birth control to be highly effective: established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device (IUD) or intrauterine system (IUS); barrier methods: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; male partner sterilization (the vasectomized partner should be the sole partner for that subject); true abstinence (when this is in line with the preferred and usual lifestyle of the subject).

5.16 Biological collection

	D0	M1	M5	M6	M12	M18
ELISA (12 serotypes)	X	X	X	X	X	X
ELISA (3 serotypes)	X			X		
OPA (12 serotypes)	X			X	X	X
Serum bank	X	X	X	X	X	X

5.16.1 Sample handling

Preparation of serum samples will be made by clinical site or associated laboratory according to each specific organization of the sites.

Serum bank: 8,5 ml of blood will be taken and centrifuged, with serum extraction that will be aliquoted into 3 cryotubes of 0,5ml and stored at -80°C by the each participating trial site.

Serum for Elisa and OPA: 1or 2 tubes of 8,5 ml of blood will be taken and aliquoted into 3 to 9 cryotubes of 0,5 ml of serum, according to the serotypes analysis performed at different visits. Sera will be stored at -80°C by the each participating trial site until transportation.

Sample handling will be documented.

Transportation and delivery of serum samples (OPA/ELISA/Serum bank) will be conducted in dry ice to each central laboratory at the Cochin hospital:
- As soon as 60 patients have performed the M6 visit
- As soon as all M6 visit have been performed
- At the end of the study (last M18 visit)
- At sponsor request

5.16.2 ELISA and OPA

The collection performed for Elisa and OPA tests will be declared to the ANSM in the context of biomedical research. Immunological analysis will be performed at the plateforme d'immunomonitoring vaccinal (Cochin hospital) as described in chapter 9. Remaining samples will be destroyed at the end of this study.

5.16.3 Serum bank (stored after the end of this trial)

The samples taken as part of the research will be included in a biological collection.
The collection will be stored at the "Neutrophile et vascularites" laboratory (Bâtiment Gustave Roussy, 6ème étage, Hôpital Cochin, 27 rue du Faubourg Saint-Jacques, 75014 Paris) under the supervision of Pr. Luc Mouthon for an unlimited duration.

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

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

Type of sample	Quantity	Storage location	Collection supervisor	Purpose of the collection	Storage period	Outcome (destruction, etc.)

Serum	8,5 ml at inclusion and M1, M5, M6, M12 et M18	Cochin Hospital	Pr. Luc Mouthon	Scientific knowledge	unlimited	Storage

The collection of samples for biological analysis is a crucial step for the quality of results. It requires a good coordination between the different protagonists involved to avoid sample degradation.

5.16.4 Samples conservation

All samples will be stored first at the trial site and then at the central laboratory under appropriate storage conditions with temperature monitoring. Storage conditions are described below.

In the case of a temperature incident, samples must be transferred to another freezer. The date, maximum temperature of the incident, the duration of the transfer to another freezer and at which temperature they have been transferred must be notified to the clinical study coordinator and the URC project manager by email and/or by fax.

Serum samples have to be kept in a freezer in which the temperature is maintained at -80°C. Then samples will be shipped for analyzes to the Laboratory following monitoring by the sponsor study monitor (CRA).

At Central Laboratories of Paris, samples will be kept in a freezer in which the temperature is maintained at -80°C.

Samples tubes will be labeled with:
- study name
- participant's code
- date of sampling
- visit number
- type of samples (serum)

5.17 Termination rules

5.17.1 Criteria and methods for prematurely terminating the research follow-up of a participant

Any participant can withdraw from participating in the research at any time and for any reason.
The investigator can temporarily or permanently end a participant's participation in the research for any reason that affects the participant's safety or which would be in the participant's best interests.
If a participant leaves the research prematurely or withdraws his consent, data relating to the participant can be used unless an objection was recorded.
The investigator must:

- Document the date and the reason(s) in the medical file
- Collect the end of research data when participation in the research ends, if the participant agrees. Ending a participant's participation in the research does not affect the normal management of the participant's illness in any way.

Premature termination of the trial intervention (vaccination) should not automatically result in early termination of follow-up, that is all participants should continue follow-up as planned in the protocol (unless they withdraw consent).

5.17.2 Follow-up of the participants after the premature termination of trial treatment

If there is serious adverse event, the investigator must notify the sponsor and monitor the participant until the end of the research. A serious adverse event notification form will be sent by fax (01 44 84 17 99) to the sponsor without delay. The serious adverse event will be monitored until it is resolved. In case of a SAE, it is up to the clinical judgement of the investigator whether trial vaccinations can be continued. The coordinating investigators can be contacted by the investigator to give advice in this case.

Premature termination of the trial intervention (vaccination) should not automatically result in early termination of follow-up, that is all participants should continue follow-up as planned in the protocol (unless they withdraw consent). Premature termination of the intervention and its reason must be notified in the eCRF and in the medical file.

5.17.3 Terminating part or all of the research

AP-HP as sponsor or the Competent Authority (ANSM) can prematurely terminate all or part of the research, temporarily or permanently, in the following situations:

- first of all, if suspected unexpected serious adverse reactions (SUSARs) are seen in an arm being treated or if there is a discrepancy in the serious adverse reactions between the 2 arms, and which require a reassessment of the benefit-risk ratio for the research, or stopping criteria are met (see details chapter 6.5).
- likewise, if unexpected facts, new information about the product, in light of which the objectives of the research are unlikely to be achieved.
- if it appears that the inclusion objectives are not met.
- Upon recommendation by the iDSMB.

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

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

Will be included in the trial participants with all the following criteria:

1. Participants with a diagnosis of ANCA-associated vasculitis, either granulomatosis with polyangiitis (GPA, Wegener) or microscopic polyangiitis (MPA), , according to ACR 1990 criteria and/or revised Chapel Hill Consensus Conference definitions and/or European Medical Agency algorithm,
2. Participants (males and females) aged of 18 years or older,
3. Participants with childbearing potential having reliable contraception for all the duration of the study, such as established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device (IUD) or intrauterine system (IUS); barrier methods: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; male partner sterilization (the vasectomized partner should be the sole partner for that subject); surgical sterilization (hysterectomy, bilateral oophorectomy, tubal ligation) or true abstinence (when this is in line with the preferred and usual lifestyle of the subject) prior to enrollment at D0
4. Participants with newly-diagnosed disease at the time of screening or presenting with a relapse of the disease. For relapsing patients, maintenance therapy at stable dose during the last 3 months will be admitted: prednisone dose ≤10 mg/day, azathioprine dose ≤3 mg/kg/day, methotrexate dose ≤25 mg/week, or mycophenolate mofetil dose ≤3 g/j,
5. Participants with an active disease defined as a BVAS ≥ 3,
6. Participants planned to receive rituximab as induction therapy using the recommended regimen (i.e. 375 mg/m2/week for 4 consecutive weeks).
7. Participants able to give written informed consent prior to participation in the study.
8. Participants covered by social security regimen or equivalent.

6.2 Non-inclusion criteria

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

1. Participants with eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss) or other vasculitis

2. Participants with acute infections or chronic active infections at inclusion visit.
3. Documented positive serology result for HIV, HBV (Ag Hbs), HCV at inclusion
4. Participants with disease associated with decreased immune response (splenectomy, hematopoietic stem cell transplantation, primary immune deficiency such as common variable immunodeficiency, cancer within the previous 5 years, drepanocytosis),
5. Participants treated with rituximab within the previous 12 months,
6. Participants who have received blood, blood products, and/or plasma derivatives including parenteral immunoglobulin preparations in the past 3 months before enrolment,
7. Participants treated with new other immunosuppressive or immunomodulatory agents within the previous 3 months (including cyclophosphamide, anti-TNF-alpha, intravenous immunoglobulins, abatacept),
8. Participants treated with prednisone dose >10 mg/day for a duration greater than 21 days before inclusion,
9. Participants with vaccination with a conjugate anti-pneumoccocal vaccine at any time,
10. Participants with vaccination with PPV23 within the previous 3 years,
11. Participants who have received any another vaccines within 4 weeks prior to enrolment or who are planning to receive any vaccine within the first 6 months of the study (except annual influenza vaccination and hepatitis B virus vaccination which are permitted before and after each vaccination visit of the study and then allowed at any time during the study follow up)
12. Pregnant women and lactation. Participants with childbearing potential should have reliable contraception for the all duration of the study,
13. Participants with contraindication to use rituximab,
14. Participants with contraindication to intramuscular injections (hemophilia, anticoagulant therapy (excepted if subcutaneously), thrombocytopenia < 50 000/mm^3)
15. Participants with hypersensitivity to previous vaccination
16. Participants with hypersenstivity to aluminium phosphate, phenol or protéine CRM-197 protein from Corynebacterium diphteriae
17. Participants included in another investigational therapeutic study in the month prior D0. Participation to an observational research is allowed.

