« Multicentre, randomized, prospective trial evaluating the efficacy and safety of Infliximab to tocilizumab in refractory or relapsing Takayasu arteritis »

INTOReTAK : INfliximab and TOcilizumab in Refractory/relapsing TAKayasu arteritis

INTERVENTIONAL STUDY PROTOCOL RELATING TO A MEDICINAL PRODUCT FOR HUMAN USE

Version N°4.0 of 20/07/2023

Project code number: **P160909** / EUDRACT No.: **2018-003753-13**

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INTERVENTIONAL RESEARCH PROTOCOL

PROTOCOL SIGNATURE PAGE

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The study will be carried out in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

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The study was approved by the Ethic committee CPP Soom 1 on 2019 march 18th and authorised by the ANSM on 2019 Febuary 11th

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1 SUMMARY

Full title	Multicentre, randomized, prospective trial evaluating the efficacy and safety of Infliximab to tocilizumab in refractory or relapsing Takayasu arteritis
Acronym	INTOReTAK (INfliximab and TOcilizumab in Refractory/relapsing TAKayasu arteritis)
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Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	Takayasu arteritis (TA) is a vasculitis of unknown origin, resulting in progressive thickening and stenosis of large and medium arteries (the aorta and its major branches, and the pulmonary arteries). First line therapy of TA consists of high dose corticosteroids (CS) (Mukhtyar *et al*, 2009). Between 20 and 50% of cases respond to CS alone, with subsequent resolution of symptoms and stabilization of vascular abnormalities (Shelhamer *et al*, 1985; Maksimowicz-McKinnon *et al*, 2007). Although second-line agents (methotrexate, azathioprine, mercaptopurine, mycophenolate mofetil) may result in initial remission, relapses remain common when prednisone is tapered (Maksimowicz-McKinnon *et al*, 2007). Thus, 50% of CS-resistant or relapsing TA patients may achieve sustained remission with the addition of methotrexate (Hoffman *et al*, 1994). During the last decade, biologics such as anti-tumor necrosis factor alpha (anti-TNFα) and anti-interleukin-6 (anti-IL-6) have been used as third-line treatment in refractory or relapsing TA. Almost 90% of CS–methotrexate resistant TA cases responded to infliximab, an anti-TNFα, and sustained remission was obtained in 37 to 76% of the cases (Schmidt *et al*, 2012; Comarmond *et al*, 2012; Mekinian *et al*, 2012). Tocilizumab, an anti-IL-6 has given similar results with 68% of sustained remission in refractory TA (Abisror *et al*, 2013). Irrespective of classical cardiovascular risk factors, the systemic inflammation and CS use play a pivotal role in the occurrence of cardiovascular thrombotic events (CVEs) (Roubille *et al*, 2015). As CVEs overlap with TA complications it is primordial to drastically taper CS in that vasculitis. We therefore hypothesize that Infliximab or Tocilizumab can achieve a remission in more than 70% of refractory/relapsing TA cases to CS associated to a second-line agent. INTOReTAK, first randomized prospective study in TA, has an original design testing Infliximab and Tocilizumab propensity to achieve over 70% of sustained remission in refractory/relapsing TA and evaluating jointly the 2 arms.
Primary objective and assessment criterion	To obtain, by arm, ≥ 70% of patients at 6 months post-treatment with prednisone (or the prednisolone)* ≤ 0.1mg/kg per day and inactive disease (NIH score ≤ 1) during the last 3 months. Proportion at 6 months post-treatment of patients with prednisone (or the prednisolone) ≤ 0.1mg/kg per day and sustained inactive disease (NIH score ≤ 1) from M3 to M6 and same biological therapy from since the treatment, among randomized patients in each arm.
Secondary objectives and assessment criteria	To estimate the incidence of relapse between 3 and 6 months post-treatment in each arm. To estimate the incidence of traitement failure at 3 months post-treatment in each arm.

	To estimate the incidence of revascularization procedures (endovascular or surgical) required due to the disease at 6 & 12 months post-treatment in each arm. To estimate the cumulative dose of prednisone (or the prednisolone) at 6 & 12 months post-treatment in each arm. To estimate the incidence of adverse events at 6 & 12 months post-treatment in each arm. To estimate the mean change in SF-36 quality-of-life values from D1 of treatment to 6 & 12 months post-treatment in each arm. To estimate the proportion of new vascular lesions at 6 & 12 months post-treatment in each arm measured by angio-computorized tomography or magnetic resonance imaging angiography. Incidence of relapse as defined by the NIH criteria between 3 and 6 months after Day1 of treatment. Incidence of revascularization procedures (endovascular or surgical) from D1 of treatment to 6 months post-treatment. incidence of traitement failure at M3 after Day1 of treatment i.e disease still active according to the NIH criteria Proportion at 6 months after Day1 of treatment of patients with prednisone (or the prednisolone) ≤ 0.1mg/kg per day and sustained inactive disease (modified NIH score (without criterion 3) ≤ 1) from M3 to M6 and same biological therapy from Day1 of treatment among the randomized patients in the same arm. Incidence of relapse as defined by the modified NIH criteria (without criterion 3) ≥2 between M3 and M6 after Day1 of treatment. incidence of traitement failure at M3 after Day1 of treatment i.e disease still active according to the modified NIH criteria (without criterion 3) ≥2 Cumulative doses of prednisone (or the prednisolone) in each arm at 6 & 12 months after Day1 of treatment. Incidence of adverse events of grades III or IV at 6 & 12 months after Day1 of treatment. Mean change in the quality of life questionnaire SF-36 from D1 of treatment to 6 & 12 months after treatment. Proportion of new vascular lesions at 6 & 12 months after Day1 of treatment assessed measured by angio-CT or MR angiography
Experimental design	This open randomized clinical trial is based on a Simon's two-stage design (Simon, 1989) that will be used separately, in both arms. The randomization and thus allocation concealment between both arms will insure the absence of selection bias in allocating the experimental treatments to the patients, with no between-arm comparison test. Only estimates of difference in the end points between treatment arms will be provided.
Population involved	Adult patients with refractory or relapsing Takayasu arteritis
Inclusion criteria	Diagnosis of Takayasu arteritis if at least 3 of the 6 ▪ Criteria of the **American College of Rheumatology (ACR)** are met (appendix 1) ▪ Age at disease onset or 1st symptoms ≤ 40 years old. ▪ Limb claudication. ▪ Anisotension >10mm Hg between brachial systolic arterial pressures. ▪ Decreased brachial artery pulse (one or both arteries). ▪ Bruit over subclavian arteries or aorta.

	▪ Arteriogram abnormality: arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia, or similar causes; changes usually focal or segmental. ▪ Or otherwise if at least two major or one major and two minor criteria or four minor criteria **<u>of the Ishikawa's criteria modified by Sharma</u>** are met (appendix 1) **Three major criteria**: ▪ **Left Mid subclavian artery lesion**: The most severe stenosis or occlusion present in the mid portion from the point 1 cm proximal to the vertebral artery orifice up to that 3 cm distal to the orifice determined by angiography ▪ **Right Mid subclavian artery lesion**: The most severe stenosis or occlusion present in the mid portion from the right vertebral artery orifice up to that 3 cm distal to the orifice determined by angiography ▪ **Characteristic signs and symptoms of at least one month duration**: these include limb claudication, pulselessness or pulse differences in limbs, an unobtainable or significant blood pressure difference (> 10 mmHg systolic blood pressure difference in limbs), fever, neck pain, transient amaurosis, blurred vision, syncope, dyspnea or palpitations **Ten minor criteria:** 1. **High ESR**: unexplained persistent high ESR > 20 mm/h (Westergren) at diagnosis or presence of the evidence in patient's history 2. **Carotid artery tenderness**: unilateral or bilateral tenderness of common arteries on palpation. Neck muscle tenderness is unacceptable. 3. **Hypertension**: Persistent blood pressure > 140/90 mmHg brachial or > 160/90 mmHg popliteal 4. **Aortic regurgitation or Annuloaortic ectasia**: by auscultation or echocardiography or angiography 5. **Pulmonary artery lesion**: lobar or segmental arterial occlusion or equivalent determined by angiography or perfusion scintigraphy, or presence of stenosis, aneurysm, luminal irregularity or any combination in pulmonary trunk or in unilateral or bilateral pulmonary arteries determined by angiography. 6. **Left mid common carotid lesion**: presence of the most severe stenosis or occlusion in the mid portion of 5 cm in length from the point 2 cm distal to its orifice determined by angiography. 7. **Distal brachiocephalic trunk lesion**: presence of the most severe stenosis or occlusion in the distal third determined by angiography. 8. **Descending thoracic aorta lesion**: narrowing, dilation or aneurysm, luminal irregularity or any combination determined by angiography: tortuosity alone is unacceptable. 9. **Abdominal aorta lesion**: narrowing, dilation or aneurysm, luminal irregularity or aneurysm combination. 10 **Coronary artery lesion**: documented on angiography below the age of 30 years in the absence of risk factors like hyperlipidemia or diabetes mellitus ▪ Active disease according to the international **<u>criteria of the National Institute of Health (NIH)</u>** (appendix 2) if at least 2 of the following criteria are met **Criterion 1**: if at least 1 of the following systemic characteristics, without any other cause identified

	▪ erythema nodosum ▪ Fever > 38°C for more than a week ▪ polyarthralgia / arthritis ▪ episcleritis **Criterion 2**: at least 1 of the following clinical signs have appeared since the previous visit ▪ carotidodynia, vascular claudication or pain along an arterial pathway ▪ constituted or transient ischemic stroke, acute coronary syndrome, angina ▪ abolition of a pulse ▪ vascular bruit ▪ anisotension **Criterion 3**: at least 2 of the following biological signs ▪ C-reactive protein >10 mg/L ▪ fibrinogen >4 g/L ▪ Orosomucoïde > 1,2 g/L ▪ Haptoglobine > 2,5 g/L **Criterion 4**: at least 1 of the following radiological signs ▪ arterial wall thickening AND wall contrast measurement in angio-MRI or angio-TDM ▪ appearance of new vascular lesions in angio-MRI or angio-TDM ▪ Refractory/relapsing disease or symptomatic severe arterial involvement Refractory/relapsing disease is considered if one of the following conditions are met: 1. Inability to taper corticosteroids below 1mg/kg/day within 1 month because the disease is still active 2. Inability to taper corticosteroids below 10mg/day within 6 months 3. Inability to discontinue corticosteroids after 1 year of treatment 4. Relapse of disease after gradual decrease of corticosteroids therapy Or Symptomatic severe arterial involvement defined as follows: stroke, retinopathy, symptomatic coronary artery stenosis, symptomatic pulmonary artery stenosis, symptomatic mesenteric arteries or celiac trunk stenosis, symptomatic renal artery stenosis. ▪ Patients with one immunosuppressive agent (methotrexate, azathioprine, mercaptopurine or mycophenolate mofetil, leflunomide, ciclosporine, hydroxychloroquine) with no change in dosage within the last 30 days unless allergy/intolerance or contraindication to immunosuppressive agents. ▪ Age of 15~~8~~ years or older ▪ Weight 40 – 120 kg ▪ Medical follow-up in a university or general hospital in France ▪ Social insurance

	▪ Willing and able to provide written informed consent ▪ Willing and able to comply with treatment and follow-up procedures required by the study protocol ▪ For female subjects of child-bearing age, a negative serum pregnancy test and no pregnancy plans within 12 months. ▪ For subjects with reproductive potential, a willingness to use contraceptive measures adequate to prevent the subject or the subject's partner from becoming pregnant during the study. Adequate contraceptive measures include hormonal methods used for two or more cycles prior to Screening (e.g., oral contraceptive pills, contraceptive patch, or contraceptive vaginal ring), barrier methods (e.g., contraceptive sponge, diaphragm used in conjunction with contraceptive foam or jelly, or condom used in conjunction with contraceptive foam or jelly), intrauterine methods (IUD), sterilization (e.g., tubal ligation or a monogamous relationship with a vasectomized partner), and abstinence. ▪ Chest X-ray results (postero-anterior and lateral) or chest CT within 12 weeks prior to the inclusion & randomization visit with no evidence of active tuberculosis, active infection, or malignancy ▪ Tuberculosis assessment meeting one of the following conditions: 1. Active Tuberculosis infection treatment achieved 2. Completion of at least 3 weeks treatment for Latent Tuberculosis infection 3. Negative tuberculin skin test (TST) or interferon-gamma release assay (IGRA) (e.g., QuantiFERON®-TB Gold or T-spot TB® Test) 4. A potential subject with a positive TST or IGRA at inclusion is eligible if her/his chest X-ray does not show evidence suggestive of active tuberculosis infection and there are no clinical signs and symptoms of pulmonary and/or extra-pulmonary tuberculosis infection. These subjects with a latent tuberculosis infection should have completed the full or currently receive since at least 3 weeks the treatment for latent tuberculosis infection. ▪ Negative human immunodeficiency virus (HIV) serology, negative hepatitis C RNA, and hepatitis B surface antigen within 3 months.
Non-inclusion criteria	▪ Active tuberculosis or untreated latent tuberculosis infection currently treated less than 3 weeks ▪ Evidence of active infection (includes chronic infection) ▪ Infection requiring treatment with antibiotics within 2 weeks prior to the inclusion & randomization visit ▪ Infection with positive human immunodeficiency virus (HIV) serology, positive hepatitis C RNA , or a positive hepatitis B surface antigen. ▪ Pregnancy or lactation ▪ Inability to comply with study guidelines ▪ Inability to provide informed consent ▪ Alcohol or drug abuse, that, in the investigator's opinion, could prevent a subject from fulfilling the study requirements or that would increase the risk of study procedures

	▪ Severe renal insufficiency (creatinine clairance <30mL/min/1,73m^2) ▪ Hepatic dysfunction as shown by aspartate transaminase (AST) or alanine transaminase (ALT) levels >5-fold the upper limit of normal ▪ Heart failure ≥ stage III / IV NYHA, ▪ History of any malignant neoplasm except adequately treated basal or squamous cell carcinoma of the skin, or solid tumors treated with curative therapy and disease free for at least 5 years. ▪ History of multiple sclerosis and/or demyelinating disorder ▪ History of severe allergic or anaphylactic reactions to infliximab, any chimeric murine monoclonal antibody, tocilizumab, and their respective excipients or prednisone (or the prednisolone) ▪ History of immediate hypersensitivity reaction to iodinated and gadolinium-based contrast media ▪ Cytopenia: Hemoglobin < 8.5 g/dL, absolute neutrophil < 1.5 G/L, Platelet count < 80 G/L ▪ Any live (attenuated) vaccine fewer than 4 weeks before enrolment. Recombinant or killed virus vaccines fewer than 2 weeks before the inclusion & ransomization visit. ▪ Use of the following systemic treatments during the specified periods a-Treatment with biologic therapy (infliximab, adalimumab, certolizumab pegol, golimumab, anakinra, tocilizumab, etanercept, abatacept, ixekizumab, secukinumab, ustekinumab, alemtuzumab) within 3 months prior to the inclusion & randomization visit b-Past treatment with rituximab within the past 12 months, or past treatment with rituximab more than 12 months ago where the B lymphocytes count has not returned to normal at time of the inclusion & randomization visit c-Treatment with any systemic alkylating agents within 3 months prior to the inclusion & randomization visit (e.g., cyclophosphamide, chlorambucil) ▪ Indication to initiate infliximab or tocilizumab for another active disease than Takayasu arteritis ▪ Lack of affiliation to a social security benefit plan (as a beneficiary or assignee) ▪ Presence of any of the following on-ongoing and on-treatment disease processes: o Microscopic polyangiitis o Granulomatosis with polyangiitis o Eosinophilic granulomatosis with polyangiitis o Polyarteritis nodosa o Cogan's syndrome o Behcet's disease o Kawasaki's disease o Atypical mycobacterial infections o Deep fungal infections o Lymphoma, lymphomatoid granulomatosis, or other type of malignancy that mimics vasculitis o Cryoglobulinemic vasculitis o Systemic lupus erythematosus o Rheumatoid arthritis

	○ Mixed connective tissue disease or any overlap autoimmune syndrome ○ Known constitutive immunodeficiency
Treatment being tested	**Arm A :** patients will receive infliximab 5mg/kg intravenously at week 0; 2; 6; 14; 22, following prescription recommendations, during 6 months. **Arm B :** patients will receive tocilizumab 8mg/kg intravenously at week 0; 4; 8; 12; 16; 20; 24, following prescription recommendations, during 6 months.
Risks added by the research	Risk C
Number of subjects chosen	50 patients
Number of centres	Multicentre national study including 18 centres
Research period	Duration of inclusions: 48 months Duration of participation of each patient: 12 months Total duration of the study: 60 months
Number of inclusions expected per centre and per month	0.06 patients/month/centre
Statistical analysis	We will randomize 25 patients in each arm. For each arm, the null hypothesis (response rate 0.40) will be tested against a one-sided alternative (response rate 0.70) with 0.0248 type I error rate and power 0.8061. The first stage includes 10 patients in each arm. If 5 or fewer responses are observed in these patients, the arm is stopped. Otherwise, 15 additional patients are accrued. The null hypothesis will be rejected if 14 or more responses are observed in the 25 patients.
Funding source	PHRC-N 2016 – *French Ministry of Health*
Data Safety Monitoring Board anticipated	Yes

Prednisone (or the prednisolone)*: « In case of supply difficulties with Prednisone, the equivalent use of Prednisolone will be possible at the same posology. »

2 SCIENTIFIC JUSTIFICATION FOR THE STUDY

2.1 Hypothesis for the study

Takayasu arteritis (TA) is a vasculitis of unknown origin, resulting in progressive thickening and stenosis of large and medium arteries (the aorta and its major branches, and the pulmonary arteries). First line therapy of TA consists of high dose corticosteroids (CS) (Mukhtyar *et al*, 2009). Between 20 and 50% of cases respond to CS alone, with subsequent resolution of symptoms and stabilization of vascular abnormalities (Maksimowicz-McKinnon *et al*, 2007; Shelhamer *et al*, 1985). Although second-line agents (methotrexate, azathioprine, mercaptopurine, mycophenolate mofetil,) may result in initial remission, relapses remain common when prednisone is tapered (Maksimowicz-McKinnon *et al*, 2007). Thus, 50% of CS-resistant or relapsing TA patients may achieve sustained remission with the addition of methotrexate (Hoffman *et al*, 1994). During the last decade, biologics such as anti-tumor necrosis factor alpha (anti-TNFα) and anti-interleukin-6 (anti-IL-6) have been used as third-line treatment in refractory or relapsing TA. Almost 90% of CS–methotrexate resistant TA cases responded to infliximab, an anti-TNFα, and sustained remission was obtained in 37 to 76% of the cases (Schmidt *et al*, 2012; Comarmond *et al*, 2012; Mekinian *et al*, 2012). Tocilizumab, an anti-IL-6 has given similar results with 68% of sustained remission in refractory TA (Abisror *et al*, 2013). Irrespective of classical cardiovascular risk factors, the systemic inflammation and CS use play a pivotal role in the occurrence of cardiovascular thrombotic events (CVEs) (Roubille *et al*, 2015). As CVEs overlap with TA complications it is primordial to drastically taper CS in that vasculitis.

We therefore hypothesize that infliximab or tocilizumab can achieve a remission in more than 70% of refractory/relapsing TA cases to CS associated to a second-line agent.

2.2 Description of knowledge relating to the pathology in question

2.2.1 Takayasu arteritis

TA is a chronic inflammatory arteritis of unknown etiology with segmental involvement of the aorta and its main branches (coronary, carotid, subclavian, vertebral, renal and iliac arteries) and the pulmonary arteries. Initially described in Japan, TA is ubiquitous but is seen with greater frequency in Asia, South America and the Mediterranean countries. The incidence of the disease in Japan is 100 to 150 cases per year. In Western countries, epidemiological data show an annual incidence of about 2 to 3 cases per million inhabitants. Some autopsy studies with histological analysis have reported a much higher prevalence of about 1 to 30 cases per 1000 subjects. TA affects young woman in 80-90% of cases, with a less pronounced female/male ratio in Western countries. The third decade of life is the period of in which onset of the disease is highest.

It is usual to distinguish an acute period, called pre-occlusive, from an occlusive phase characterized by ischemic events. These two phases can be separated by an asymptomatic period or overlap. The pre-occlusive stage combines non-specific symptoms with fever, arthralgia, skin lesions, and pain in arterial distribution (particularly a carotidodynia). The occlusive phase is the result of arterial lesions (stenosis, occlusions, and aneurysms) of the aortic arch, the thoracoabdominal aorta and its branches. There is no specific diagnostic marker of Takayasu arteritis. An inflammatory syndrome, indicated by elevated ESR, C-reactive protein (CRP), and fibrinogen, is an indicator of disease activity and its reduction or normalization can indicate a response to treatment.

The diagnosis of TA is based on a set of clinical and imaging criteria proposed by the American College of Rheumatology (Arend *et al*, 1990) (Appendix 1) which have a sensitivity of 90.5% and a specificity of 97.8% for the diagnosis. Fifteen and 20-year survival are 85% and 75% respectively.

2.2.2 Pathophysiology

Histological study of the arterial wall in TA reveals a characteristic infiltration by lymphocytes and macrophages, a feature also noted in giant cell arteritis (Weyand & Goronzy, 2003). This suggests activation of similar immunopathological mechanisms, resulting in recruitment of the same cell populations in both pathologies. The histology of the arterial wall in giant cell arteritis (GCA) reveals infiltration essentially of CD4+ T lymphocytes and macrophages, often in the form of granulomas. Sometimes there are a few giant cells located close to the internal elastic lamina, which is often

fragmented. CD8+ T lymphocytes are rare, and the infiltration contains few or no neutrophils. In TA, the infiltrate consists of the same cells as in GCA, but there is also an increased proportion of CD8+ T lymphocytes and a significant contingent of γδ T cells and NK cells (Seko *et al*, 1994). In both cases, B cells are virtually absent, underlining the important role of cellular immunity in the immunopathology of these diseases. During the course of large vessel arteritis, dendritic cells are activated under the influence of stimuli, which involve toll-like receptor (TLR) 2 and 4 pathways, and acquire a mature phenotype. A high frequency of certain HLA class II alleles (HLA-DRB1*1501, DRB5*0102, DQA1*0103, DQB1*0601, DPA1*02, DPB1*0401) and certain HLA class I alleles (HLA-B5201, HLA-B39) has been reported in Takayasu disease (Weyand & Goronzy, 2003). Moreover, study of the rearrangement of the T-cell receptors (TCR) of cells present in the arterial wall reveals an oligoclonal restriction of the heterogeneity of TCR in TA (Seko *et al*, 1996).

2.2.3 Imaging of Takayasu arteritis

Arterial imaging plays a major role in the positive diagnosis of the disease and the monitoring of its evolution. B-mode vascular ultrasound to measure the thickness of the wall of the carotid has good sensitivity but its use is limited by the inaccessibility of some vessels such as the aorta and the pulmonary arteries. Angiographic CT or magnetic resonance angiography are useful when they show arterial wall thickening or to visualize arterial stenoses and aneurysms. Angiographic MRI has also been used in the radiological evaluation of TA. A theoretical advantage of this technique is the detection of signs of vascular inflammation such as edema and parietal inflammation using injected gadolinium (Jiang *et al*, 2012). Another advantage is the lack of use of iodinated contrast material. Nevertheless, the place of this technique in the evaluation of the vascular lesions of TA remains to be validated(Jiang *et al*, 2012). Some work on the monitoring of TA by positron emission tomography has been carried out, but we do not yet know the sensitivity and specificity of this technique (Meller *et al*, 2003; Arnaud *et al*, 2009).

2.2.4 Criteria of disease activity

There are no definitive criteria for progression of TA. Criteria for disease activity have been proposed based on a series of 60 patients at the National Institutes of Health (NIH) followed prospectively (Kerr *et al*, 1994)(Appendix 2). They are based on the recent emergence or worsening of at least two of the following four criteria.

- signs of ischemia or vascular inflammation
- systemic symptoms not attributable to other causes
- angiographic abnormalities
- an increase in inflammatory markers (ESR, CRP, fibrinogen, orosomucoid, haptoglobin)

In this study, 88% of patients with clinically active disease according to these criteria had emergence of new arterial lesions. More recently, a Turkish group attempted to validate an activity score for TA (Disease activity index-Takayasu), which seems very close to the NIH activity score (Aydin *et al*, 2010). Monitoring of Takayasu disease by positron emission tomography has been tried, but we do not know yet the sensitivity and specificity of this imaging technique (Meller *et al*, 2003; Arnaud *et al*, 2009). One study showed a good correlation between the concentrations of interleukin-6 and RANTES and disease activity in a series of 18 patients followed prospectively (Noris *et al*, 1999). These molecules reflect the activity of the inflammatory process, but an advantage of interleukin-6 and RANTES compared to other markers of inflammation (ESR, CRP and fibrinogen) remains to be demonstrated.

2.3 Summary of relevant pre-clinical experiments and clinical trials

2.3.1 Drugs most studied in Takayasu arteritis

To date there is no clear therapeutic consensus in TA. Most data come from retrospective studies and small cohorts of patients (Hoffman *et al*, 1994; Clifford & Hoffman, 2014). No randomized study has so far been carried out in this condition. The treatment of TA is currently based on medical treatment of the inflammatory aspect of the disease and on angioplastic or surgical revascularization where necessary.

- Corticosteroid treatment

In the absence of immunosuppressive therapy, life-threatening vascular complications may occur. Corticosteroids are used as standard in the treatment of TA. The initial dose is often 0.5 to 1 mg/kg/day, then decreases over a period of 12 months. Corticosteroids are most useful and effective if the diagnosis of the disease has been made early, in the pre-occlusive phase. Corticosteroids alone achieve remission in 25-50% of cases (Shelhamer *et al*, 1985; Maksimowicz-McKinnon *et al*, 2007). Relapses during the tailing of corticosteroids are frequently described, occurring in 30-40% of cases (Maksimowicz-McKinnon *et al*, 2007).In the NIH prospective series of 60 patients, 48 had signs of disease activity and received corticosteroids (prednisone 1mg/kg/day) (Kerr *et al*, 1994). Of these 48 patients, 25 (52%) went into remission. Sixteen patients (64%) relapsed and were retreated with corticosteroids with a favorable response in half of the cases. Long-term corticosteroid use may be deleterious in this disease mainly because of the cardiovascular complications it can cause. Depending on the series, 20-50% of patients develop side effects associated with corticosteroids, including cataracts, peripheral edema, myopathy, fractures, infection and diabetes (Robb-Nicholson *et al*, 1988; Nesher *et al*, 1994; 1997). Frequent relapses require the resumption of high doses of corticosteroids, which leads to a cumulative toxicity. Irrespective of classical cardiovascular risk factors, the systemic inflammation and CS use play a pivotal role in the occurrence of cardiovascular thrombotic events (CVEs) (Roubille *et al*, 2015). As CVEs overlap with TA complications it is primordial to drastically taper CS in that vasculitis.

- Immunosuppressive agent

In Takayasu arteritis, when there is no response or a relapse during the tailing of corticosteroids, the addition of an immunosuppressive agent is usually suggested. The use of methotrexate in this indication appears to be worthwhile. Indeed, addition of methotrexate to corticosteroids allows to achieve remission in 50-80% of cases of steroid-resistance or steroid-dependence diseases (Kerr *et al*, 1994; Hoffman *et al*, 1994). In a pilot study of 16 patients with steroid-resistant Takayasu arteritis, 13 of 16 (81%) went into remission (Hoffman *et al*, 1994). Relapses occurred in 44% of cases (7 of 13 patients). After a mean follow up of 18 months, 50% of patients relapsed. Optimum duration of the immunosuppressive therapy has not been clearly defined. Other immusuppresive agents have been tested but more confidentially: azathioprine, mercaptopurine or mycophenolate mofetil. Globally, 50% of patients relapsed after more or less one year of treatment.

Although second-line agents (methotrexate, azathioprine, mercaptopurine or mycophenolate mofetil) may result in initial remission, relapses remain common when prednisone is tapered (Maksimowicz-McKinnon *et al*, 2007). Thus, 50% of CS-resistant or relapsing TA patients may achieve sustained remission with the addition of methotrexate (Hoffman *et al*, 1994). During the last decade, biologics such as anti-tumor necrosis factor alpha (anti-TNFα) and anti-interleukin-6 (anti-IL-6) have been used as third-line treatment in refractory or relapsing TA.