    Participants under legal guardianship or mental incapacity

6.3 Recruitment methods

Participants 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 ANCA-associated vasculitis.
Each of the previous trials conducted by the FVSG network have included all participants planned by the protocol and have been published in high ranked journals.

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).

The study will be conducted with the REIVAC network (French clinical research network in vaccinology). When applicable, each service will collaborate with the CIC of the REIVAC located at the same site.
Management and quality control of participants data will be made jointly by the Clinical Research Unit Cochin-Necker and investigators.

	Number of participants
Total number of participants to be enrolled	*120*
Number of centres	*42*
Inclusion period (months)	*24*
Number of participants/centre	*2,8*
Number of participants/centre/month	***0,1***

In addition, a small explanatory film intended for patients has been produced. This film is accessible on the following link: https://youtu.be/Cx-UfME3Jpw and also accessible on the GFEV website in the protocol section: https://www.vascularites.org/protocoles/. These links will be sent to the different investigative centers who will be free to use them or not.

6.4 Criteria for delaying of vaccination and/or blood sampling

As with other vaccines, the administration of PCV13 and PPV23 should be postponed in participants suffering from acute severe febrile illness, body temperature >38.0°C the day of vaccination. The presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

6.5 Criteria for holding vaccination

Prior to receipt of additional study vaccination, each subject must be evaluated to confirm that they are eligible for subsequent vaccination.

There are also circumstances under which performing vaccination is a contraindication in this study. These circumstances include pregnancy and anaphylaxis or severe hypersensitivity reactions following vaccination. In these cases, the participant must not receive additional vaccinations.

If subject meets any of the original non-inclusion criteria or the criteria listed below, he should not receive additional vaccination.

In case related/suspected related SAE will occur, further vaccination will be on hold for the participant and immunization of the remaining participants will be immediately (but not finally) discontinued until the decision of sponsor according to the independent DSMB's recommendation.

- The independent DSMB meeting will be held, if possible, within 48 h following the SAE to conclude if the causality of the event was unrelated or related to the vaccine
- The independent DSMB will recommend to halt or pause or continue the vaccination
- The vaccination will only be resumed upon the decision of the sponsor according to the independent DSMB's recommendation

If a patient develops any condition which, in the opinion of the investigator that may pose additional risk to the subject if he/she continues to participate in the study, the investigator should contact the coordinating investigator to discuss the case.

7 TREATMENT ADMINISTERED TO RESEARCH PARTICIPANTS

7.1 Description of the experimental medication or medications

7.1.1 Experimental medication 1

Prevenar 13® (Pfizer LTD) is a vaccine approved for the prevention of pneumococcal pneumonia and invasive disease caused by 13 *Streptococcus pneumoniae* strains (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F), conjugated to non-toxic diphtheria CRM_{197} protein (see addendum 20.1).
Prevenar 13® is injected intra-muscular at Day 0 in all arms, and Day 7 in ArmB.

7.1.2 Experimental medication 2

Pneumovax® (MSD Vaccins) is a non-conjugated vaccine approved for the prevention of pneumococcal pneumonia and invasive disease caused by 23 *Streptococcus pneumoniae* strains (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F) (see addendum 20.2).
Pneumovax® is injected intra-muscular at Month 5 in all arms.

7.1.3 Pharmaceutical circuit

Prevenar 13® and Pneumovax® will be provided by clinical trial department of AGEPS (Agence Générale des Equipements et Produits de Santé) that will ensure the secondary labelling according to the good manufacturing practices, and the supply to the pharmacy of each clinical site according to the good distributing practices.

Vaccines will be stored by the pharmacies. Dispensing will be made on presentation of a specific nominative prescription in the study.

Experimental vaccines must be stored at +2 to +8 °C.

7.1.4 Administration

In arm A, PCV13 injection will be performed in the non-dominant arm at Day 0, and PPV23 injection in the dominant arm at Month 5.

In arm B, PCV13 injections (x2) will be performed in the non-dominant arm and the homolateral thigh at Day 0, PCV13 injections (x2) will be performed in the dominant arm and the homolateral thigh at Day 7, and PPV23 in the non-dominant arm at Month 5.
In arm C, PCV13 injections (x4) will be performed in the non-dominant arm (x2, at 2 different sites) and the homolateral thigh (x2, at 2 different sites) at Day 0, and PPV23 in the dominant arm at Month 5.

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

7.2.1 Non-experimental medication 1

All participants will receive corticosteroids as induction and maintenance therapy, according to the standard of care of these participants recommended by the FVSG. According to these recommendations, participants are treated with prednisone 1 mg/kg/day for 3-4 weeks, followed by a progressive tapering schedule that reached roughly 10 mg/day at month 6 and 5 mg/day at month 12 and month 18.

7.2.2 Non-experimental medication 2

All participants will receive rituximab as induction therapy at 375 mg/m^2/week, at Days 0 (± 2 days), 7 (± 2 days), 14 (± 2 days) and 21 (± 2 days), according to the standard of care of these participants recommended by the FVSG. Participants will then receive 500 mg-fixed dose of rituximab at Months 6, 12 and 18, according to the standard of care of these participants recommended by the FVSG.

7.3 Authorised and prohibited treatments (medicinal, non medicinal, surgical), including rescue medications during study.

Authorized treatments will include:

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

- Vaccines for influenza virus and hepatitis B virus are permitted before and after each vaccination visit of the study and then allowed at any time during the study follow up.

Prohibited treatments will include:

- Vaccines for *Streptococcus pneumoniae*
- Participants treated with intravenous immunoglobulins,
- Participants treated with new other immunosuppressive or immunomodulatory agents (including cyclophopshamide, anti-TNF-alpha, intravenous immunoglobulins, abatacept),
- Participants who have received any another vaccines who are planning to receive any vaccine within the first 6 months of the study (except annual influenza vaccination and hepatitis B virus vaccination which are permitted before and after each vaccination visit of the study and then allowed at any time during the study follow up)

7.4 Methods for monitoring compliance with the treatment

Injections of vaccines will be done in consultation or one-day hospitalization by the physicians in charge of the participants.
For corticosteroids, a collection book reporting prednisone tapering will be completed by the participants and transmitted to the investigators at each visit.

7.5 Emergency medical support and participant card

In compliance with the GMP obligations dated 26 May 2006, the participant will receive a participant card in which the study staff contact details is provided.

The participant card will indicate the mention: “Please keep this card with you at all times”. This card shall specify the name, address, phone number of the investigator (or the main contact, if different), information related to the investigational product or the research (such as the acronym of the biomedical research), and participant code (see below).

CARTE DE PARTICIPATION A UNE RECHERCHE BIOMEDICALE

Nom : ..... Prénom : .....**Je participe à la recherche clinique PNEUMOVAS intitulée**

«Essai multicentrique, randomisé, contrôlé, comparant l'immunogénicité et la tolérance de deux stratégies vaccinales innovantes anti-pneumococcique au schéma de vaccination standard chez les patients atteints d'une vascularite à ANCA et traités par rituximab»

Dont le promoteur est l'AP-HP

Sous le code d'identification patient:

|__|__|__| / |__|__|__|__| / |__|__|

Merci de garder cette carte en permanence avec vous

J'ai reçu les vaccins Prévenar 13® et Pneumovax ®

Vaccination réalisée le : ____ / ____ / _____ (1ère administration)

Vaccination réalisée le : ____ / ____ / _____ (2ème administration)

Vaccination réalisée le : ____ / ____ / _____ (3ème administration)

Je suis suivi(e) par le Dr……..

A l'hôpital…… .

Tél. :……

En cas d'urgence vitale, composer le 15

V2.0 du 28/08/2017

8 ASSESSMENT OF IMMUNOGENICITY

Immunogenicity will be assessed according to immune response at M6 against 12 pneumococcal serotypes. Response will be categorized as follows: positive response to 0-3, 4-6, 7-9, or 10-12 serotypes common to the PCV13 and PPV23 vaccines. Such categorical variable has been previously proposed for anti-pneumococcal vaccine trials (21).