- Anti-TNFα

Anti-TNFα medications are the first biologic agents tried for treatment of TAK. Unlike giant cell arteritis (GCA), they proved to be effective in the majority of patients with TAK, as demonstrated in multiple retrospective observational studies recently summarized by Clifford & Hoffman. Based on observational studies including 120 patients with refractory TAK receiving anti-TNFα agents, it is notable that infliximab (IFX) was used in a vast majority (80%) of those cases, while remaining patients had used either etanercept (ETA) or adalimumab (ADA). Considering all patients, response rate was 80%, and CS treatment could be tapered or discontinued in over 40% of the patients. However, relapses occurred in 37% of patients and nearly one-half of relapsing patients required either an increase in dose or frequency, or switched to a different anti-TNFα (Clifford & Hoffman, 2014). Following this review, Novikov et al. reported nine new patients with high disease activity resistant to conventional immunosuppressive agents. Similarly, the majority of the patients (8/9) were treated with IFX while the remaining single patient received ADA. The numbers of patients reaching complete and partial remission were five (56%) and three (34%), respectively. The dose of daily prednisolone could be reduced to less than 10 mg in all patients. In this study, positron emission tomography (PET) was used to confirm remission and reduction of vascular inflammation was detected in 86% of TAK patients. However, nearly half (4/9) of the patients relapsed following increasing the dose intervals of anti-TNFα [14]. Using the French Takayasu Network, Mekinian et *al*. retrospectively analyzed the data of 49 patients with TAK who used various biological agents from different centers with the median

treatment duration of 16 months (2–85 months). Among those patients, 35 had received anti-TNFα biologics (IFX 28, ETA 6, ADA 1). While 32 patients received anti-TNFα agents as second line treatment after resistance to conventional immunosuppressive agents, three patients had received these agents as the first line treatment. Complete responses were seen in 35%, 61%, and 74% of the patients at months 3, 6, and 12, respectively. Nearly 91% of those patients did not experience any relapse at three years. However during follow-up, at least one switch to another biologic agent had to be performed in 40% of the patients. The utility of anti-TNFα in newly diagnosed patients with TAK is not known. With this regard, Serra et al. reported five newly diagnosed patients treated with TNFi agents in an open label parallel group. Enrolled patients initially received treatment with prednisone for 5 or 7 months. Then two patients received ADA plus MTX, two patients IFX plus MTX, and the remaining patient was treated with ADA alone, because of adverse events caused by MTX. All five patients responded with clinical and laboratory remission, suggesting the efficacy of anti-TNFα agents early in the disease course. On the other hand, TAK may sometimes progress despite the use of anti-TNFα. Osman et al. recently reported two patients with TAK, one with progressive TAK despite management with IFX and later with ADA, and another who developed TAK while treated with IFX for the management of pre-existing Crohn's disease . In summary, the results of observational studies, confirm that anti-TNFα agents may be beneficial in refractory TAK. Lack of randomized controlled trials with anti-TNFα is an important problem preventing to conclude the exact role of these agents in treatment of TAK.

2.3.2 Drugs recently used in Takayasu arteritis

- Anti-Interleukin 6

Among biologic treatment options, Tocilizumab (TCZ) is a promising agent for the treatment of TAK. interleukin-6 (IL-6) has critical role in the pathogenesis of TAK, based upon elevated levels of serum IL-6 in patients with TAK, also correlating with disease activity, as well as evidence of increased expression of IL-6 in vascular lesions and genetic association of IL-6 with TAK . First description of clinical efficacy of TCZ in TAK by Nishimoto et al appeared in literature in 2008. Following this initial report, many studies concerning use of TCZ in TAK patients with relapsing/refractory disease appeared in literature. The majority of the patients reported were treated with a TCZ dose of 8 mg/kg every 4 weeks, while minority of patients were treated with 4 mg/kg every 4 weeks or 8 mg/kg every 3 weeks. In 2013, Abisror et al. retrospectively analyzed the data of 44 patients with TAK treated using TCZ: five patients from the three French university hospitals and 39 cases from the literature review. Median duration of TCZ treatment and median follow-up after initiation of TCZ were 9 months [3–180 months] and 15 months [8–33 months], respectively. Disease activity significantly decreased within 3 months, and daily steroid dose could be decreased to 10 mg/day [2–30] at 6 months. Significant decrease of arterial FDG uptake was also noted at 6 months. At the last visit, conti- nuation rate of TCZ was 53% (17/32). In the 15 remaining cases, TCZ was discontinued because of remission (n=5), relapse (n=3), persistent radiological activity (n=3), cutaneous rash (n=2), severe infection (n=1) and lack of care welfare system (n=1). In other words, TCZ was stopped due to inefficacy in six patients, and due to adverse effects in three patients. No death related to TCZ treatment was noted. The authors concluded that TCZ was effective in the treatment of TAK in terms of clinical, biological and radiological responses, and reducing CS dose. Osman et al. retrospectively reported 33 patients with TAK treated using TCZ (three patients from their case series, plus 30 patients from literature review)(Osman *et al*, 2015). Notably, most of those 30 patients from literature overlapped with those reported previously by Abisror at al. Overall, Osman et al. concluded that TCZ was an effective and relatively safe steroid-sparing agent in TAK, as only 12.5% of patients included in this review reported significant adverse effects requiring cessation or dis- continuation of treatment. Furthermore, they concentrated on the results of TCZ use in TAK patients with neurological manifestations. Altogether, four patients (two from their case series, and two from literature) had presented with stroke-like symptoms. Considering those four patients, they pointed out that three of them achieved remission and their disease was stabilized, following TCZ treatment. In literature, there are also reports defining TCZ as rescue treatment for TAK patients resistant to anti-TNFα. Among 49 patients of the French Takayasu Network, who used various biological agents, there were 14 TAK patients who received TCZ. While 11 patients received TCZ as second line treatment after resistance to conventional immunosuppressive agents, three patients received TCZ as first line treatment. At least one switch to another biologic agent was necessary during

the follow-up period in 29% of patients receiving TCZ. Most notably, the authors also compared their patients treated with anti-TNFα with those receiving TCZ, and found out that these two groups of patients were similar with respect to proportion of responders, vascular interventions, vascular complications, and relapse-free survival. Overall, TCZ treatment was reported to be effective in TAK with greater than 80% of patients having clinical and laboratory response by 3 months. Unfortunately, some of these patients experienced a relapse during treatment. For instance, in the case series of Goel et al., although all of the 10 patients with TAK refractory to CS and second-line agents went into remission by the fourth infusion, three patients (30%) relapsed both clinically and radiographically by the sixth infusion . More importantly, radiographic worsening occurred in the setting of normal acute phase reactants. This observation is really very important, and the evidence of silent vascular progression despite normalized acute phase reactants during treatment with TCZ was also reported in other studies. Indeed the message obtained from those observations is clear: given that TCZ inhibits IL-6 driven hepatic production of CRP and other similar acute-phase proteins, normalization of circulating inflammatory markers with TCZ is inescapable and this response may be independent from ongoing vascular inflammation. Therefore, close monitoring with regular clinical assessment and serial imaging are imperative during TCZ treatment. Other than secondary unresponsiveness to TCZ, primary failure may also be seen in some patients. In one series up to 29% of TAK patients treated with TCZ, required at least one switch to another biologic treatment. Another problem is that, like many immunosuppressive and biologic agents, TCZ is also not curative and relapse may be seen between 2 and 6 months after discontinuation of TCZ. It is unknown whether maintenance therapy with a conventional immunosuppressive agent should be started when treatment with a biologic agent is discontinued. Although TCZ appears effective in refractory TAK, information on its use in newly diagnosed patients naive to conventional immunosuppresseive agents or anti-TNF therapy is limited.

- Other biologics

Abatacept (ABA) is a fusion protein composed of the Fc region of IgG1 fused to the extracellular domain of CTLA-4. ABA binds to CD80/86 on antigen presenting cells preventing CD80/86 from binding to CD28 on the surface of the T cell, resulting in failure of the costimulatory signal required for T cell activation. Case reports showing efficacy of ABA in patients with TAK are rare [39]. However, since the pathology of both GCA and TAK are granulomatous vasculitis, it was assumed that ABA may be effective by means of inhibiting T cell activation. Therefore, a multicenter clinical trial that evaluated the efficacy of ABA concurrently for GCA and TAK was started and this trial has recently been completed (Clincaltrials.gov identifier: NCT00556439). In this study, all patients received remission induction therapy with oral prednisone plus ABA infusions 10 mg/kg on days 1, 15, 29, and week 8. Study participants who achieved remission by month 3 continued with a standardized prednisone taper and were randomized to receive either monthly infusions of ABA or placebo. Thirty-four eligible patients with TAK were enrolled and treated with prednisone and abatacept; of these, 26 reached the week 12 randomization and underwent a blinded randomization to receive either abatacept or placebo. The relapse-free survival rate at 12 months was 22% for those receiving abatacept and 40% for those receiving placebo (P = 0.853). Treatment with abatacept in patients with TAK enrolled in this study was not associated with a longer median duration of remission (median duration 5.5 months for abatacept versus 5.7 months for placebo). There was no difference in the frequency or severity of adverse events, including infection, between the treatment arms.

Although TAK is considered primarily a T-cell-mediated disease, increasing evidence supports additional dysregulation of B-cell homeostasis, suggesting a possible pathologic role of B lymphocytes as well in the pathogenesis of TAK. Immunohis- tochemical analyses of aortic wall samples from patients with TAK have shown that, B cells are among the most prominent cells in the inflamed arterial adventitia, in addition to T cells. Furthermore, circulating newly generated plasmablasts and memory B cells are increased, while naive B cells are decreased in patients with active TAK as compared with inactive and control patients. Based upon such data, RTX which is a chimeric anti-CD20 monoclonal antibody, causing lysis of B lymphocytes and being used in many autoimmune and neoplastic diseases, was also tried in TAK. There are case reports of RTX treatment in patients with refractory TAK who had failed to respond to conventional immunosuppressive agents or anti-TNF therapy. RTX was used according to the protocol established for rheumatoid arthritis (1000 mg at day 0 and 15). RTX treatment was reported not only to result in clinical remission, but also to reduce the expansion of

newly generated plasmablasts in TAK cases. As recently reviewed by Koster et al., seven of the eight reported treatment-resistant TAK cases experienced an initial favorable response to RTX therapy, but long term results remain unknown. Besides, clinical relapse and persistent imaging evidence of vasculitis despite use of RTX have also been reported. Although RTX may be a possible treatment in refractory TAK, currently more data is needed.

Ustekinumab is a monoclonal antibody targeting Interleukin 12 (IL-12/23p40). In a pilot study, Terao et *al.* used 40 mg of ustekinumab at day 0 and day 28 to three patients with refractory TAK. They evaluated clinical, laboratory, and MRI imaging at baseline and at day 84. Although inflammatory markers decreased and there were no prominent adverse effects, suppression of vessel wall inflammation could not be achieved based upon imaging findings. This may be due to low dose of ustekinumab and/or short duration of use. Further clinical studies are clearly needed to determine the future role of ustekinumab in TAK treatment.

2.4 Identification and description of the experimental medication or medications

There is no randomized prospective study, which has evaluated the efficacy of infliximab or tocilizumab in TA. INTOReTAK is designed to test these two biologics therapies in selected patients with refractory or relapsing Takayasu arteritis treated by immunosuppressant therapy and corticosteroids.

We will randomize 25 patients in each arm, arm A to receive Infliximab infusions, arm B to receive Tocilizumab infusions. For each arm, the null hypothesis (response rate 0.40) will be tested against a one-sided alternative (response rate 0.70) with 0.0248 type I error rate and power 0.8061. The first stage includes 10 patients. If 5 or fewer responses are observed in these patients, the arm is stopped. Otherwise, 15 additional patients are accrued. The null hypothesis will be rejected if 14 or more responses are observed in the 25 patients.

2.4.1 Name and description of the investigation medicinal products

After the collection of their free and informed consent, eligible patients will be randomized into one of the 2 arms at the inclusion visit:

- **Arm A** : patients will receive infliximab 5mg/kg intravenously at week 0; 2; 6; 14; 22, following prescription recommendations and temporay recommendations for use (RTU). Remicade® or any bioequivalent (Flixabi®, Inflectra®, Remsima®) prescription will be at the discretion of each center. However, no interchangeability with another brand-name drug will be accepted for randomized patients during the first six-month therapy.
- **Arm B** : patients will receive tocilizumab [Roactemra®, Roche pharmaceutics company] 8mg/kg intravenously at week 0; 4; 8; 12; 16; 20; 24, following prescription recommendations.

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

Administration design will be extensively detailed in chapter 5. Dosage of infliximab and frequency of the infusions have been determined according to previous publications on small series of TA patients (Schmidt *et al*, 2012; Comarmond *et al*, 2012; Mekinian *et al*, 2012) and industrial recommandations. Dosage of tocilizumab, and frequency of the infusions have been determined according to previous publications on small series of TA patients (Abisror *et al*, 2013) and industrial recommandations.

2.4.3 Summary of the known and foreseeable benefits and risks for the STUDY participants

This is the first randomized study for therapeutic management of Takayasu arteritis. It will allow the validation of two targeted therapies of Takayasu arteritis resistant or relapsing to corticosteroids and immunosuppressant drug, in the same trial. Each patient will receive one active treatment either infliximab or tocilizumab. Moreover, in case of failure of treatment to obtain remission, i.e. inactive TA diseases according to the NIH criteria, a swich from one arm to another is planned in the study protocole. Therefore, the patients will not suffer any potential inefficacy of one of the experimental treatments.

This study may confirm the efficacy of a biologic therapy in terms of steroid sparing. This study will further provide estimation of the difference of the two biologic therapies used (Infliximab and

Tocilizumab) in terms of steroid sparing. It could thus improve the care of patients with Takayasu arteritis. The expected benefit is both individual, in reduced morbidity for patients with Takayasu arteritis, and collective, in reducing costs of hospitalization, and surgery or endovascular procedures.

- Side effects of infliximab

The most commonly reported Adverse Drug Reactions of infliximab are:

- Upper respiratory tract infections, sinusitis
- Hypersensitivity reaction: rash, pruritus, urticarial, fever, chills, chest pain, flushing of the face, nasal congestion.
- Viral infection (e.g. influenza, herpes virus infection)
- Neutropenia, leucopenia, anaemia, lymphadenopathy
- Depression, insomnia
- Headache
- Dizziness, vertigo, hypoaesthesia, paresthesia
- Conjunctivitis
- Tachycardia, palpitation
- Hypertension, hot flush, flushing, hypotension, ecchymosis
- Abdominal pain, nausea, diarrhoea, dyspepsia, gastroesophageal reflux, constipation
- Increased ALT, AST, total bilirubin
- New onset or worsening psoriasis including pustular psoriasis (primarily palm & soles), urticarial, rash, pruritus, hyperhidrosis, dry skin, fungal dermatitis, eczema, alopecia.
- Arthralgia, myalgia, back pain
- Urinary tract infection
- Infusion-related reaction, pain, inection site reaction
- Chest apin, fatigue,
- Intestinal or perianal abscess
- Serious hypersensitivity reaction

- Refer to SmPC of Remicade®, Flixabi®, Inflectra®, Remsima® for more details. Side effects of tocilizumab

The most commonly reported Adverse Drug Reactions of tocilizumab are:

- Upper respiratory tract infections
- Nasopharyngitis
- Headache, dizziness
- Hypertension
- Increased ALT, AST, total bilirubin
- Hypercholesterolemia
- Leukopenia, neutropenia
- Conjunctivitis
- Oral herpes simplex
- Abdominal pain, pouth ulceration, gastritis
- Cough, dyspnoea
- Mild or moderate hypersensitivity reaction: rash, pruritus, urticarial, fever, chills, chest pain, flushing of the face, nasal congestion.