According to international criteria, a participant will be considered as responder to given serotype if he has, at M6, i.e. one month after the PPV23 injection, a titer of specific IgG ≥1

µg/mL using ELISA, and two-fold increase in antibody titer at M6 compared to the titer at Day 0. Specific responses to the 12 serotypes common to both conjugate and unconjugated vaccines (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) will be tested by ELISA.
ELISA is the reference method to quantitatively measure antibodies against each serotype after pneumococcal vaccine injection.

Titer of specific IgG against the 12 serotypes common to both conjugate and unconjugated vaccines (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19 A, 19F and 23F) will be also measured by OPA, and the proportion of responding participants at M6 (defined by a titer ≥ LLOQ and a four-fold increase of antibody titer at M6 compared to level at Day 0) will be also assessed according to the four predefined categories.
Opsonophagocytosis is a functional method to assess in vitro phagocytosis induced by anti-pneumococcal antibodies, and correlates with the in vivo protection against Streptococcus pneumoniae.

Immunogenicity measurements will be performed in a central laboratory blinded to randomization group.

Finally, the number of serious infections during the study period, in particular invasive pneumococcal infections, will be described, in order to explore the clinical benefit of “reinforced” innovative pneumococcal vaccine strategies compared to standard vaccination regimen.

9 STATISTICAL ASPECTS

The statistical analyses will be performed by a biostatistician at the EUCLID/F-CRIN Clinical Trials Platform (CIC1401, Bordeaux).

A statistical analysis plan (SAP) will be produced by the statistician before inclusion of the first participant (version n°1) and validated by the Steering Committee. The SAP may be revised during the course of the study in case of substantial modification of the protocol or following recommendations of the Independent Data Safety Monitoring Board. Any revision of the SAP will be validated by the Steering Committee.

9.1 Calculation of sample size

The primary objective is the comparison of immunogenicity at month 6 (M6) of two "reinforced" innovative antipneumococcal vaccine strategies to standard vaccination regimen in participants with ANCA-associated vasculitides receiving rituximab therapy:

- Arm A (standard vaccination regimen): prime-boost strategy combining a single dose of 13-valent pneumococcal conjugate vaccine (Prevenar, PCV13) at Day 0 (same day as first infusion of rituximab), followed by a single dose of 23-valent unconjugated vaccine (Pneumovax® PPV23) at month 5 (M5);
- Arm B (innovative vaccine strategy 1): prime-boost strategy combining 2 doses of PCV13 at Day 0 and 2 doses of PCV13 at Day 7, followed by a single dose of PPV23 at M5;
- Arm C (innovative vaccine strategy 2): prime-boost strategy combining 4 doses of PCV13 at Day 0, followed by a single dose of PPV23 at M5.

The primary efficacy endpoint is the proportion of responding participants against pneumococcal serotypes at M6, according to four categories of response:

- Participants with positive response against 0 to 3 serotypes.
- Participants with positive response against 4 to 6 serotypes.
- Participants with positive response against 7 to 9 serotypes.
- Participants with positive response against 10 to 12 serotypes.

For the estimation of sample size, two comparisons are foreseen, and as such two statistical tests will be conducted:

- Arm B versus Arm A
- Arm C versus Arm A

To maintain an overall (2-sided) type 1 error at 5%, a Bonferroni-correction will be used and the type-1 error will be set at 2.5% for each statistical test (2-sided).

- Estimation of the sample size for the comparison of Arm B (Innovative vaccine strategy n°1) versus Arm A (Standard vaccination strategy)
  - Hypotheses
    - Null hypothesis: There is no statistical difference in efficacy between Arm A (Standard vaccination strategy) and Arm B (Innovative vaccine strategy n°1). We present below the expected proportions of participants for each category of response against serotypes. Expected proportions for the standard arm have been derived from a consensus between experts in vaccinology, immunology and rheumatology involved in the protocol development:

Category	*Expected proportion in Arm A*	*Expected proportion in second Arm B under the null hypothesis*
Response against 0 to 3 serotypes	30%	30%
Response against 4 to 6 serotypes	40%	40%
Response against 7 to 9 serotypes	20%	20%
Response against 10 to 12 serotypes	10%	10%

- Alternative hypothesis: There exists a statistical difference in efficacy between Arm A (Standard vaccination strategy) and Arm B (Innovative vaccine strategy n°1). We present below the expected proportions of participants for each category of response against serotypes. Expected proportions in Arm B have been derived from a minimally clinically and biologically significant difference between the arms, determined by a consensus between experts in vaccinology, immunology and rheumatology involved in the protocol development:

Category	*Expected proportion in Arm A*	*Expected proportion in Arm B under the alternative hypothesis*
Response against 0 to 3 serotypes	30%	10%
Response against 4 to 6 serotypes	40%	20%
Response against 7 to 9 serotypes	20%	45%
Response against 10 to 12 serotypes	10%	25%

- Power: 90%
- Type-1 error (2-sided 2.5%)

Under the assumption of proportional odds, and following the method of Whitehead for sample size calculations for categorical ordered data (24), **sample size of 40 in Arm A and 40 in Arm B** will have 90% power to reject the null hypothesis that both arms show the same efficacy with a 2.5% 2-sided type 1 error (Estimations performed with NQuery Advisor).

- Estimation of the sample size for the comparison of Arm C versus Arm A
  - Hypotheses
    - Null hypothesis: There is no statistical difference in efficacy between Arm A (Standard vaccination strategy) and Arm C (Innovative vaccine strategy n°2). Expected proportions of participants for each category of response against serotypes for Arm

A are those presented above. Expected proportions of participants for each category of response against serotypes for Arm C are those presented above for Arm B.

- Alternative hypothesis: There exists a statistical difference in efficacy between Arm A (Standard vaccination strategy) and Arm C (Innovative vaccine strategy n°2). Expected proportions of participants for each category of response against serotypes for Arm A are those presented above. Expected proportions of participants for each category of response against serotypes for Arm C are those presented above for Arm B.
- Power: 90%
- Type-1 error (2-sided 2.5%)

Under the assumption of proportional odds, and following the method of Whitehead for sample size calculations for categorical ordered data (Whitehead, Stat in Medicine 1993), a **sample size of 40 in Arm A and 40 in Arm C** will have 90% power to reject the null hypothesis that both arms show the same efficacy with a 2.5% 2-sided type 1 error (Estimations performed with NQuery Advisor).

Arm A is the common comparator arm for each comparison.

- **Overall sample size**
  - **Arm A: 40 participants**
  - **Arm B: 40 participants**
  - **Arm C: 40 participants**

    Total: 120 participants

9.2 Description of statistical methods to be used

9.2.1 Definition of the analysis population

- Intention-to-treat population (ITT): All randomized participants. Participants will be analyzed in the arm they were allocated to by randomization.
- Modified Intention-to-treat population (mITT): All randomized participants who are eligible and have started their allocated treatment (at least one vaccine injection). Participants will be analyzed in the arm they were allocated to by randomization.
- Safety population: All participants who have started their allocated treatment (at least one vaccine injection). Participants will be analyzed in the arm corresponding to the vaccine strategy actually received.

A participant will be included in the analyses if s/he did not have any major deviations from the participant eligibility criteria listed in Chapter 6 of the protocol. Any exclusion from the analysis will be assessed by the Steering Committee based on the review of the participant's screening and baseline data, and blinded to the randomization allocation and to the participant's evolution after inclusion.

9.2.2 Missing data

For each variable, the number of missing data will be described. The reason for being missing will be documented as much as possible in order to interpret the results.

For dates, a missing day will be imputed by the 15th, which corresponds to the middle of a month. A missing month will be imputed by 7 (July), and missing day and month will be imputed by 30/06. Imputation of dates will permit to calculate time to events. However, the consistency of an imputed date will have to be verified before the calculation of time to events.

Missing data for the primary endpoint in the main analysis will be replaced by a failure (i.e. imputation of the lowest response category of the primary endpoint) of the vaccine strategy (missing=failure strategy). Sensitivity analyses of missing data will be conducted (extreme case analyses, only on available data, changed case by case after discussion with the scientific committee, changed by multiple imputation, etc.).

9.2.3 Type I error rate

The two statistical 2-sided tests conducted to answer our primary objective will be conducted at the 2.5% level. All other statistical tests will be performed with a type I error rate of 5% (2-sided).

9.2.4 Descriptive statistical methods

- Categorical variables

  Variables will be described with counts and proportions.

  Frequency tables will be tabulated (by intervention group) for all categorical variables by the levels of the variables as they appear on the CRF (counts and proportions).

  Categories with a text field specification will be tabulated as categories and then supplemented by a listing with the following information for the participant's fulfilling the condition for the specification (participant id, institution, treatment group, value of the item and text field contents).

- Dates and delays

  Dates relating to events prior to entry will be presented as the delay in days (or weeks, months, or years) between the past event and the date of entry and summaries presented using the median and range.

  Other delays (e.g. re-treatment delays) are presented as continuous variables using the median and range.

  Delays will also be described with survival probabilities and curves using Kaplan-Meier method.

- Continuous variables

  Continuous variables for which a coding system exists (such as for laboratory data) will be recoded into categories (for adverse events, the grading scale specified in the protocol will be used).

  Other continuous variables (for example age) are presented using the median and range (minimum, maximum). If appropriate, continuous data may also be presented in categories (for example age may also be grouped in decades)

  Antibody titers will be presented using the geometric mean.

9.2.5 Calculation rules in the statistical analyses

- Duration between two dates in months: (Date 2 – Date 1 + 1) / 30.4375.
- Duration between two dates in years will be calculated as number of years between the two dates.
- Duration between two dates in days will be calculated as the number of days between the two dates.
- Difference between two measurements will be calculated according to the following formula: Delta = (measurement at time 1 – measurement at time 2)

9.3 Analysis plan

9.3.1 Description of the inclusions and follow-up

Data will be presented pooled as well as independently for each randomization group (no statistical comparison will be performed):

- Number of included participants
- Number of participants included in the analyses and reasons of exclusion if needed
- Protocol deviations

- Inclusions curve (evolution of participants frequency between first and last inclusion)
- Flow chart according CONSORT recommendations will be presented.

9.3.2 Characteristics of the participants

Data will be presented pooled as well as independently for each randomization group (no statistical comparisons will be performed for baseline data). The participants will be described at baseline and during follow-up according to the following variables:

- Demographics
- Medical history
- Clinical data
- Biology
- Vaccine strategy (compliance [e.g. number of injections, delays between injections], quality)
- Concomitant treatments
- Adverse events
- Deviations
- Deaths

9.4 Primary endpoint

The primary statistical analysis of the ordered categorical endpoint will use a proportional odds model as recommended (20). The primary endpoint analysis will be conducted in the mITT population, with imputation of missing endpoint data as failure.

For each arm, the proportion of participants of responding participants against pneumococcal serotypes at M6 will be presented (with 95% confidence interval) according to four categories of response:

  - Participants with positive response against 0 to 3 serotypes.
  - Participants with positive response against 4 to 6 serotypes.
  - Participants with positive response against 7 to 9 serotypes.
  - Participants with positive response against 10 to 12 serotypes.

- Comparison of Arm B versus Arm A, and of Arm C versus Arm A

The comparison between Arm B and Arm A, and between Arm C and Arm A, respectively, of the participants' distribution according to four categories of response will be performed using a proportional odds model (20)(POM; McCullagh, Journal of the Royal Statistical Society: Series B, 1980).

An odds-ratio (OR) for each comparison will be estimated in the model and reported with its 97.5% confidence interval. The OR provides a measure of the benefit interms of immunogenicity of being treated with the given “Innovative vaccine strategy” (Arm B or C, respectively) compared to “Arm A: Standard vaccination strategy”.
A statistical test will be conducted at the 2.5% level to assess whether the OR is statistically different from 1 (null effect). An OR significantly greater (lower) than 1 will indicate that participants in the given experimental arm have improved (poorer) serotypic responses compared to participants in Arm A.

- Pre-planned sensitivity analyses

In case 5% of more participants in one of the 3 arms did not receive any injection of the vaccine strategy, a sensitivity analysis will be conducted by analyzing the primary efficacy endpoint in the ITT population.

- Secondary analyses of the primary endpoint

The comparisons between Arm A and Arm B; and Arm A and C, respectively, of the participants’ distribution according to four categories of response will be performed using Chi² test, or corrected Chi² test or with non-parametric Fisher's exact test, according to the size of the expected values under the hypothesis of independence.

9.5 Secondary endpoint(s)

- Analyses of categorical endpoints

These analyses concern the following variables:

- Responding participants at M6 based on titer of specific IgG against the 12 serotypes common to both conjugate and unconjugated vaccines measured by OPA at Day 0 and M6;
- Responding participants at M6 based on titer of specific IgG against the 3 specific serotypes of PPV23 at M0 and M6;
- Immune response against the 12 serotypes common to both conjugate and unconjugated vaccines measured by ELISA and OPA at M12 and M18;
- Type of adverse events;
- Adverse events related to vaccine injections;
- Number of serious infections;
- Participants with vasculitis flare according to EULAR criteria during the study period, and time to disease relapse.

The following statistical methods will be used:

- Counts and proportions will be reported for each modality of the variable.
- Comparisons of Arm A versus Arm B and Arm A versus Arm C will be performed with a Chi² test, or corrected Chi² test or with non-parametric Fisher's exact test, according to the size of the expected values under the hypothesis of independence. For secondary endpoints with an ordered categorical response variable, proportional odds models will also be used.
- Logistic regression models will be used to adjust on stratification factors and other major confounding factors. Assumption of the models (log-linearity of the associations) will be systematically checked.

- Analyses of survival endpoints:
  - Time to disease relapse will be compared between Arm A and Arm B as well as between Arm A and Arm C using a 2-sided log-rank test stratified for pre-specified stratification factors and other major confounding factors and tested at the 5% 2-sided significance level.
  - Time to severe infections during the study period, in particular invasive pneumococcal infections, will be explored with the same approach
  - A Cox regression model stratified for pre-specified stratification factors and other major confounding factors will be fit to estimate the size of the vaccination strategy effect. The estimated hazard ratio and its 95% confidence interval will be reported.
- Modeling of the determinants of immunogenicity level at M6 will be performed using a POM stratified for pre-specified stratification factors. The candidate prognostic factors of immunogenicity that will be investigated include: vaccine strategy, age, sex, previous immunosuppressive or immunomodulatory agents, time from previous unconjugated vaccination, previous PPV23 injections. The prognostic value of the candidate variables will be measured by the estimated odds ratios and their respective 95% confidence intervals.

9.6 Interim statistical analysis

No interim statistical analysis is foreseen for early stopping for efficacy or futility.

10 SAFETY ASSESSMENT - RISKS AND RESTRICTIONS ADDED BY THE RESEARCH

10.1 Definitions

According to Article R1123-46 of the French Public Health Code:

Adverse event

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

Adverse reaction to an investigational medicinal product

Any adverse event occurred in a trial subject, which has a causal relationship with the clinical trial or with the investigational medicinal product.

Serious adverse event or reaction

Any adverse event or reaction that at any dose of medication, results in death, threatens the life of the research subject, requires hospitalisation or prolongs hospitalisation, causes a severe or long-term disability or handicap, or results in a congenital abnormality or deformity.

Unexpected adverse reaction to an investigational medicinal product

Any adverse reaction to the product, whose nature, severity, frequency or outcome is inconsistent with the safety information described in the Reference Safety Information (summary of product characteristics, or the investigator's brochure if the product is not authorised).

According to Article R.1123-46 of the Code de la Santé Publique and the guidelines for sponsors of clinical trials conducted on investigational medicinal product (ANSM):

- **Emerging safety issue**

Any new safety information that may lead to a reassessment of the risk/benefit ratio of the trial or the investigational medicinal product, modifications in the investigational medicinal product use, the conduct of the clinical trial, or the clinical trial documents, or a suspension, interruption or modification of the protocol of the clinical trial or other similar trials..

Examples:

a) any clinically significant increase in the frequency of an expected serious adverse reaction

b) suspected unexpected serious adverse reactions in patients who have terminated their participation in the clinical trial that are notified by the investigator to the sponsor together with follow-up reports

c) any new safety issue relating to the conduct of the clinical trial or the development of the investigational medicinal product, that may impact the safety of the trial subjects.

Examples:

- a serious adverse event likely to be related to the interventions and the trial's diagnostic procedures and which may impact the conduct of the clinical trial,
- a significant risk on the trial subjects such as ineffectiveness of the investigational medicinal product in treating a life-threatening illness under investigation,
- significant safety results from a recently completed non-clinical study (such as a carcinogenicity study),
- the premature termination, or temporary suspension, of a trial conducted on the same investigational medicinal product in another country, for safety reasons,
- an unexpected serious adverse reaction associated with a non-experimental medication required for the conduct of the clinical trial, (e.g. challenge agents, rescue treatment)

d) recommendations from the Data Safety Monitoring Board (DSMB), if applicable, that may affect the safety of the trial subjects

e) any suspected unexpected serious adverse reaction (SUSAR) reported to the sponsor by another sponsor of a trial carried out in a different country but relating to the same medication.