Refer to SmPC of Roactemra® for more details

- In case of Latent TB infection treatment

Possible adverse effects of Isoniazid (INH)

Asymptomatic elevation of serum liver enzyme concentrations occurs in 10%–20% of people taking INH; and liver enzyme concentrations usually return to normal even when treatment is continued. It is generally recommended that INH be withheld if a patient's transaminase level exceeds 3 times the upper limit of normal if associated with symptoms or 5 times the upper limit of normal if the patient is asymptomatic.

Clinical hepatitis occurs in about 0.1% of people taking INH, and is more common when INH is combined with other hepatotoxic agents. Factors that may increase either of these rates or the severity of hepatitis include daily alcohol consumption, underlying liver disease or risks for liver disease, and the concurrent use of other medications which are metabolized in the liver. Symptomatic hepatitis is rare in patients younger than 20 years of age, but severe and fatal cases have been reported. Younger patients with underlying risk factors for liver disease should be monitored clinically with the same precautions as older patients.

Peripheral neuropathy occurs in less than 0.2% of people taking INH at conventional doses. It is more likely in the presence of other conditions associated with neuropathy such as diabetes, HIV, renal failure, and alcoholism. Pyridoxine (vitamin B6) supplementation is recommended only in such conditions or to prevent neuropathy in pregnant or breastfeeding women.

Refer to SmPC of Rimifon® for more details

Possible adverse effects of rifampin (RIF)

Hepatotoxicity, evidenced by transient asymptomatic hyperbilirubinemia, may occur in 0.6% of persons taking RIF. Hepatitis is more likely when RIF is combined with INH.

Cutaneous reactions, such as pruritis (with or without a rash), may occur in 6% of persons taking RIF. They are generally self-limited and may not be a true hypersensitivity; continued treatment may be possible.

Rarely, rifamycins can be associated with hypersensitivity reactions, including hypotension, nephritis or thrombocytopenia, and manifested by symptoms such as fever, headache, dizziness/lightheadedness, musculoskeletal pain, petechiae, and pruritis.

Gastrointestinal symptoms such as nausea, anorexia, and abdominal pain are rarely severe enough to discontinue treatment.

Orange discoloration of body fluids is expected and harmless, but patients should be advised beforehand. Soft contact lenses and dentures may be permanently stained.

RIF and RPT interact with several drugs, causing drug-drug interactions. They are known to reduce concentrations of methadone, warfarin, hormonal contraceptives, and phenytoin. Women using hormonal contraceptives should be advised to consider an alternative method of contraception (e.g., a barrier method).

RIF is contraindicated, or should be used with caution, in HIV-infected individuals being treated with certain antiretroviral medications. Substitution of rifabutin for RIF in the 4-month regimen many be considered for such patients. RPT should not be used in HIV-infected persons taking antiretroviral therapy.

Refer to SmPC of Rifinah®, Rifadine® or Rimactan® for more details

- Side effects of corticosteroids:

- Glucocorticoids have been used therapeutically in humans since 1949 and their side effects are well recognized. The main toxicities of prednisone (or the prednisolone) include infections, hyperglycemia, hypertension, cataracts, osteoporosis, avascular necrosis, gastrointestinal irritation, mood disturbances (including psychosis), bruising, skin changes including acne and striae, increase in appetite and weight, and redistribution of fat. Prednisone (or the prednisolone) is not known to have teratogenic effects on the developing fetus and there has been no evidence to date of an effect on fertility. However, prednisone (or the prednisolone) can cause problems during pregnancy for both the mother (risks of weight gain, gestational diabetes, and infection) and the developing fetus as a result of the maternal problems.

These are related to the cumulative dose administered, i.e. the amount taken from the onset of the disease. See the Adult adverse event severity rating scale.

- Weight gain. It is logical to suggest a diet low in fat, salt and rapidly-absorbed sugars
- Abnormal behavior such as nervousness, irritability, tremors, insomnia, and bulimia, at high doses
- Cushing's syndrome with moon facies, linked to a change in fat distribution observed at high doses
- Hypertension and leg edema. These can be reduced by a low-salt diet
- Muscle wasting and cramping. These can be reduced by a diet rich in potassium (bananas, dried fruit...) and supplementary potassium and protein, as well as by regular muscular activity
- Small vessel and capillary fragility. Ecchymoses and hematomata are more common and can occur after minimal impact
- The skin may also be affected by acne and delayed healing
- Osteoporosis can also occur after prolonged treatment. Supplementation with calcium and vitamin D associated with bisphosphonates reduces the risk of fracture
- Steroids can induce the onset of diabetes

For more details refer to the SmPC of Cortancyl®, Prednisone Arrow®, Prednisone Biogaran®, Prednisone Cristers®, Prednisone EG®, Prednisone Mylan®, Prednisone Sandoz®, Prednisone Zentiva® or SmPC of Prednisolone.

- Risks related to corticosteroids tapering:

TA relapses or progression, exacerbation of TA symptoms

- Side effects of methotrexate: refer to the SmPC of Novatrex®, Methotrexate Belon®, Imeth®, Metoject® or Nordimet®
- Side effects of azathioprine: refer to the SmPC of Azathioprine EG®, Azathioprine Mylan®, Azathioprine Teva® or Imurel®
- Side effects of mercaptopurine: refer to SmPC of Purinéthol®
- Side effects of mycophenolate mofetil: refer to the SmPC of Cellcept®, Mycophénolate mofétil Biogaran®, Mycophénolate mofétil EG®, Mycophénolate mofétil Mylan®, Mycophénolate mofétil Sandoz® or Mycophénolate mofétil Teva®

3 OBJECTIVES

3.1 Primary objective

To obtain, by arm, ≥ 70% of patients at 6 months post-treatment with prednisone (or the prednisolone) ≤ 0.1mg/kg per day and inactive disease during the last 3 months.

3.2 Secondary objectives

- To estimate the incidence of relapse between 3 and 6 months post-treatment in each arm
- To estimate the incidence of traitement failure at 3 months post-treatment in each arm
- To estimate the incidence of revascularization procedures (endovascular or surgical) required due to the disease at 6 & 12 post-treatment in each arm
- To estimate the cumulative dose of prednisone(or the prednisolone) at 6 & 12 months post-treatment in each arm
- To estimate the incidence of adverse events at 6 & 12 months post-treatment in each arm
- To estimate the mean change in SF-36 quality-of-life values from Day1 of treatment to 6 & 12 months post-treatment in each arm
- To estimate the proportion of new vascular lesions at 6 & 12 months post-treatment in each arm measured by angio-computorized tomography or magnetic resonance imaging angiography.

4 DESCRIPTION OF THE TRIAL

4.1 Concise description of the primary and secondary assessment criteria

4.1.1 Primary endpoint: (Primary assessment criterion)

Proportion at 6 months after Day1 of treatmentof patients with prednisone (or the prednisolone) ≤ 0.1mg/kg per day and sustained inactive disease from M3 to M6 and same biological therapy from Day1 of treatment among the randomized patients in the same arm.

Inactive disease is defined according to the NIH criteria (Appendix 2), by the presence of at most one of the following criteria.

Criterion 1: if at least 1 of the following systemic characteristics, without any other cause identified

- erythema nodosum
- Fever > 38°C for more than a week
- polyarthralgia / arthritis
- episcleritis

Criterion 2: at least 1 of the following clinical signs have appeared since the previous visit

- carotidodynia, vascular claudication or pain along an arterial pathway
- constituted or transient ischemic stroke, acute coronary syndrome, angina
- abolition of a pulse
- vascular bruit
- anisotension

Criterion 3: at least 2 of the following biological signs

- C-reactive protein >10 mg/L
- fibrinogen >4 g/L
- Orosomucoïde > 1,2 g/L
- Haptoglobine > 2,5 g/L

Criterion 4: at least 1 of the following radiological signs

- arterial wall thickening AND wall contrast measurement in angio-MRI or angio-TDM

- appearance of new vascular lesions in angio-MRI or angio-TDM

Clinical and biological assessments will be performed at every drug infusion ie at week 0; 2; 6; 12; 14; 22 and 24 and month 9 & 12 for arm A with infliximab, at week 0; 4; 8; 12; 16; 20 and 24 and month 9 & 12 for arm B with tocilizumab.

Imaging will be repeated at week 12, week 24 and month 12.

4.1.2 Secondary endpoints (Secondary assessment criteria)

- Incidence of relapse as defined by the NIH criteria between M3 and M6 after Day1 of treatment.
- incidence of traitement failure at M3 after Day1 of treatment i.e disease still active according to the NIH criteria
- Proportion at 6 months after Day1 of treatment of patients with prednisone (or the prednisolone) ≤ 0.1mg/kg per day and sustained inactive disease (modified NIH score (without criterion 3) ≤ 1) from M3 to M6 and same biological therapy from Day1 of treatment among the randomized patients in the same arm.
- Incidence of relapse as defined by the modified NIH criteria (without criterion 3) ≥2 between M3 and M6 after Day1 of treatment.
- incidence of traitement failure at M3 after Day1 of treatment i.e disease still active according to the modified NIH criteria (without criterion 3) ≥2
- Incidence of revascularization procedures (endovascular or surgical) from Day1 of treatment to M6 and M12 after Day1 of treatment
- Cumulative doses of prednisone (or the prednisolone) in each arm at M6 and M12 after Day1 of treatment
- Incidence of adverse events of grades III or IV at M6 and M12 after Day1 of treatment
- Mean change in the quality of life questionnaire SF-36 from D1 of treatment to M6 and M12 after treatment
- Proportion of new vascular lesions at M6 and M12 after Day1 of treatment assessed by angio-CT or MR angiographyDescription of study methodology.

4.2 Design of the trial (*Experimental plan*)

The trial is based on a Simon's two-stage design (Simon, 1989) that will be used separately, in both arms. The randomization and thus allocation concealment between both arms will insure the absence of selection bias in allocating the experimental treatments to the patients, with no between-arm comparison test. Only estimates of difference in the end points between treatment arms will be provided.

Eligibility for enrollment is determined within 2 weeks prior to starting study treatment (inclusion & randomization visit). Patients who satisfy all entry criteria including written informed consent are randomized in a 1:1 ratio to Arm A (infliximab) or Arm B (tocilizumab). The randomization will be centralized, performed on a Web Site, from prespecified lists based on permutation blocks of non-reported size.

All treatment groups will receive the same corticosteroid regimen. All patients will receive oral prednisone (or the prednisolone) at 1 mg/kg/day (up to 60 mg/day) from the inclusion & randomization visit until the Day 1 of treatment visit.

At Day1 of treatment, patients receive treatment allocated by randomization. The following schedule of reduction of prednisone (or the prednisolone) will apply to both groups as long as the disease is inactive:

- Week 1 : 0.7mg/kg/day
- Week 2 : 0.5mg/kg/day
- Week 3 & 4 : 0.4mg/kg/day
- Week 5 to 8 : 0.3mg/kg/day

- Week 9 to 12 : 0.2mg/kg/day
- Week ≥13 : $\leq$ 0.1mg/kg/day

Other immunosuppressants agents (methotrexate, azathioprine, mercaptopurine, or mycophenolate mofetil) should be maintained without any dose change during the study follow-up as long as the disease is inactive.

Monitoring: All patients will be reviewed for systemic physical examination at the inclusion & randomization visit, Day1 of treatment visit and the follow-up visits at every infusion during the first 6 months and at month 9 and 12. Monitoring will also include laboratory testing at the inclusion & randomization visit, Day1 of treatment visit and the follow-up visits at every infusion during the first 6 months and at month 9 and 12.

Monitoring will also include imaging (angiographic CT scan or angiographic MRI according to the imaging modality present at the inclusion & randomization visit) at week 12; week 24 and month 12 post-treatment.

Phone call will be given to each participant 4 to 6 weeks after last infusion to check out any adverse event that may have occurred. Phone call at month 13 will be performed to check out that a follow-up is planned If not organized in the study center.

Additional visits will take place in case of any clinical or laboratory findings suggestive of a flare-up of the disease.

4.3 Number of participating sites

Multicentre national study including 18 recruiting centres: List of Investigators (in appendix)

4.4 Identification of subjects

For this study, the subjects will be identified by a 9 characters sequence consisting of the center number (3 digits), the inclusion number of the patient at the center (4 digits), the surname initial, the first name initial and a code of 2 letters.|__|__|__|-|__|__|__|__|-|__|-|__|. This reference is unique and will be retained for the entire study period.

4.5 Inclusion & Randomization

Once the inclusion and exclusion criteria are validated and the consent signed by the patient and the investigator (after information), the patient will be included and randomized by connecting the eCRF. The patient's identification number will be assigned. The randomization will be centralized and performed using a computerized system on the eCRF website according to a predefined randomization list. The allocation to the two groups will be done in a 1:1 ratio.

The randomization list will be designed by the Saint Louis Clinical Research Unit and will be stratified by center. It will match each number assigned to one of the study arms.

5 PROCEDURE FOR THE STUDY

Recruitment will occur throught the clinical practices of each site investigator.

Subject enrollment at the participating center will not begin until the Institutional Review Board (IRB) has approved this protocol as well as the consent corms to be used. Details of the goals of the study and the risk and benefits of the protocol will be reviewed with each potential study subject. Recruitment will occur by physicians and study coordinators.

Subjects who decline to participate in any or all parts of the study will still have available the opportunity of evaluation by a vascultits expert if they or their physician feels this is appropriate.

Strict subject confidentiality will be observed throughout all aspects of the study. While medical records will be reviewed by members of the study team, no individually identifiable subject data will be distributed to non-study or care-giving team members.