10.2 Role of the investigator

The investigator must **assess the seriousness criteria of each adverse event** and record all serious and non-serious adverse events in the case report form (eCRF).

The investigator must **document** serious adverse events **as thoroughly as possible** and provide a definitive medical diagnosis, if possible.

The investigator must **assess the severity** of the adverse events by using an adverse events rating scale, attached to the protocol, Common Terminology Criteria for Averse Events (v4.3) [National Cancer Institute].

For local and systemic reactions due to vaccine injections, the following grading system will be used (based on FDA scale, September 2007):

Local reactions:

Local Reaction to Injectable Product	**Mild (Grade 1)**	**Moderate(Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

Systemic reactions:

Systemic (General)	**Mild (Grade 1)**	**Moderate(Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

The investigator must **assess the causal relationship** between the serious adverse events and the investigational medicinal products.

The method used by the investigator, is based on the WHO method (WHO Uppsala Monitoring Centre), and includes the following causality terms:

- Certain
- Probable/Likely
- Possible
- Unlikely (not ruled out)

These terms are defined as follows (extracted from the WHO-UMC causality categories, version dated 17/04/2012).

Causality term	Assessment criteria*
Certain	· Event or laboratory test abnormality, with plausible time relationship to drug intake · Cannot be explained by disease or other drugs · Response to withdrawal plausible (pharmacologically, pathologically) · Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) · Rechallenge satisfactory, if necessary
Probable / Likely	· Event or laboratory test abnormality, with reasonable time relationship to drug intake · Unlikely to be attributed to disease or other drugs · Response to withdrawal clinically reasonable · Rechallenge not required
Possible	· Event or laboratory test abnormality, with reasonable time relationship to drug intake · Could also be explained by disease or other drugs · Information on drug withdrawal may be lacking or unclear
Unlikely	· Event or laboratory test abnormality, with a time to drug intake · that makes a relationship improbable (but not impossible) · Disease or other drugs provide plausible explanations

*All points should be reasonably complied with

10.2.1 Serious adverse events that require a notification without delay by the investigator to the sponsor

According to Article R.1123-49 of the French Public Health Code (CSP), the investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of any serious adverse event which occurs during a trial as described in Article L.1121-1(1) CSP, except those which are listed in the protocol (see corresponding section) and, if applicable, in the investigator's brochure as not requiring a notification without delay. These latter should be notified by the investigator to the sponsor in an appropriate delay taking into consideration the specific features of the trial, the serious adverse events and the modalities specified in the protocol or the investigator’s brochure.

A serious adverse event is any untoward medical occurrence that:

1- results in death
2- is life-threatening
3- requires inpatient hospitalisation or prolongation of existing hospitalisation
4- results in persistent or significant disability/incapacity
5- is a congenital anomaly/birth defect

10.2.2 Specific features of the protocol

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

- Adverse events judged as "medically significant"

The investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of these adverse events, according to the same modalities and within the same timeline as for serious adverse events (see corresponding section).

- Adverse events of special interest (AESI)

The investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of these adverse events, according to the same modalities and within the same timeline as for serious adverse events (see corresponding section).

In this protocol, suspected pneumococcal invasive infection (meningitis, bacteraemia), pneumonia, pleuro-pneumonia, are AESIs. Suspected sinusitis, acute otitis media, conjunctivitis, bronchial infections are not considered as AESI.

In case of occurrence of such symptoms, a supplementary visit will be applicable.

- **In utero** exposure

Urine pregnancy test is done at each vaccination visit, before each immunization.

The investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of any pregnancy that occurs during the trial, even if not associated with an adverse event.

Notification is required if the exposure involves the mother.

If a woman participating to this trial becomes pregnant, all study vaccine regimen must be discontinued. Follow-up of pregnant volunteers continues until the end of the trial.

- Exposure **via breastfeeding**

Exposure via breastfeeding occurs if an infant or child could have been exposed *via* the breast milk of a mother being treated with an investigational medicinal product.

Even if such exposure is not associated with an adverse event, the investigator must always notify the sponsor without delay on the day when the investigator becomes aware of any exposure via breastfeeding.

10.2.2.2 Serious adverse events that do not require the investigator to notify the sponsor

These serious adverse events are simply recorded in the case report form.

- *Normal and natural course of the condition*:

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

This normal and natural evolution may also include clinical or biological manifestations related to disease relapse, including:

- Dyspnea, asthma, cough
- Sino-nasal abnormalities
- Other manifestations related to active GPA or MPA

- *Special circumstances*

- Hospitalization for a pre-existing illness or condition
- Hospitalization for a medical or surgical treatment scheduled prior to the trial
- Admission for social or administrative reasons
- Transfer to the emergency ward (< 12 hours)

- *Adverse events during the trial possibly related to treatments/acts prescribed as a part of the patient's standard care*

The investigator as health care professional must notify these events to the appropriate health surveillance institution according to the situation. Examples: Agence Régionale de Santé, quality department of your hospital, Centre Régional de Pharmacovigilance, local correspondent of the materiovigilance unit (ANSM), etc.

10.2.3 Period during which the investigator must send notification of SAEs to the sponsor without delay

The investigator notifies the sponsor without delay of all the serious adverse events listed in the corresponding section:

- starting from the date on which the subject signs the consent form throughout the whole follow-up period intended by the trial (until M18).
- indefinitely, if the SAE is likely to be due to the investigational medicinal product or to the study interventions (e.g. serious reactions that could appear at long term after exposure to the medication, such as cancers or congenital abnormalities).

10.2.4 Procedures and deadlines for notifying the sponsor

The investigator should initially complete a SAE reporting form (contained in the case report form). This report must be signed by the investigator.

The investigator must complete every section of the SAE form so that the sponsor can carry out the appropriate assessment.

The initial report sent to the sponsor must be rapidly followed up by one or more additional written reports describing the course of the event and any complementary information.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful for medical assessment of the case (medical reports, laboratory test results, results of additional exams, etc.). These documents must be anonymized. In addition, the investigator must state the study acronym and the number and initials of the study participant on each paper of the attached document.

Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the subject has terminated his participation in the trial.

The initial report, the SAE follow-up reports and all other documents must be sent to the sponsor's Safety Department by fax **only**, fax no. **+33 (0)1 44 84 17 99**.

For trials which use e-CRF

- the investigator completes the SAE report form in the e-CRF, then validates, prints and signs the form before sending it by fax;

- In case of failure to connect to the e-CRF, the investigator should complete, sign and send the SAE report form to the Safety Department. As soon as the connection is restored, the investigator must complete the SAE report form in the e-CRF.

The investigator must comply with all requests for additional information from the sponsor.
For all questions relating to an adverse event report, the Safety Department can be contacted via email at vigilance.drc@aphp.fr.

For cases of *in utero* exposure, the investigator will complete the initial notification and follow-up report forms for pregnancy exposure during trial participation".
The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy ends, and must notify the sponsor of the outcome of the pregnancy, using this form.
If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure as for reporting SAEs.
The initial pregnancy report form, the SAE follow-up forms and any other documents will be sent to the sponsor using the same modalities as described in this section.
If it was the father who was exposed, the investigator must obtain the mother's permission before collecting information about the pregnancy.

10.3 Role of the sponsor

The sponsor, represented by its Safety Department, shall continuously assess the safety of each investigational medicinal product throughout the trial.

10.3.1 Analysis and declaration of serious adverse events

The sponsor assesses:

- the **seriousness** of all reported adverse events,
- the **causal relationship** between these adverse events and investigational medicinal products and any other treatments,

  All serious adverse events for which the investigator and/or the sponsor suspect a causal relationship with the investigational medicinal product are classed as suspected serious adverse reactions.

- the **expectedness assessment** of the serious adverse reactions

  Any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the summary of product characteristics, or in the investigator's brochure if the product is not authorised, is considered unexpected.

  The sponsor, acting through its Safety Department, assesses the expectedness of the serious adverse reaction based on the information described below**.**

❖ For serious adverse events likely to be related to the investigational medicinal products:

- refer to the SmPC for **Prevenar13**®, enclosed in addendum 19.4).
- refer to the SmPC for **Pneumovax**®, enclosed in addendum 19.5).