5.1 Inclusion & Randomization visit

The inclusion & randomization visit takes place within 14 days prior to the Day 1 of treatment visit. It will be carried out by the physician responsible for the patient during the study, who will:

- verify the eligibility criteria,
- interview the patient and record:
  - medical, surgical and therapeutic histories,
  - histories of intercurrent disease and current treatments,
- perform a physical examination including a search for active lesions of Takayasu arteritis
- rule out heart failure class III or IV of the NYHA classification after interview and clinical examination of the patient, read an Electrocardiogram performed the same day.
- check the results of the investigations looking at signs of active Takayasu arteritis: contrast enhanced angiographic CT, or angiographic MRI.
- Check the results of the following laboratory tests: complete blood count with platelets, serum electrolytes, liver function tests (AST, ALT, GGT, total bilirubin, albumin), ESR, CRP, fibrinogen, haptoglobin, orosomucoid, urea, creatinine, glucose, total cholesterol and triglycerides, HIV, hepatitis C serology, hepatitis B surface antigen. and for women, ßHCG.
- Collect patient's information on risk factors for Tuberculosis (TB) exposure as: close contacts of persons known or suspected to have active TB; foreign-born persons from areas that have a high incidence of active TB (e.g., Africa, Asia, Eastern Europe, Latin America, and Russia); persons who visit areas with a high prevalence of active TB, especially if visits are frequent or prolonged; residents and employees of congregate settings whose clients are at an increased

risk for active TB (e.g., correctional facilities, long-term care facilities, and homeless shelters); health care workers who serve clients who are at an increased risk for active TB; populations defined locally as having an increased incidence of latent *Mycobacterium tuberculosis* infection or active TB, possibly including medically underserved, low-income populations, or persons who abuse drugs or alcohol; and infants, children, and adolescents exposed to adults who are at an increased risk for latent *Mycobacterium tuberculosis* infection or active TB.

- Check the tests looking at active tuberculosis and chest Xray (INPES, 2009)
- In case of positive Chest Xray, check that respiratory (e.g., sputum, bronchoalveolar lavage fluid) or other samples as clinically appropriate for acid-fast bacilli (AFB) smear and culture have been performed and specific treatment started. If samples are positive, active TB infection treatment should be started and completed before the inclusion & randomization visit. If samples are negative, latent TB infection treatment should be started and enrollment may occur after completion of at least 3-weeks treatment.(Singh *et al*, 2012; 2016; afssaps, 2005).
- Latent TB infection may be treated by one of the following protocols(afssaps, 2005; CDC, 2016)
    - Isoniazid (INH) 5mg/kg/day, maximum dose 300mg/day for 9 months
    - Isoniazid (INH) 5mg/kg/day and rifampin (RIF) 10mg/kg/day, maximum dose 600mg/day for 3 months
    - Rifampin (RIF) 10mg/kg/day, maximum dose 600mg/day for 4 months
- In case of Latent TB infection treatment already completed, one should keep in mind that patients who tested positive for TST or IGRA at baseline can remain positive for these tests even after successful treatment of TB. These patients need monitoring for clinical signs and symptoms of recurrent TB, since repeating tests will not help in the diagnosis of recurrent TB.
- Inform the patient and if applicable the holders of parental authority about the protocol, and give them the information and consent form.
- Collect the free and informed written consent of the patient and if applicable the holders of parental authority.

- Prescribe and start the oral prednisone (or the prednisolone) therapy at 1mg/kg/day (maximum 60mg/day).

Subjects whose consent is sought	**Who informs the subject and collects their consent?**	**When is the subject informed?**	**When is the subject's consent collected?**
The patient and the holders of parental authority	Patient's study doctors inform their patients and the holders of parental authority and collect the consent form	At inclusion visit	At inclusion visit, after a reflection period and before any act/procedure added by the study

The investigator will complete the Study Inclusion data in the eCRF. The Methodology and Management Centre will receaving email informing by the inclusion. Patients will be identified by a 9 characters sequence consisting of the center number (3 digits), the inclusion number of the patient at the center (4 digits), the surname initial, the first name initial and a code of 2 letters.

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

- The center number, 01 to 18
- The patient number, by order of inclusion: 01 to 99
- The surname initial, A to Z
- The first name initial, A to Z
- A randomly generated 1-letters and 4-digits randomization code, for instance A6534

If all eligibility criteria are met, the investigator will confirm inclusion and randomization by validating the e-CRF data. He will also provide them with the patient's unique ID number and give them the patient's card.

This will allow the investigator to plan the first day of treatment within 14 days.

At this visit, the physician responsible for the patient during the study will:

- inform the patient of the selected treatment arm by randomization.
- perform clinical examination.
- arrange the following laboratory tests: complete blood count with platelets, serum electrolytes, liver function tests (AST, ALT, GGT, total bilirubin, albumin), ESR, CRP, fibrinogen, haptoglobin, orosomucoid, urea, creatinine, glucose, total cholesterol and triglycerides and for women, ßHCG.
- prescribe and start the study treatment according to the randomization.
- arrange the infusion schedule according to the treatment arm.
- prescribe the oral prednisone (or the prednisolone) tapering for the next 6 months.
- Plan the imaging investigations at week 12 ± 2 days.

5.2 Follow-up Visits

Monitoring should continue for all patients until the end of the study according to the schedule, even if they discontinue. Consultations at these visits will be with the patient's usual study doctor. Patients will be reviewed at every treatment infusion.

- A physical examination will be performed by the patient's study physician at each visit.
- Attention to new or worsening symptoms of heart failure must be paid, because it would lead to stop infliximab in patients with Heart Failure class III or IV of the NYHA classification.
- Laboratory tests will be carried between visits at local laboratories and include monthly monitoring of blood count, platelets, liver functions, urea and creatinine
- At each visit ESR, CRP, fibrinogen, haptoglobin, orosomucoid, CBC, creatinine, liver function tests (AST, ALT, GGT, total bilirubin, albumin), total cholesterol and triglycerides and glucose will be measured.
- Imaging studies (angioCT scan or angio-MRI) will be performed at week 12, and week 24.
- Additional visits will take place if there are clinical signs indicating a possible flare up of the disease (see Appendix 2).

5.3 End of study visit

All subjects will be followed after the study according to their usual routine hospital at month 9 & 12 after day 1 of treatment . Monthly pregnancy tests will be performed up to 6 months after treatment for arm A and 3 months after treatment for arm B. Visit at month 12 will be the last study visit on site. Phone call at month 13 will be performed to check out that a follow-up is planned If not organized in the study center.

5.4 Expected length of participation and description of the chronology and duration of the study.

The Day 1 of treatment within 14 days after the inclusion & randomization visit. Once the patient is included, the randomization takes place within the same visit. Each patient will be treated during 6 months with a follow-up of 12 months after the Day 1 of treatment.

The duration of the inclusion phase will be 48 months.

The total duration of the study will be 60 months (5 years).

Maximum period between inclusion&randomization and Day1 of treatment	14 days
Inclusion period	48 months
Included subject follow-up period	12 months
Including: - Treatment period:	6 months

Total study period:	60 months

5.5 Table or diagram summarising the chronology of the study

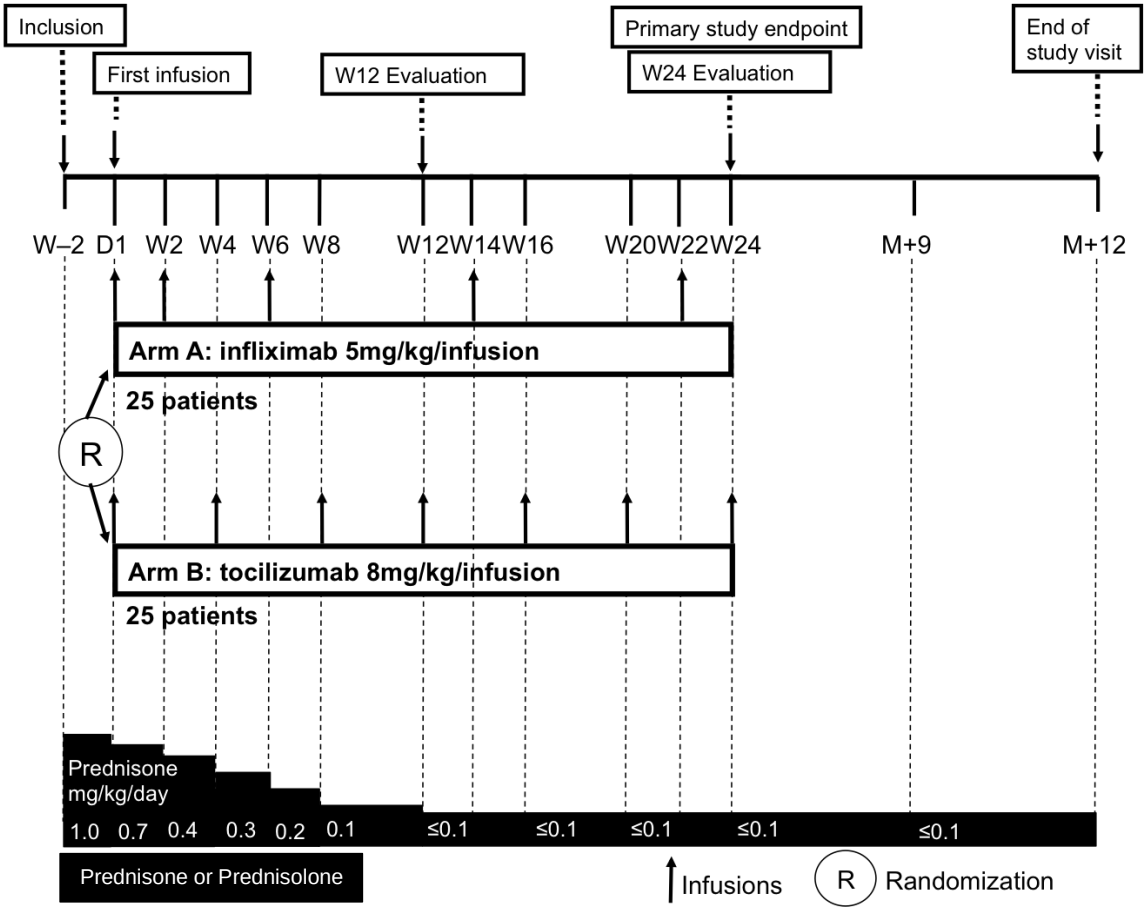

Figure 1. Scheme of the study

	≤W-2	D1	W2 ±2d	W4 ±2d	W6 ±2d	W8 ±2d	W10	W12 ±2d	W14 ±2d	W16 ±2d	W18	W20 ±2d	W22 ±2d	W24 ±2d	W27 ±7d	M8 ±7d	M9 ±7d	M10 ±7d	M11 ±7d	M12 ±7d	M13 ±7d
Informed consent	X																				
ECG	X																				
Chest X Ray	X																				
Inclusion & Randomization visit	X																				
Arm A treatment infusion		X	X		X				X				X								
Arm A adverse events		X	X		X			X	X				X	X	X		X			X	
Arm B treatment infusion		X		X		X		X		X		X		X							
Arm B adverse events		X		X		X		X		X		X		X	X		X			X	
Phone call visit															X						(X)
Follow-up visit																	X			X	
Biology tests	X	X	X_A	X_B	X_A	X_B		X	X_A	X_B		X_B	X_A	X			X			X	
βhCG (women)	X	X	X_A	X_B	X_A	X_B		X_B	X_A	X_B		X_B	X_A	X_B			X			X	
Pregnancy urinary test															X	X		X_A	X_A		
Imaging	X							X						X						X	
QOL questionnaires		X						X						X						X	

Table 1. Patient's monitoring. (Flowchart)

Biology tests includes Blood count, platelets, Urea, creatinine, and Liver function tests, ESR, CRP, fibrinogen, haptoglobin and orosomucoid.

X_A: Specific to Arm A: infliximab infusions

X_B: Specific to Arm B: tocilizumab infusions

(X) : Phone call at month 13 will be performed to check out that a follow-up is planned If not organized in the study center.

W= week; d= day; ECG= electrocardiogram; QOL= quality of life; βhCG= bêta human chorionic gonadotrophin

5.6 Distinction between standard care and study

Procedures and treatments carried out as part of the study	**Procedures and treatments associated with <u>care</u>**	**Procedures and treatments added because of <u>the study</u>**
Treatments	Infliximab 5mg/kg at W0, W2, W6, W14, W22	Tocilizumab 8mg/kg at W0, W4, W8, W12, W16, W20, W24
Consultations	Every infusion	
Blood samples	W0, at every infusion and W12, W24, M9, M12	
Imaging	At the inclusion & randomization visit, W12, W24 and M12	

Table 2: Distinction between procedures associated with "care" and procedures added because of the "study"

W= week; M= month

5.7 Termination and exit rules

5.7.1 Criteria and methods for prematurely terminating the study treatment

Different situations

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

The investigator must:

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

Criteria and methods for the premature termination of the study

Any subject can withdraw from participating in the study at any time and for any reason.

The investigator can temporarily or permanently end a subject's participation in the study for any reason that affects the subject's safety or which would be in the subject's best interests.

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

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

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

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

- Adverse effects will be assessed on the scale of side effects and categorized according to the affected organ or function.

The side effects will be classified into five levels of increasing severity according to CTCAE:

- Grade 1: minor
- Grade 2: moderate
- Grade 3: severe
- Grade 4: life-threatening
- Grade 5: death

A patient will be considered to have discontinued treatment when he or she is no longer taking the study treatment but continues to undergo monitoring according to the Protocol (visits, samples, ancillary tests...).

A form will be completed in case of premature discontinuation. The applicable reasons for such a discontinuation are:

- the patient's expressed desire
- intolerance of study treatment or the occurrence of a serious adverse event
- the onset or aggravation of a concomitant illness
- the patient's death
- progression of the disease
- pregnancy
- any medical event requiring discontinuation of treatment
- a major breach of the Protocol
- non-compliance with the Protocol which endangers the patient's health
- a need for medical treatment not authorized under the Protocol
- loss of the patient to follow-up

Discontinuation of the study for any other reasons will be considered a deviation from the Protocol. Premature discontinuation of the study must be reported promptly to the Methodology and Management Centre by fax and subsequently by letter using the dedicated form. The reasons and the date of the discontinuation must be documented.

Patients who discontinue the study will receive the best possible treatment in terms of their state of health and the current state of knowledge.

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

Ending a subject's participation does not affect the normal management of the subject's illness in any way. In case of serious adverse event, investigators must notify the sponsor and monitor the subject for at least 12 months following the premature termination of treatment. If treatment is stopped due to a serious adverse event, a serious adverse event notification form will be sent by fax (+33 1 44 84 17 99) email (eig-vigilance.drc@aphp.fr)to the sponsor. The serious adverse event will be monitored until it is resolved. The data and safety monitoring board (DSMB) specify and validate the monitoring methods.

5.7.3 Terminating part or all of the study

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

- first of all, if suspected unexpected serious adverse reactions (SUSARs) are seen in an arm being treated or if there is a discrepancy in the serious adverse reactions between the 2 arms being treated, and which require a reassessment of the benefit-risk ratio for the study.
- in the case of interim analysis: stopping treatment to demonstrate the efficacy of one of the arms being treated or on the other hand stopping due to futility**.**
- likewise, unexpected facts, new information about the product, in light of which the objectives of the study or of the clinical programme are unlikely to be achieved, can lead AP-HP as sponsor or the Competent Authority (ANSM) to prematurely halt the study**.**

- AP-HP as sponsor reserves the right to permanently suspend inclusions at any time if it appears that the inclusion objectives are not met.

If the study 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.

5.7.4 Arm experimental treatment switch

At Month 3 after randomization, if TA is still active according to the NIH criteria, experimental medication in arm A or B will be stopped and patient will be switched to experimental medication in arm B or A respectively. For the intention to treat analysis this case will considered as a failure of first arm treatment for the primary assessment criterion, and second treatment will not be taken into account this primary assessment criterion.

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

The eligibility criteria will be checked at the inclusion & randomization visit The consent document will be given to the patient during the visit. Adult patients meeting the following criteria may be included in the study:

- Diagnosis of Takayasu arteritis

if at least 3 of the 6 criteria of the American College of Rheumatology (ACR) are met (appendix 1)

1. age at disease onset or 1st symptoms ≤ 40 years old
2. limb claudication
3. decreased brachial pulse (one or both arteries)
4. anisotension >10mm Hg between brachial systolic arterial pressures
5. bruit over subclavian arteries or aorta
6. imaging in favour of Takayasu arteritis: arterial narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia, or similar causes; changes usually focal or segmental

or otherwise if at least two major or one major and two minor criteria or four minor criteria of the Ishikawa's criteria modified by Sharma are met (appendix 1)

Three major criteria:

1. **Left Mid subclavian artery lesion**: The most severe stenosis or occlusion present in the mid portion from the point 1 cm proximal to the vertebral artery orifice up to that 3 cm distal to the orifice determined by angiography
2. **Right Mid subclavian artery lesion**: The most severe stenosis or occlusion present in the mid portion from the right vertebral artery orifice up to that 3 cm distal to the orifice determined by angiography
3. **Characteristic signs and symptoms of at least one month duration**: these include limb claudication, pulselessness or pulse differences in limbs, an unobtainable or significant blood pressure difference (> 10 mmHg systolic blood pressure difference in limbs), fever, neck pain, transient amaurosis, blurred vision, syncope, dyspnea or palpitations

Ten minor criteria:

1. **High ESR**: unexplained persistent high ESR > 20 mm/h (Westergren) at diagnosis or presence of the evidence in patient's history
2. **Carotid artery tenderness**: unilateral or bilateral tenderness of common arteries on palpation. Neck muscle tenderness is unacceptable.

3. **Hypertension**: Persistent blood pressure > 140/90 mmHg brachial or > 160/90 mmHg popliteal
4. **Aortic regurgitation or Annuloaortic ectasia**: by auscultation or echocardiography or angiography
5. **Pulmonary artery lesion**: lobar or segmental arterial occlusion or equivalent determined by angiography or perfusion scintigraphy, or presence of stenosis, aneurysm, luminal irregularity or any combination in pulmonary trunk or in unilateral or bilateral pulmonary arteries determined by angiography.
6. **Left mid common carotid lesion**: presence of the most severe stenosis or occlusion in the mid portion of 5 cm in length from the point 2 cm distal to its orifice determined by angiography.
7. **Distal brachiocephalic trunk lesion**: presence of the most severe stenosis or occlusion in the distal third determined by angiography.
8. **Descending thoracic aorta lesion**: narrowing, dilation or aneurysm, luminal irregularity or any combination determined by angiography: tortuosity alone is unacceptable.
9. **Abdominal aorta lesion**: narrowing, dilation or aneurysm, luminal irregularity or aneurysm combination.
10. **Coronary artery lesion**: documented on angiography below the age of 30 years in the absence of risk factors like hyperlipidemia or diabetes mellitus

- Active disease according to the international criteria of the National Institute of Health (NIH) (appendix 2) if at least 2 of the following criteria are met
    - **Criterion 1**: if at least 1 of the following systemic characteristics, without any other cause identified
        - erythema nodosum
        - Fever > 38°C for more than a week
        - polyarthralgia / arthritis
        - episcleritis
    - **Criterion 2**: at least 1 of the following clinical signs have appeared since the previous visit
        - carotidodynia, vascular claudication or pain along an arterial pathway
        - constituted or transient ischemic stroke, acute coronary syndrome, angina
        - abolition of a pulse
        - vascular bruit
        - anisotension
    - **Criterion 3**: at least 2 of the following biological signs
        - C-reactive protein >10 mg/L
        - fibrinogen >4 g/L
        - Orosomucoïde > 1,2 g/L
        - Haptoglobine > 2,5 g/L
    - **Criterion 4**: at least 1 of the following radiological signs
        - arterial wall thickening AND wall contrast measurement in angio-MRI or angio-TDM
        - appearance of new vascular lesions in angio-MRI or angio-TDM
- Refractory/relapsing disease or symptomatic severe arterial involvement

  Refractory/relapsing disease is considered if one of the following conditions are met:
    - Inability to taper corticosteroids below 1mg/kg/day within 1 month because the disease is still active

- Inability to taper corticosteroids below 10mg/day within 6 months
- Inability to discontinue corticosteroids after 1 year of treatment
- Relapse of disease after gradual decrease of corticosteroids therapy

Or

Symptomatic severe arterial involvement defined as follows: stroke, retinopathy, symptomatic coronary artery stenosis, symptomatic pulmonary artery stenosis, symptomatic mesenteric arteries or celiac trunk stenosis, symptomatic renal artery stenosis.

- Patients with one immunosuppressive agent (methotrexate, azathioprine, mercaptopurine or mycophenolate mofetil, leflunomide, ciclosporine, hydroxychloroquine) with no change in dosage within the last 30 days unless allergy/intolerance or contraindication to immunosuppressive agents.
- Age of 15 years or older
- Weight 40 – 120 kg
- Medical follow-up in a university or general hospital in France
- Social insurance
- Willing and able to provide written informed consent
- Willing and able to comply with treatment and follow-up procedures required by the study protocol
- For female subjects of child-bearing age, a negative serum pregnancy test and no pregnancy plans within 12 months.
- For subjects with reproductive potential, a willingness to use contraceptive measures adequate to prevent the subject or the subject's partner from becoming pregnant during the study. Adequate contraceptive measures include hormonal methods used for two or more cycles prior to Screening (e.g., oral contraceptive pills, contraceptive patch, or contraceptive vaginal ring), barrier methods (e.g., contraceptive sponge, diaphragm used in conjunction with contraceptive foam or jelly, or condom used in conjunction with contraceptive foam or jelly), intrauterine methods (IUD), sterilization (e.g., tubal ligation or a monogamous relationship with a vasectomized partner), and abstinence.
- Chest X-ray results (postero-anterior and lateral) or chest CT within 12 weeks prior to the inclusion & randomization visit with no evidence of active tuberculosis, active infection, or malignancy
- Tuberculosis assessment meeting one of the following conditions:
  - Active Tuberculosis infection treatment achieved
  - Completion of at least 3 weeks treatment for Latent Tuberculosis infection
  - Negative tuberculin skin test (TST) or interferon-gamma release assay (IGRA) (e.g., QuantiFERON®-TB Gold or T-spot TB® Test)
  - A potential subject with a positive TST or IGRA at inclusion is eligible if her/his chest X-ray does not show evidence suggestive of active tuberculosis infection and there are no clinical signs and symptoms of pulmonary and/or extra-pulmonary tuberculosis infection. These subjects with a latent tuberculosis infection should have completed the full or currently receive since at least 3 weeks the treatment for latent tuberculosis infection.
- Negative human immunodeficiency virus (HIV) serology, negative hepatitis C RNA, and hepatitis B surface antigen within 3 months.

6.2 Non-inclusion criteria

Subjects will be excluded from the study if they meet any of the following criteria:

- Active tuberculosis or latent tuberculosis infection currently treated less than 3 weeks
- Evidence of active infection (includes chronic infection)

- Infection requiring treatment with antibiotics within 2 weeks prior to the inclusion & randomization visit
- Infection with positive human immunodeficiency virus (HIV) serology, positive hepatitis C RNA, or a positive hepatitis B surface antigen.
- Pregnancy or lactation
- Inability to comply with study guidelines
- Inability to provide informed consent
- Alcohol or drug abuse, that, in the investigator's opinion, could prevent a subject from fulfilling the study requirements or that would increase the risk of study procedures
- Severe renal insufficiency (creatinine clairance <30mL/min/1,73m^2)
- Hepatic dysfunction as shown by aspartate transaminase (AST) or alanine transaminase (ALT) levels >5-fold the upper limit of normal
- Heart failure ≥ stage III / IV NYHA,
- History of any malignant neoplasm except adequately treated basal or squamous cell carcinoma of the skin, or solid tumors treated with curative therapy and disease free for at least 5 years.
- History of multiple sclerosis and/or demyelinating disorder
- History of severe allergic or anaphylactic reactions to infliximab, any chimeric murine monoclonal antibody, tocilizumab, and their respective excipients or prednisone (or the prednisolone).
- History of immediate hypersensitivity reaction to iodinated and gadolinium-based contrast media
- Cytopenia: Hemoglobin < 8.5 g/dL, absolute neutrophil < 1.5 G/L, Platelet count < 80 G/L
- Any live (attenuated) vaccine fewer than 4 weeks before enrolment. Recombinant or killed virus vaccines fewer than 2 weeks before the inclusion & randomization visit.
- Use of the following systemic treatments during the specified periods:
  a. Treatment with biologic therapy (infliximab, adalimumab, certolizumab pegol, golimumab, anakinra, tocilizumab, etanercept, abatacept, ixekizumab, secukinumab, ustekinumab, alemtuzumab) within 3 months prior to the inclusion & randomization visit
  b. Past treatment with rituximab within the past months, or past treatment with rituximab more than months ago where the B lymphocytes count has not returned to normal at time of the inclusion & randomization visit
  c. Treatment with any systemic alkylating agents within 3 months prior to the inclusion & randomization visit (e.g., cyclophosphamide, chlorambucil)
- Indication to initiate infliximab or tocilizumab for another active disease than Takayasu arteritis
- Lack of affiliation to a social security benefit plan (as a beneficiary or assignee)
- Presence of any of the following on-ongoing and on-treatment disease processes:
  - Microscopic polyangiitis
  - Granulomatosis with polyangiitis
  - Eosinophilic granulomatosis with polyangiitis
  - Polyarteritis nodosa
  - Cogan's syndrome
  - Behcet's disease
  - Kawasaki's disease
  - Atypical mycobacterial infections
  - Deep fungal infections

- Lymphoma, lymphomatoid granulomatosis, or other type of malignancy tha mimics vasculitis
- Cryoglobulinemic vasculitis
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Mixed connective tissue disease or any overlap autoimmune syndrome
- Known constitutive immunodeficiency

6.3 Recruitment methods

The French national reference center for rare vascular diseases located in the Georges-Pompidou European Hospital (HEGP), in Paris, is a leading center in the field of Takayasu arteritis with a cohort of more than 150 patients. The French Takayasu's network is composed of 18 competence centers for Takayasu arteritis all over the country, related to the French national reference center for rare vascular diseases.

	Number of subjects
Total number of subjects chosen	50
Number of centres	18
Inclusion period (months)	48
Number of subjects/centre	2.8
Number of subjects/centre/month	0.06

7 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

7.1 The investigational medicinal product(s)

7.1.1 Investigational medicinal product 1 : Experimental medication in arm A

ANSM has developed, in collaboration with the pharmaceutical companies selling the generic-drug infliximab under brand-names: Remicade®, Flixabi®, Inflectra® and Remsima® temporary recommendations of use (RTU) aimed at securing the use of infliximab in the treatment of
Takayasu arteritis refractory to immunosuppressant with corticosteroids.
Infliximab Injection, powder, lyophilized, for solution 100mg/10mL, route intravenous.

Remicade® or any bioequivalent (Flixabi®, Inflectra®, Remsima®) prescription will be at the discretion of each center. However, no interchangeability with another brand-name drug will be accepted for randomized patients during the first six-month therapy. Subjects will receive a dose of infliximab at 5mg per kilogram of body weight. Infliximab will be administered over at least 2-hours as an intravenous infusion in 250 mL of physiologic serum (0.9%) on day 1, week 2 and week 6 and over at least 1 hour on week 14 and week 22. All subjects will be monitored for at least 1 hour after the end of the intravenous infusion to detect any anaphylactic adverse reaction. A premedication with paracetamol 1g and/or dexchlorpheniramine 5mg can be prescribed to reduce such adverse reaction.

Time windows of one week before or after the scheduled date of administration will be permissible. In the absence of toxicity or relapse, subjects will remain on infliximab until the end of the last scheduled infusion. Infliximab will be discontinued should the subject experience any event listed below in Discontinuation of Study Drug.

Infliximab is a chimeric human-murine anti-human tumor necrosis factor (TNF) monoclonal antibody. It binds to tumor necrosis factor alpha (TNFa) and inhibits binding of TNFa with its receptors. This reduces production of pro-inflammatory cytokines such as interleukins (IL) 1 and 6. This also limits leukocyte migration and expression of adhesion molecules by endothelial cells and leukocytes. Infliximab also limits the activation of neutrophil and eosinophil functional activity, reduces production of tissue degrading enzymes produced by synoviocytes and/or chondrocytes. Infliximab decreases synovitis and joint erosions in collagen-induced arthritis and allows eroded joints to heal. Infliximab neutralizes the biological activity of TNFa by binding with high affinity to the soluble and transmembrane forms of TNFa and inhibits binding of TNFa with its receptors. Infliximab does not neutralize TNFb (lymphotoxin a), a related cytokine that utilizes the same receptors as TNFa. TNFa activation normally induces the release of proinflammatory cytokines, the enhancement of leukocyte migration and activation of neutrophils among others. Neutralization of the biological activity of TNFa leads to an overall reduction in inflammation.

Metabolism: infliximab is most likely removed by opsonization via the reticuloendothelial system when bound to T lymphocytes, or by human antimurine antibody production. It is not metabolized by the CYP enzymes. Half-life of infliximab is 9.5 days (7–12 days) in patients with Crohn's disease, plaque psoriasis and rheumatoid arthritis.

At Month 3 after the Day1 of treatment, if TA is still active according to the NIH criteria, experimental medication in arm A will be stopped and patient will be switched to experimental medication in arm B. For the intention treatment analysis this case will considered as a failure of treatment.