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs), within the regulatory time frame, to the ANSM (French Health Products Safety Agency).

- The sponsor must send the initial report without delay upon receipt of the unexpected serious adverse reaction if it is fatal or life-threatening, or otherwise within 15 days from receipt of any other type of unexpected serious adverse reaction;
- The sponsor must provide all relevant additional information by sending follow-up reports, within 8 calendar days following receipt.

Any suspected unexpected serious adverse reaction must also be declared electronically using the Eudravigilance European adverse drug reactions database managed by the European Medicines Agency (EMA).

The sponsor must notify all the investigators about any information that could adversely affect the safety of the trial subjects.

10.3.2 Analysis and declaration of other safety data

This relates to any new safety data that may lead to a reassessment of the risk/benefit ratio of the trial or the investigational medicinal product, modifications in the investigational medicinal product use, the conduct of the clinical trial, or the clinical trial documents, or a suspension, interruption or modification of the protocol of the clinical trial or other similar trials.

The sponsor will inform the competent authority and the Ethics committee without delay after becoming aware of the emerging safety issue and, if applicable, describe which urgent safety measures have been taken by the sponsor.

Following the initial declaration of any emerging safety issue, the sponsor will report to ANSM and the Ethics committee any additional relevant information about the emerging safety issue in the form of a follow-up report, which must be sent no later than 8 days upon knowledge of the sponsor.

If the suspected unexpected serious adverse reaction meets the definition of an emerging safety issue, the sponsor will report both the SUSAR and the emerging safety issue to the ANSM according to the appropriate modalities and within the regulatory timelines as previously described.

10.3.3 Annual safety report

The sponsor must prepare once yearly throughout the trial duration an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:
- an analysis of safety data concerning trial subjects
- a description of the patients included in the trial (demographic profile etc.)
- a list of all the suspected serious adverse reactions that occurred during the period covered by the report,
- cumulative summary tabulation of all the serious adverse events that have occurred since the beginning of the clinical trial,

The report must be transmitted to ANSM and the Ethics Committee no later than 60 days after the anniversary date corresponding to the date of authorization of the clinical trial by ANSM.

10.4 Independent Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) can be set up by the sponsor. Its primary mission is to monitor safety data. It can have other missions, such as monitoring efficacy data (especially if the protocol includes interim analyses).
The sponsor is responsible for justifying the creation or absence of a DSMB to the Competent Authority (ANSM) and to the Ethics committee.

A DSMB will be set up for this trial. The DSMB must hold its first meeting before the first subject's enrollment.

The members of the DSMB are:

- M. Laurent Chouchana : Pharmacien
- Mme Christine Durier : Biostatisticien
- Mme Solen Kerneis : Infectiologue

All missions as well as the precise operating procedures of the DSMB are described in the DSMB charter of the clinical trial.

The DSMB has a consultative role. The final decision concerning the conduct of the clinical trial relies on the sponsor.

11 SPECIFIC RESEARCH COMMITTEES

11.1 Steering committee

This will consist of the clinicians who initiated the project, the biostatistician and clinical epidemiologists in charge of the project, representatives of the sponsor, CIC 1417, and the URC.

- Members of the committee:
  Dr. Benjamin Terrier, Pr. Odile Launay, Dr. Matthieu Groh, Pr. Frédéric Batteux, Mme Corinne Desaint, a representative of the EUCLID/F-CRIN clinical trials platform (Laura Richert – Cédrick Wallet – Carine Bellera), representatives of the sponsor named for this research (DRCD URC and DRCD-siège).

- Missions: to define the global organisation of the research, to coordinate informations, to define the methods and to monitor the research

If members of this study committee or other applicants propose to carry out further biological studies from the study material and if these biological studies have not been provided by the protocol, the steering committee reviews and defines the conditions for access to data and the rules of results publication.

The steering committee will meet according to the state of progress and difficulties encountered in the study.

11.2 Endpoint Adjudication Committee

- Members of the committee: Dr Virginie De Latours, Thomas Hanslik, Dr Hélène Poignard

- Missions: to validate, blinded to trial arms, the outcomes which are important for the secondary endpoint definitions (diagnosis, causal relationship, grade) : The committee will make the review of the grade ≥3 adverse events or reactions and the failures of vaccination
  The members of this committee are not necessarily independent (it can be investigators) of the research but have to work blinded to trial arm, i.e. members of this committee will not participate in the adjudication of events of participants followed at their own study site.

In case of discrepancy in the outcomes, the proposal done by the members of the Endpoint Adjudication Committee will be transmitted to the investigator via a query. The investigator will have the opportunity to take, or not, into account the proposal. The opinion of the End point Adjudication Committee will not override the judgment of the investigator and sponsor in terms pharmacovigilance.

11.3 Independent Data Safety Monitoring Board

See chapter 10.7.

12 DATA MANAGEMENT

12.1 Data collection methods

Information required in the research protocol must be collected in the case report form (CRF) and an explanation must be given by the investigator for each missing data.
Data must be reported in the electronic CRF when they are available, for clinical or para-clinical data.

Correction of discordant data on CRF will be asked through queries. In the CRF, the changes in the data will be tracked.
Anonymization of the participants will be ensured using a code number and initials, reported on each needed documents for the research, or by erasing nominative data on copies of source documents.

12.2 Right to access source data and documents

Access to data

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

Source documents

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

Data confidentiality

Those responsible for biomedical research quality control (Article L.1121-3 of the French Public Health Code) will take all necessary precautions to ensure the confidentiality of information about the experimental medications, the research, the research participants and in particular the identity of the participants and the results obtained.
These individuals, as well as the investigators themselves, are participant to professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the Penal Code).
During or after the biomedical research, the data collected about the research participants and sent to the sponsor by the investigators (or any other specialised parties) will be made non-identifying.

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

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

12.3 Data processing and storage of documents and data

Data entry

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

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

This research falls under the "Méthodologie de référence" (MR-001) according to the provisions of Article 54, paragraph 5 of modified Law No. 78-17 of 6 January 1978 relating to information technology, data files and privacy. This change was approved in a decision made on 5 January 2006. AP-HP, the research sponsor, has signed a commitment to comply with this " Méthodologie de référence "

Archival

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

12.4 Ownership of the data

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

13 QUALITY CONTROL AND ASSURANCE

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

13.1 General organisation

The sponsor must be responsible for the safety and respect of those participants who have agreed to participate in the research. The sponsor must implement a quality assurance system to best monitor the conduct of the research in the investigation centres.
For this purpose, the sponsor shall delegate Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the research locations, after having carried out initial visits.

13.2 Level of centre monitoring

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

13.3 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 DRCD and in accordance with the French Good Clinical Practices as well as with the legislative and regulatory provisions in force.
The investigator and the members of the investigator's team agree to make themselves available during Quality Control visits carried out at regular intervals by the Clinical Research Associate. During these visits, the following elements will be reviewed:

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

13.4 Case Report Form

All information required according to the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Each missing data item must be coded.

This digital case report form will be implemented in each of the centres thanks to a web-based data collection medium. Investigators will be given a document offering guidance in using this tool.

When the investigators complete the case report via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. Thus, the investigator must validate any changes to the values in the case report form. These modifications will be participant to an audit trail. A justification can be added when applicable, as a comment. A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the research. The investigator must archive a copy of the authenticated document that was delivered to the sponsor.

13.5 Identification of the participants

At the screening visit, each patient will be assigned a unique participant code in order to ensure confidentiality during the study.

The participant code consists of a 9-digit number resulting from the combination of :

- Study site number (3 digit: 001; 002…) :
- Selection number: given the order of participant's arrival in the research (4 digits): 0001, 0002, 0003…
- Participant's initials (the 1st letter of the last name–the 1st letter of the first name)

|__|__|__| / |__|__|__|__| / |__|__|

This reference is unique and will be retained for the entire research period. Once assigned to a participant, the participant number cannot be reused.

13.6 Management of non-compliances in the conduct of the study

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

13.7 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 participant to regulatory audits and inspections. Medical secrecy cannot be invoked in opposition to these audits and inspections.

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

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

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

13.8 Primary investigator's commitment to assume responsibility

Before starting the research, each investigator will give the sponsor's representative a copy of his/her personal curriculum vitæ, signed and dated, with his/her number in the RPPS (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals).
Each investigator will undertake to comply with the legislation and to carry out the research according to French GCP, adhering to the Declaration of Helsinki terms in force.
The primary investigator at each participating centre will sign a responsibility commitment (standard DRCD document) which will be sent to the sponsor's representative.
The investigators and their employees will sign a delegation of duties form specifying each person's role.