7.1.2 Investigational medicinal product 2 : Experimental medication in arm B

Tocilizumab (Roactemra®, Roche) Injection, solution, concentrate 20mg/mL, route intravenous.

Subjects will receive a dose of tocilizumab at 8mg per kilogram of body weight. Tocilizumab will be administered over at least 2-hours as an intravenous infusion in 250 mL of physiologic serum (0.9%) on day 1 and at week 4, 8, 12, 16, 20, and 24. All subjects will be monitored for at least 1 hour after the end of the intravenous infusion to detect any anaphylactic adverse reaction. A premedication with paracetamol 1g and/or dexchlorpheniramine 5mg can be prescribed to reduce such adverse reaction.

Time windows of one week before or after the scheduled date of administration will be permissible. In the absence of toxicity or relapse, subjects will remain on tocilizumab until the end of the last

scheduled infusion. Tocilizumab will be discontinued should the subject experience any event listed below in Discontinuation of Study Drug.

Tocilizumab is a recombinant, humanized, anti-human interleukin 6 (IL-6) receptor monoclonal antibody that achieves a significant therapeutic response rate. The light chain is made up of 214 amino acids. The heavy chain is made up of 448 amino acids. The four polypeptide chains are linked intra- and inter-molecularly by disulfide bonds.

IL-6 plays essential roles not only in the immune response, but also in haematopoiesis and the central nervous system. Deregulated production of IL-6 has been found in chronic inflammatory autoimmune diseases, such as rheumatoid arthritis (RA), systemic onset juvenile idiopathic arthritis (soJIA), Crohn's disease (CD) and systemic lupus erythematosus (SLE). Furthermore, IL-6 activities can explain many symptoms of these diseases. More importantly, serum levels of IL-6 are correlated with disease activity. Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit IL-6-mediated signaling through these receptors. A decrease in C-reactive protein (CRP) was noted as early as week 2. Changes in pharmacodynamic parameters were observed (i.e., decreases in rheumatoid factor, erythrocyte sedimentation rate (ESR), serum amyloid A and increases in hemoglobin) with both doses, however the greatest improvements were observed with 8 mg per kg tocilizumab. Similar pharmacodynamic changes were also observed in active polyarticular juvenile idiopathic arthritis and active systemic juvenile idiopathic arthritis patients.

The half-life of tocilizumab is concentration-dependent. The concentration-dependent apparent half-life is up to 11 days for 4 mg/kg and up to 13 days for 8 mg/kg every 4 weeks in patients with RA at steady-state. The clearance of tocilizumab decreases with increasing dose. At the 8 mg/kg single dose in RA patients, mean clearance was 0.29 ± 0.10 mL/hr/kg. The total clearance of tocilizumab is concentration-dependent and is the sum of the linear clearance and the nonlinear clearance. At low concentrations, concentration-dependent nonlinear clearance is dominant. At high concentrations, linear clearance dominates. The estimated linear clearances for RA patients is 12.5 mL/h.

At Month 3 after the Day1 of treatment, if TA is still active according to the NIH criteria, experimental medication in arm B will be stopped and patient will be switched to experimental medication in arm A. For the intention treatment analysis this case will considered as a failure of treatment.

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

Immunosuppressants agents (methotrexate, azathioprine, mercaptopurine or mycophenolate mofetil) should be maintained without any dose change during the study follow-up as long as the disease is inactive.

Patients may receive oral prednisone (or the prednisolone) at 1 mg/kg/day (up to 60 mg/day) before the inclusion visit.

A diet low in fat, salt and rapidly-absorbed sugars will be recommended for all participants.

At Day1 of treatment, patients receive experimental treatment allocated by randomization. The following standardized schedule of prednisone (or the prednisolone) dose-tapering will apply to both groups as long as the disease is inactive:

- Week 1 : 0.7mg/kg/day
- Week 2 : 0.5mg/kg/day
- Week 3 & 4 : 0.4mg/kg/day
- Week 5 to 8 : 0.3mg/kg/day
- Week 9 to 12 : 0.2mg/kg/day
- Week ≥13 : $\leq$ 0.1mg/kg/day

Schedule of Prednisone (or the prednisolone) Dose-Tapering according to body weight at the inclusion & randomization visit

Week	prednisone (or the prednisolone)	40.0–44.9 kg	45.0–49.9 kg	50.0–54.9 kg	55.0–59.9 kg	≥ 60.0 kg
< 1	1	40	45	50	55	60
1	0.7	28	31.5	35	38.5	42
2	0.5	20	22.5	25	27.5	30
3	0.4	16	18	20	22	24
4	0.4	16	18	20	22	24
5	0.3	12	13.5	15	16.5	18
6	0.3	12	13.5	15	16.5	18
7	0.3	12	13.5	15	16.5	18
8	0.3	12	13.5	15	16.5	18
9	0.2	8	9	10	11	12
10	0.2	8	9	10	11	12
11	0.2	8	9	10	11	12
12	0.2	8	9	10	11	12
≥13	≤ 0.1	≤ 4	≤ 4.5	≤ 5	≤ 5.5	≤ 6

Once tapering has been started, prednisone (or the prednisolone) will be reduced in a standardized fashion in order to reach prednisone (or the prednisolone) ≤ 0.1 by week 13.

In case of Latent TB infection treatment with the isoniazid and rifampin protocol, in order to compensate the increased metabolism of prednisone (or the prednisolone) for patients on rifampin, prednisone-dose (or the prednisolone-dose) should be increased by 30% during the treatment with rifampin and until 4 weeks after rifampin cessation. Nevertheless, standardized schedule of prednisone (or the prednisolone) dose tapering should be maintained.(Buffington *et al*, 1976; Barman *et al*, 2016; Baciewicz & Self, 1984).

As some subjects enrolled in this study may have been on longstanting glucocorticoid therapy, it is possible that they may develop adrenal insufficiency. In instances where the investigators feels that there is compelling clinical evidence to support adrenal insufficiency, they will be permitted to receive prednisone(or the prednisolone) at which the symptoms and/or signs of insufficiency are absent (usually between 5 and 10 mg/day). While such doses will be captured on the data collections sheets, this will be differentiated from prednisone (or the prednisolone) being used in the treatment of Takayasu arteritis and will not be considered a protocol deviation or an off-study criteria and will not be counted as a treatment failure.

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

7.3.1 Authorised prophylactic treatments

To reduce the adverse effects associated with the use of methotrexate, the following supportive treatment will be administered routinely: folic acid 5 to 15 mg once a week to be taken 48 hours after taking methotrexate, or folinic acid 5mg once a day, which decreases the side effects of methotrexate.

Prophylaxis against prednisone(or the prednisolone) -induced osteoporosis will be recommended in all participants. This cannot be standardized across all subjects as the choice of bone protection regimen must be influenced by individual subject factors that include age, pre-menopausal status for women, pre-existing osteoporosis, and medication contraindications. Following drugs will therefore be permitted:

- oral supplementation of calcium
- oral supplementation of colecalciferol, calcifediol, alfacalcidol, calcitriol
- oral or intravenous bisphosphonate medication (e.g. risedronic acid, alendronic acid, zoledronic acid, ibandronic acid)
- sub-cutaneous injection of recombinant parathyroid hormone (e.g teriparatide)
- sub-cutanenous injection of human monoclonal antibody binding to and inhibiting RANKL (e.g. denosumab)
- sub-cutaneous injections of salmon calcitonin
- oral strontium ranelate medication
- oral selective estrogen receptor modulator (e.g. raloxifene) medication

To reduce the other adverse effects associated with the use of corticosteroids, the following treatment may be permitted:

- a potassium-sparing diuretic medication (e.g. amiloride)
- an oral potassium supplementation
- a sedative medication for the treatment of trouble sleeping
- a minor tranquilizer medication resulting in sedative, anxiolytic properties (e.g. benzodiazepine, …)
- a proton pump inhibitor

In case of supply difficulties with Prednisone, the equivalent use of Prednisolone will be possible at the same posology.

7.3.2 Authorised concomitant treatments

Aspirin 75 to 300 mg per day may be prescribed for its platelet-aggregation inhibiting action, although there have as yet been no data on the utility of aspirin in Takayasu arteritis.

It is expected that many of the subjects in this study will be on multiple medications including antihypertensives and medications for glycemic control. Subjects will be allowed to continue these medications and make any changes in their dose, as it may be necessary due to the effect of glucocorticoids therapy or other reasons. In the absence of toxicity, subjects who are on statins at the time of the inclusion & randomization visit should continue these medications and be maintained at a consistent dosage throughout the trial.

Rifampicin (300mg/day) and isoniazid (150mg/day) (prophylactic tuberculosis treatment) will be prescribed for 3 months in patients with a positive interferon-gamma release assay (IGRA) (e.g., QuantiFERON®-TB Gold or T-spot TB® Test) at the selection visit.

All treatments taken by the patient during the trial but not prescribed in the Protocol will be considered "treatments other than study treatments". Whether allowed or not, they must be reported on the

appropriate page of the CRF. The risks and benefits of using such drugs must be carefully assessed for all included patients.

7.3.3 Prohibited treatments

Any other biologic immunomodulatory agent than infliximab and tocilizumab, (e.g., adalimumab, certolizumab pegol, golimumab, anakinra, etanercept, abatacept, ixekizumab, secukinumab, ustekinumab, alemtuzumab, rituximab…) is prohibited.

Treatment with any systemic alkylating agents (e.g., cyclophosphamide, chlorambucil) is prohibited.

Any live (attenuated) vaccine is prohibited during the overall study follow-up.

Any other investigational medications are prohibited.

Non steroidal anti-inflammatory drugs are prohibited

Any other glucocorticoids (oral or injected) than prednisone (or the prednisolone) prescribed according to the study protocol are prohibited

7.4 Accountability and destruction

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

7.5 Methods for monitoring compliance with the treatment

Infliximab and tocilizumab will be administered IV and will be easily monitored for compliance.

The administration will be reported in the nursing notebook.

7.6 Description of the traceability elements that accompany the experimental medications

Tocilizumab (Roactemra®, Roche) will be provided by sponsor and specifically labelled for the trial. The labelling will be performed by the DEC AGEPS.

Infliximab will be administered according to RTU so it will be provided by the local pharmacy of each centre.

Local pharmacy will be in charge of accountability and traceability of the experimental medications. Dispensation will be made upon receipt of a specific prescription form.

Tocilizumab (Roactemra®, Roche) will be sent by Clinical Trial Department AGEPS to each Hospital Pharmacy of study site. Treatment management on site will be the responsibility of the pharmacist of the healthcare establishment.

Treatment management will be verified on a regular basis by the study monitor. The center's pharmacist will receive the treatment deliveries.

A Drug Circuit specifying and detailing these points will be provided to the Hospital Pharmacy of each center during the opening visit.

8 ASSESSMENT OF EFFICACY

8.1 Description of parameters for complete remission

Inactive disease is defined according to the NIH criteria (Appendix 2), by the presence of at most one of the following criteria.

Criterion 1: if at least 1 of the following systemic characteristics, without any other cause identified

- erythema nodosum
- Fever > 38°C for more than a week
- polyarthralgia / arthritis
- episcleritis

Criterion 2: at least 1 of the following clinical signs have appeared since the previous visit

- carotidodynia, vascular claudication or pain along an arterial pathway
- constituted or transient ischemic stroke, acute coronary syndrome, angina
- abolition of a pulse
- vascular bruit
- anisotension

Criterion 3: at least 2 of the following biological signs

- C-reactive protein >10 mg/L
- fibrinogen >4 g/L
- Orosomucoïde > 1,2 g/L
- Haptoglobine > 2,5 g/L

Criterion 4: at least 1 of the following radiological signs

- arterial wall thickening AND wall contrast measurement in angio-MRI or angio-TDM
- appearance of new vascular lesions in angio-MRI or angio-TDM

8.2 Description of parameters for treatment failure

Changes in therapy may be required in case of treatment failure, which will be defined by the presence of at least one of the following:

- Death related to persistent disease activity
- Lack of remission at week 12 or inability to tolerate decreasing doses of corticosteroids at the week 12 visit because of persistent or recurrent disease. Such a patient will be considered as an early treatment failure (treatment resistant) will be analysed in the intention to treat analysis as first arm treatment. He will receive ongoing clinical care according to good medical practice and infusion of the alternative treatment arm.
- Relapse of disease activity according to the NIH criteria (Appendix 2) or severe disease flare, which requires increased doses of corticosteroids. These patients will be considered as treatment failure and included in the intention to treat analysis. They will receive ongoing clinical care according to good medical practice and infusion of the alternative treatment arm.

9 SPECIFIC STUDY COMMITTEES

9.1 Endpoint Adjudication Committee

This committee will have the role of validating under blind conditions the following assignments: complete remission, treatment failure and relapse of the disease. It will consist of persons not necessarily external to the Study: Clinicians specializing in the pathology under consideration: Dr D. Saadoun and Prof B Wechsler (Pitié-Salpétrière Hospital). Radiologist: Prof P Cluzel and Dr A Bertrand (Pitié-Salpétrière Hospital). It will meet every month for the duration of the study.

9.2 Scientific committee

This committee will consist of the Coordinating Investigator (Dr Tristan Mirault, CHU HEGP), a representative of the associated centers (Pr David Saadoun, CHU Pitié-Salpétrière), and a representative of the sponsor (Dr Mathieu Resche Rigon, Hôpital Saint Louis, Clinical Research Unit). The management committee will meet regularly to assess study recruitment, to provide scientific answers to questions from investigators, and to consider operational aspects of the trial and the recommendations of the committee for the evaluation of adverse events. It will be able to remove the blind if requested by an investigator who considers this necessary.

9.3 Independent Validation Committee

This committee will have the role of validating under blind conditions the following assignments: complete remission, treatment failure and relapse of the disease. It will consist of persons external to the study: Clinicians specializing in the pathology under consideration: Prof J Emmerich (Paris

Descartes university, Hôtel Dieu Hospital) and Prof P Cacoub (Pitié-Salpétrière Hospital). Radiologist: Dr A Azarine (HEGP Hospital) and Dr A Bertrand (Pitié-Salpétrière Hospital). It will meet every month for the duration of the study.