14 ETHICAL AND LEGAL CONSIDERATIONS

14.1 Methods for obtaining information and consent from research participants

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

The participant will be granted a reflection period, between the time when the participant receives the information and the time when he or she signs the consent form.
The free and informed consent, in writing, of the participant is obtained by the investigator, or by a doctor representing the investigator, before the inclusion of the participant in the research.
The information sheet and a copy of the consent form, signed and dated by the research participant and by the investigator or the doctor representing the investigator, are given to the individual prior to his or her participation in the research.
In addition, the investigator will specify in the research participant's medical file the methods used for obtaining his or her consent as well as the methods used for providing information with the goal of obtaining their consent. The investigator will retain the original signed and dated copy of the participant's consent form.

Special case: Mention of the possibility for the investigator of withholding certain information relating to the diagnosis, as applicable, in accordance with paragraph 4 of Article L1122-1 of the French Public Health Code.

14.2 Participation in another research

Participation in another interventional trial will be prohibited, but observational studies will be accepted.

14.3 Compensation for participants

No compensation is anticipated for the participants as compensation for the inconveniences relating to the research

14.4 Legal obligations

The sponsor's role

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

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

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

Request for authorisation to ANSM

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

Commitment to compliance with the MR 001 "Méthodologie de Reference"

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

14.5 Modifications to the research

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

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

14.6 Final research report

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

15 FUNDING AND INSURANCE

15.1 Funding source

The present study is funded by the PHRC-N 2015.

15.2 Insurance

For the duration of the research, the Sponsor will take out an insurance policy covering the sponsor's own civil liability as well as the civil liability of all the doctors involved in carrying out the research. The sponsor will also provide full compensation for all harmful consequences of the research for the research participants and their beneficiaries, unless

the sponsor can prove that the harm is not the fault of the sponsor or any agent. The act of a third party or the voluntary withdrawal of the person who initially consented to participate in the research cannot be invoked against said compensation.

Assistance Publique-Hôpitaux de Paris (AP-HP) has taken out insurance from HDI-GERLING through BIOMEDIC-INSURE for the full research period, covering its own civil liability and that of any agent (doctor or research staff), in accordance with Article L.1121-10 of the French Public Health Code.

16 PUBLICATION RULES

The Steering Committee must be informed within a reasonable delay prior to each submission of any communication (abstract; written publication, other) regarding this trial.
The first signatories of publications will be those individuals who actually took part in the preparation and conduct of the protocol, the analysis and interpretation of the results, and the writing up of results. Authorship definitions will follow the Vancouver rules.

For the other contributors, the order of authors will be allocated according to the number of participants included in the study site compared to the expected participants and their usable data. The next-to-last one will be reserved for the study coordinators. Concerning the biological contributors, their name should be in the list of authors but insignificantly in their position.,

The URC/CIC Paris Descartes Necker Cochin must be acknowledged for implementation, monitoring and data management in the "Acknowledgment" section.

The AGEPS will be also acknowledged in the "Acknowledgment" section.

16.1 Mention of the affiliation of AP-HP for projets sponsored by AP-HP

Each author affiliation must appear.
For AP-HP members, the terms “Assistance Publique-Hôpitaux de Paris” or “AP-HP” must appear in the authors’ address.
In case an author has multiple affiliations, each affiliation should appear. The order in which the institution (AP-HP ; University , INSERM) is quoted has no importance.

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

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

16.3 Mention of the funding source in the acknowledgements of the text

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

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

17 DATA PROCESSING AND STORAGE OF DOCUMENTS AND DATA RELATING TO THE RESEARCH

Documents pertaining to research that falls within the framework of the law on biomedical research must be archived by all parties involved for a period of 15 years after the end of the research.

This indexed archive will include:

- Copies of the ANSM authorization letter and the mandatory CPP opinion
- Successive versions of the protocol (identified by the version no. and date)
- Correspondence with the sponsor
- The participants’ signed ICFs in sealed envelopes (in the case of participants who are minors, signed by persons with parental authority) with the corresponding enrolment list or register
- A completed and validated case report form for each participant enrolled
- All appendices specific to the study
- The final study report based on statistical analysis and quality control of the study (copy sent to the sponsor).
- Any audit certificates produced during the research

The database from which the statistical analysis was drawn must also be stored by the Analysis Manager (paper or electronic medium).

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19 LIST OF ADDENDA

19.1 Birmingham Vasculitis Activity Score (BVAS) version 3

Ne cocher que les manifestations témoignant d'une maladie active (les séquelles présentes depuis plus de 3 mois sont appréciées par le VDI). Si toutes les manifestations représentent une maladie chronique active, mais faiblement (smoldering/grumbling disease) et qu'il n'y aucune manifestation nouvelle récente ou d'aggravation franche, cocher la case dans le coin en bas à droite. Les scores indiqués sont ceux pour une maladie active récemment / maladie faiblement active, « grumbling » (case du bas cochée). Ne faire que la somme d'une seule des colonnes.

	Oui		Oui
1. Signes généraux	**|__| (maximum 3 / 2)**	**6. Signes cardiaques**	**|__| (maximum 6 / 3)**
Myalgies	☐ 1 / 1	Disparition d'un pouls	☐ 4 / 1
Arthralgies ou arthrites	☐ 1 / 1	Atteinte valvulaire	☐ 4 / 2
Fièvre ≥ 38°C	☐ 2 / 2	Péricardite	☐ 3 / 1
Amaigrissement ≥ 2 kg	☐ 2 / 2	Angor	☐ 4 / 2
		Cardiomyopathie	☐ 6 / 3
2. Signes cutanés	**|__| (maximum 6 / 3)**	Insuffisance cardiaque congestive	☐ 6 / 3
Nécrose	☐ 2 / 1		
Purpura	☐ 2 / 1	**7. Manifestations digestives**	**|__| (maximum 9 / 4)**
Ulcération(s)	☐ 4 / 1	Péritonite	☐ 9 / 3
Gangrène	☐ 6 / 2	Diarrhée sanglante	☐ 9 / 3
Autre(s) lésion(s) liée(s) à la vascularite	☐ 2 / 1	Douleur abdominale (angor digestif)	☐ 2 / 6
3. Atteintes muqueuses et oculaires	**|__| (maximum 6 / 3)**	**8. Signes rénaux**	**|__| (maximum 12 / 6)**
Ulcération buccale / granulome	☐ 2 / 1	HTA	☐ 4 / 1
Ulcération génitale	☐ 1 / 1	Protéinurie > 1 +	☐ 4 / 2
Inflammation lacrymale ou salivaire	☐ 4 / 2	Hématurie > 10 GR / champ	☐ 6 / 3
Exophtalmie	☐ 4 / 2	Créatininémie 125–249 µmol/l	☐ 4 / 2
Episclérite	☐ 2 / 1	Créatininémie 250–499 µmol/l	☐ 6 / 3
Conjonctivite / blépharite / kératite	☐ 1 / 1	Créatininémie > 500 µmol/l	☐ 8 / 4
Baisse progressive d'acuité visuelle / vue trouble	☐ 3 / 2	Augmentation de la Créatininémie > 30% ou diminution de la clairance de la créatinine > 25%	☐ 6 / -
Baisse brutale d'acuité visuelle / cécité	☐ 6 / -		
Uvéite	☐ 6 / 2	**9. Atteinte neurologique**	**|__| (maximum 9 / 6)**
Vascularite rétinienne Thrombose / hémorragie / exsudats rétiniens	☐ 6 / 2	Céphalées	☐ 1 / 1
		Méningite	☐ 3 / 1
4. Signes ORL	**|__| (maximum 6 / 3)**	Confusion, trouble de la conscience	☐ 3 / 1
Epistaxis / croûtes nasales / ulcération ou granulome nasal	☐ 6 / 3	Convulsions (non liées à l'HTA)	☐ 9 / 3
Sinusite	☐ 2 / 1	Atteinte médullaire (myélite)	☐ 9 / 3
Sténose sous-glottique	☐ 6 / 3	Accident vasculaire cérébral	☐ 9 / 3
Baisse d'audition de transmission (conduction)	☐ 3 / 1	Atteinte de(s) paire(s) crânienne(s)	☐ 6 / 3
Baisse d'audition de perception (sensorielle)	☐ 6 / 2	Neuropathie périphérique sensitive	☐ 6 / 3
		Neuropathie périphérique motrice	☐ 9 / 3
5. Signes pulmonaires	**|__| (maximum 6 / 3)**		
Wheezing / sibilants	☐ 2 / 1	**10. Autre atteinte spécifique** ☐	
Nodule(s) / Nodule(s) excavé(s)	☐ 3 / -	Préciser :……	
Epanchement pleural	☐ 4 / 2	……	
Infiltrat pulmonaire radiologique	☐ 4 / 2	……	
Sténose endobronchique	☐ 4 / 2	……	
Hémorragie intra-alvéolaire	☐ 6 / 4		
Détresse respiratoire	☐ 6 / 4		

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

19.2 Vasculitis damage Index (VDI)

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

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

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

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

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

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

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

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

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

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

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

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

TOTAL = ☐ (= nombres de cases cochées)

19.3 Collection book to report prednisone tapering

Etude PNEUMOVAS Carnet de suivi de l'observance des corticoïdes	Code d'identification patient |__|__|__| / |__|__|__|__| / |__|-|__|	CARNET n° 1 / 3 De l'inclusion à la visite à 6 mois

Etude PNEUMOVAS

Essai multicentrique, randomisé, contrôlé, comparant l'immunogénicité et la tolérance de deux stratégies innovantes de vaccination anti-pneumococcique au schéma de vaccination standard chez des patients atteints de vascularites associées à des ANCA et devant recevoir un traitement par rituximab.

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

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

Etude PNEUMOVAS Carnet de suivi de l'observance des corticoïdes	Code d'identification patient |__|__|__| / |__|__|__|__| / |__|-|__|	CARNET n° 1 / 3 De l'inclusion à la visite à 6 mois

Nous vous remercions de bien vouloir remplir ce carnet à partir du 1er jour dans l'étude et pendant vos 18 mois de participation, et de le rapporter à votre médecin lors de chaque consultation.

Dans 6 MOIS, N'OUBLIEZ PAS DE DEMANDER A VOTRE MEDECIN,
LE CARNET POUR LES 6 MOIS SUIVANTS.

Aide au remplissage :

Notez le jour de la semaine qui correspond au premier jour de votre participation à l'étude (lundi, mardi, … ou dimanche) = jour de la signature du formulaire de consentement.

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

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

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

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

Etude PNEUMOVAS Carnet de suivi de l'observance des corticoïdes	Code d'identification patient |__|__|__| / |__|__|__|__|__| / |__|-|__|	CARNET n° 1 / 3 De l'inclusion à la visite à 6 mois

MOIS 1

Date du début de votre participation à l'étude : __ __ /__ __ /__ __ __ __ A quel jour de la semaine cela correspond : _____	CORTICOIDES : Dose en mg/jour |__|__|, |__| = Semaine 1	Noter dans cette colonne tous les changements dans les doses de corticoïdes que vous prenez avec les dates correspondantes		Les doses de corticoïdes prescrites ont-elles été respectées ? Oui ❒ Non ❒ Si non (traitement non pris ou partiellement pris), indiquez-en le motif ci-dessous :
Semaine 2 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |__|__|, |__| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____
Semaine 3 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |__|__|, |__| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____
Semaine 4 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |__|__|, |__| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____

Etude PNEUMOVAS Carnet de suivi de l'observance des corticoïdes	Code d'identification patient |__|__|__| / |__|__|__|__|__| / |__|-|__|	CARNET n° 1 / 3 De l'inclusion à la visite à 6 mois

MOIS 2		Noter dans cette colonne tous les changements dans les doses de corticoïdes que vous prenez avec les dates correspondantes		Les doses de corticoïdes prescrites ont-elles été respectées ? Oui ❒ Non ❒ Si non (traitement non pris ou partiellement pris), indiquez-en le motif ci-dessous :
Semaine 5 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |__|__|, |__| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____
Semaine 6 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |__|__|, |__| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____
Semaine 7 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |__|__|, |__| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____
Semaine 8 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |__|__|, |__| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____

Etude PNEUMOVAS Carnet de suivi de l'observance des corticoïdes	Code d'identification patient |__|__|__| / |__|__|__|__| / |__|-|__|	CARNET n° 1 / 3 De l'inclusion à la visite à 6 mois

MOIS 3		Noter dans cette colonne tous les changements dans les doses de corticoïdes que vous prenez avec les dates correspondantes		Les doses de corticoïdes prescrites ont-elles été respectées ? Oui ❒ Non ❒ Si non (traitement non pris ou partiellement pris), indiquez-en le motif ci-dessous :
Semaine 9 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |__|__|, |__| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____
Semaine 10 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |__|__|, |__| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____
Semaine 11 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |__|__|, |__| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____
Semaine 12 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |__|__|, |__| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____

Etude PNEUMOVAS Carnet de suivi de l'observance des corticoïdes	Code d'identification patient |__|__|__| / |__|__|__|__| / |__|-|__|	CARNET n° 1 / 3 De l'inclusion à la visite à 6 mois

MOIS 4		Noter dans cette colonne tous les changements dans les doses de corticoïdes que vous prenez avec les dates correspondantes		Les doses de corticoïdes prescrites ont-elles été respectées ? Oui ❒ Non ❒ Si non (traitement non pris ou partiellement pris), indiquez-en le motif ci-dessous :
Semaine 13 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |__|__|, |__| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____
Semaine 14 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |__|__|, |__| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____
Semaine 15 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |__|__|, |__| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____
Semaine 16 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |__|__|, |__| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____

Etude PNEUMOVAS Carnet de suivi de l'observance des corticoïdes	Code d'identification patient |__|__|__|__| / |__|__|__|__|__| / |__|-|__|	CARNET n° 1 / 3 De l'inclusion à la visite à 6 mois

MOIS 5		Noter dans cette colonne tous les changements dans les doses de corticoïdes que vous prenez avec les dates correspondantes		Les doses de corticoïdes prescrites ont-elles été respectées ? Oui ❒ Non ❒ Si non (traitement non pris ou partiellement pris), indiquez-en le motif ci-dessous :
Semaine 17 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |__|__|, |__| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____
Semaine 18 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |__|__|, |__| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____
Semaine 19 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |__|__|, |__| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____
Semaine 20 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |__|__|, |__| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____

Etude PNEUMOVAS Carnet de suivi de l'observance des corticoïdes	Code d'identification patient |__|__|__|__| / |__|__|__|__|__| / |__|-|__|	CARNET n° 1 / 3 De l'inclusion à la visite à 6 mois

MOIS 6		Noter dans cette colonne tous les changements dans les doses de corticoïdes que vous prenez avec les dates correspondantes		Les doses de corticoïdes prescrites ont-elles été respectées ? Oui ❒ Non ❒ Si non (traitement non pris ou partiellement pris), indiquez-en le motif ci-dessous :
Semaine 21 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |__|__|, |__| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____
Semaine 22 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |__|__|, |__| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____
Semaine 23 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |__|__|, |__| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____
Semaine 24 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |__|__|, |__| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____

Etude PNEUMOVAS Carnet de suivi de l'observance des corticoïdes	Code d'identification patient |__|__|__| / |__|__|__|__| / |__|-|__|	CARNET n° 1 / 3 De l'inclusion à la visite à 6 mois

Si la date de la visite à 6 mois est décalée (7 jours maximum autorisés)

		Noter dans cette colonne tous les changements dans les doses de corticoïdes que vous prenez avec les dates correspondantes		Les doses de corticoïdes prescrites ont-elles été respectées ? Oui ❒ Non ❒ Si non (traitement non pris ou partiellement pris), indiquez-en le motif ci-dessous :
Semaine 25 __ __ /__ __ /__ __ __ __	Y-a-t-il eu un changement de dose depuis la date précédente ?	Oui ❒ Non ❒	Si oui : A quelle date : __ __ / __ __ / __ __ __ __ Nouvelle dose : |__|__|, |__| mg/jour	❒ Oubli : combien de jours : ___ ❒ Effet(s) Indésirable(s) : précisez : _____ ❒ Autre : _____

19.4 SmPC for the PREVENAR 13

Link to the SmPC for the PREVENAR 13
http://ec.europa.eu/health/documents/community-register/2017/20171023139254/anx_139254_fr.pdf

19.5 SmPC for the Pneumovax®

Link for the SmPC for the Pneumovax®
http://agence-prd.ansm.sante.fr/php/ecodex/rcp/R0205191.htm

19.6 Form for reporting Serious Adverse Events

19.7 Form for monitoring a pregnancy that developed during a biomedical research