10 SAFETY ASSESSMENT - RISKS AND RESTRICTIONS ADDED BY THE STUDY

10.1 Safety endpoints [include if necessary]

10.2 Anticipated methods and timetable for measuring, collecting and analysing the safety endpoints [include if necessary]

10.3 Recording and reporting adverse events

10.3.1 Definitions

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

- Adverse event

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

- Adverse drug reaction

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

- Serious adverse event (SAE)

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

- Unexpected adverse reaction

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

According to the notice to sponsors of clinical trials for medications (ANSM):

- New safety issue

Any new information regarding safety:

- that could significantly alter the assessment of the benefit-risk ratio for the experimental medication, or for the trial

- or which could lead to the possibility of altering the administration of the experimental medication or altering the conduct of the trial

- Examples:

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

b) suspected unexpected serious adverse reactions (SUSAR) occurring in patients who have finished the trial and about whom the sponsor is notified by the investigator, who also provides any follow-up reports

c) any new fact relating to the conduct of the clinical trial or the development of the experimental medication, if the new fact is likely to affect participant safety

Examples:

- a serious adverse event likely to be related to the investigations and to the trial's diagnostic procedures and which could modify the conduct of this trial

- a significant risk for the trial participants such as ineffectiveness of the experimental medication used in the trial in treating a life-threatening illness

- significant safety results from a recently completed study carried out on animals (such as a carcinogenicity study)

- the premature termination, or temporary interruption, of a trial conducted with the same experimental medication in another country, for safety reasons

- an unexpected serious adverse reaction associated with a non-experimental medication required for carrying out the trial, (e.g., challenge agents, rescue treatment)

d) recommendations from the data safety monitoring board (DSMB), if applicable, if they are relevant to the safety of the participants

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

10.3.2 The role of investigator

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

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 (CRF or 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:

The investigator must assess the **causal relationship** between the serious adverse events and the investigational medicinal product(s) or the study procedure(s).

The method used by the investigator is based on the WHO Uppsala Monitoring Centre method and uses 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).

Table N°X (to adapt): WHO-UMC causality categories (extract)

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

** Or study procedures

10.3.3 Serious adverse events that require the investigator to immediately notify 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 section 9.2.1.1) and, if applicable, in the investigator's brochure as not requiring a notification without delay.

Infliximab and tocilizumab are medicines under additional monitoring. This means that both drugs are being monitored even more intensively than other medicines.

A serious adverse event is any untoward medical occurrence that result in:

- Death
- Life threatening situation
- Any unexpected adverse event requiring hospitalization hospitalization
- Any persistent or significant disability or incapacity
- congenital anomaly/birth defect

10.4 Specific features of the protocol

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

- *Adverse events judged as "medically significant"*

- Myocardial infarction or acute coronary syndrome
- Stroke
- Infections including all opportunistic infections and non-serious infections as defined by those treated with IV anti-infectives with grade ≥3
- Malignancy
- Demyelinating disorders
- Hepatic events with grade > or= 3 or with clinical symptomatology
- Serious hypersensitivity reaction and anaphylaxis with grade >or = 3
- Gastrointestinal perforation and related events
- Bleeding / haemorrhagic event

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 section 10.3.3).

- *In utero* exposure

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

Notification is required if the exposure involves:

- the mother,

- the father if the experimental medication is genotoxic.

The events are reported using a special form, appended to the protocol.

- *Exposure while breastfeeding*

Exposure while breastfeeding occurs if an infant or child could have been exposed to a medication *via* the breast milk of a mother being treated with an experimental medication.

Even if such exposure is not associated with an adverse event, the investigator must always notify the sponsor about exposure while breastfeeding as soon as the investigator becomes aware.

10.4.2 Serious adverse events that do not require the investigator to immediately notify the sponsor:

These serious adverse events are simply recorded in the case report form. A CRF extraction of these serious adverse events will be performed every year on the occasion of redaction of annual safety

report, this extraction is to be sent to the sponsor's vigilance department by email (expertisecsi.drc@aphp.fr)

- *Normal and natural course of the condition*:

- Serious Adverse Events related to Takayasu arteritis
  - Aortic valve insufficiency
  - Loss of vision due to retinal involvement of Takayasu arteritis
  - Pulmonary artery involvement due to Takayasu arteritis
- scheduled inpatient hospitalisation for monitoring the condition under investigation [with no deterioration in the subject's medical condition compared to baseline]
- inpatient hospitalisation for routine treatment or monitoring the condition under investigation, not associated with a deterioration in the subject's medical condition
- emergency inpatient hospitalisation upon enrollment or prolongation of hospitalisation upon enrollment for monitoring the condition under investigation
- worsening of the condition under investigation

- *Special circumstances*
- Hospitalization for a disease other than Takayasu arteritis pre-existing to study enrollment
- Hospitalization planned for surgery or medical treatment before study enrollment
- Hospitalization for social purpose
- Emergency room visit with no hospital admission

- *Serious Adverse Events related to investigational medicinal products:*
  -hepatic toxicity < grade 3 and without clinical symptomatology
  - nausea, vomiting, constipation, diarrhea, headache, infection < grade 3 and without complications
  - allegic and anaphylactic reactions < grade 3
  -Aplasia and febrile aplasia, neutropenia, leucopenia, thrombopenia and anemia < grade 4 without infectious complications

Serious Adverse Events related to methotrexate, mycophenolate mofetil, azathioprine, mercaptopurine, and prednisone (or the prednisolone)*: all adverse events listed in the SmPC of each specialty ® exept those leading to death or life threatening.* For more details refer to the SmPC of Cortancyl®, Prednisone Arrow®, Prednisone Biogaran®, Prednisone Cristers®, Prednisone EG®, Prednisone Mylan®, Prednisone Sandoz®, Prednisone Zentiva® or Prednisolone (Solupred®); Novatrex®, Methotrexate Belon®, Imeth®, Metoject® or Nordimet®; Azathioprine EG®, Azathioprine Mylan®, Azathioprine Teva® or Imurel®; Purinéthol®; Cellcept®, Mycophénolate mofétil Biogaran®, Mycophénolate mofétil EG®, Mycophénolate mofétil Mylan®, Mycophénolate mofétil Sandoz® or Mycophénolate mofétil Teva®

- *Serious Adverse Events related to angioCT or angioMRI:*

Immediate hypersensitivity reaction, allergic shock< grade 4, renal insufficiency< grade 4,

-claustrophobia

-panic attack

-vasovagal attack< grade 4

-anxiety, fear, distress

- *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

10.5 Period for notifying the sponsor

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 begins treatment with the investigational medicinal products.
- throughout the whole follow-up period intended by the trial (12 months)
- until 6 months after the end of the subject's treatment with the investigational medicinal products.
- with no time limit, if the sae is likely to be due to the investigational medicinal products or to the study procedures (for example, serious reactions that could appear long after exposure to the medication, such as cancers or congenital abnormalities)

10.6 Procedures and deadlines for notifying the sponsor

Notification of a SAE must initially be provided in a written report using the special form for reporting SAE. The report must be signed by the investigator.

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

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

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

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

The initial report, the SAE follow-up reports, and all other documents must be sent to the sponsor by e-mail (eig-vigilance.drc@aphp.fr) to the sponsor's safety department. It is possible to send the SAE to the Safety department by fax to the sponsor's safety department, fax No. +33 (0)1 44 84 17 99 only in case of unsuccessful attempt to send the SAE by e-mail and in order to avoid duplicates.

The investigator must comply with all requests from the sponsor for additional information.

For all questions relating to the notification of an adverse event, the Vigilance Division of the DRCI can be contacted via email: r vigilance.drc@aphp.fr

In utero exposure

The investigator completes the "Pregnancy notification form", and sends it by email to the Vigilance Division at eig-vigilance.drc@aphp.fr.

The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy is terminated, and must notify the sponsor of the outcome of the pregnancy, using this form.

If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, pregnancy termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAE.

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

The initial pregnancy notification, the SAE follow-up reports and all other documents must be sent to the sponsor via email only to the Vigilance Division - of the DRCI, email: eig-vigilance.drc@aphp.fr.

10.7 The role of sponsor

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

10.7.1 Analysis and declaration of serious adverse events

The sponsor assesses:

- the seriousness of all adverse events reported

  the causal relationship of these events with each experimental medication and/or specific medical procedures/exams added by the study and with other possible treatments
- the expected or unexpected nature of these 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 of Flixabi® and Roactemra®.

The most serious Adverse Drug Reactions of infliximab are:

- Hepatitis B virus reactivation
- Cardiac heart failure
- Serious infections (including sepsis, opportunistic infections and tuberculosis)
- Serum sickness (delayed hypersensitivity reactions)
- Haematologic reactions
- Systemic lupus erythematosus/lupu-like syndrome
- Demyelinating disorders
- Hepatobiliary events
- Lymphoma
- Hepatosplenic T-Cell Lymphoma
- Leukaemia
- Merkel cell carcinoma
- Melanoma
- Sarcoidosis/sarcoid-like reaction

The most serious Adverse Drug Reactions of tocilizumab are:

- Serious infections
- Complications of diverticulitis
- Serious hypersensitivity reaction

- For serious adverse events likely to be related to the the study procedures are:
  - Serious Adverse Drug Reactions <u>of corticosteroids:</u>

Refer to the SmPC of Cortancyl®, Prednisone Arrow®, Prednisone Biogaran®, Prednisone Cristers®, Prednisone EG®, Prednisone Mylan®, Prednisone Sandoz® or Prednisone Zentiva® or to the SmPC of Prednisolone.

Glucocorticoids have been used therapeutically in humans since 1949 and their side effects are well recognized. The main toxicities of prednisone (or the prednisolone) include infections, hyperglycemia, hypertension, cataracts, osteoporosis, avascular necrosis, gastrointestinal irritation, mood disturbances (including psychosis), bruising, skin changes including acne and striae, increase in appetite and weight, and redistribution of fat. Prednisone (or the prednisolone) is not known to have teratogenic effects on the developing fetus and there has been no evidence to date of an effect on fertility. However, prednisone (or the prednisolone) can cause problems during pregnancy for both the mother (risks of weight gain, gestational diabetes, and infection) and the developing fetus as a result of the maternal problems.

These are related to the cumulative dose administered, i.e. the amount taken from the onset of the disease. See the Adult adverse event severity rating scale.

- Weight gain. It is logical to suggest a diet low in fat, salt and rapidly-absorbed sugars
- Abnormal behavior such as nervousness, irritability, tremors, insomnia, and bulimia, at high doses
- Cushing's syndrome with moon facies, linked to a change in fat distribution observed at high doses
- Hypertension and leg edema. These can be reduced by a low-salt diet
- Muscle wasting and cramping. These can be reduced by a diet rich in potassium (bananas, dried fruit...) and supplementary potassium and protein, as well as by regular muscular activity
- Small vessel and capillary fragility. Ecchymoses and hematomata are more common and can occur after minimal impact
- The skin may also be affected by acne and delayed healing
- Osteoporosis can also occur after prolonged treatment. Supplementation with calcium and vitamin D associated with bisphosphonates reduces the risk of fracture
- Steroids can induce the onset of diabetes

- Serious Adverse Drug Reactions methotrexate, mycophenolate mofetil, azathioprine, mercaptopurine: refer to the SmPC of ®Novatrex®, Methotrexate Belon®, Imeth®, Metoject® or Nordimet®; Azathioprine EG®, Azathioprine Mylan®, Azathioprine Teva® or Imurel®; Purinéthol®; Cellcept®, Mycophénolate mofétil Biogaran®, Mycophénolate mofétil EG®, Mycophénolate mofétil Mylan®, Mycophénolate mofétil Sandoz® or Mycophénolate mofétil Teva®

- Adverse events related to corticosteroids tapering *and which are expected are*:

Takayasu Arteritis (TA) relapses or progression, exacerbation of TA symptoms.

- *Adverse events related to angioCT or angioMRIwhich are expected are:*

Immediate hypersentivity reaction, allergic shock, renal insufficiency,-claustrophobia, panic attack, vasovagal attack, anxiety, fear, distress

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

All suspected unexpected serious adverse reactions (SUSAR) are declared by the sponsor, within the legal time frame, to the Agence Française de Sécurité Sanitaire des Produits de Santé (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 in the Eudravigilance European database for adverse events due to medications, established by the European Medicines Agency (EMA).

The sponsor must notify all relevant investigators about any data that could adversely affect the safety of the study subjects.

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10.7.2 Analysis and declaration of other safety data

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

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

10.7.3 Annual safety report

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

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

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

10.7.4 Data Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) will be established by the sponsor. Its primary mission is to serve as a committee for monitoring safety data. It can have other missions, such as monitoring efficacy data (especially if the protocol includes interim analyses).

The DSMB is mentioned in Article L. 1123-7 of the French Public Health Code.

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

A DSMB will be convened for this biomedical study. The members of the DSMB will be named after the study starts. During the first meeting of the DSMB, a chairman will be appointed and the members will determine their operating methods and the meeting schedule.

The members of the DSMB are:

Nathanaël Lapidus, Unité de Santé Publique, Hôpital Saint Antoine, Paris

Raphaël Porcher, Centre d'épidémiologie clinique, Hôpital Hôtel-Dieu, Paris

Boris Oehmichen , Service de médecine vasculaire, Hôpital Saint-Joseph, Paris

Elie El-Rassy, Service d'oncologie, Institut Gustave Roussy, Villejuif

Thomas Quémeneur, Service de médecine interne et vasculaire, Centre Hospitalier de Valenciennes, Valenciennes

All missions as well as the precise operating methods of the DSMB will be described in the DSMB's charter for the study.

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

- to continue the study with no modifications
- to continue the study with a modification to the protocol and/or to the monitoring of subjects

- to temporarily halt inclusions
- to permanently terminate the study in light of:
  - safety data: serious adverse reactions
  - efficacy data: proven futility or efficacy.

The competent authority and the Ethic committee will be informed of the DSMB recommandations (reports) after each meeting.

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

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

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

Definition of the DSMB's missions:

Validation of the study methodology:

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

Validation of tolerance monitoring methods: nature of the evaluated parameters and frequency of the evaluations, consultation schedule

Validation of termination criteria:

criteria for terminating a subject's participation for tolerance reasons

criteria for the temporary or permanent termination of the study (leading to the establishment of certain recommendations ("stopping rules"))

Modification of the protocol and recommendations:

In light of the analysis of tolerance data for the study, the DSMB can, when applicable:

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

Definition of the DSMB's operating methods:

meeting types (open session, then closed sessions) and schedule

desired methods and format of SAE notification from the sponsor to the DSMB

The DSMB appoints its chairman at the first meeting.

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

11 DATA MANAGEMENT

11.1 Identification of data recorded directly in the CRFs which will be considered as source data

11.2 Right to access source data and documents

11.2.1 Access to data

In accordance with French Good Clinical Practices (GCPs):

- the sponsor is responsible for obtaining the permission of all parties involved in the study to guarantee direct access to all locations where the study 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 study 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)

11.2.2 Source documents

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

11.2.3 Data confidentiality

Those responsible for biomedical study 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 study, the study subjects and in particular the identity of the subjects and the results obtained.

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

During or after the biomedical study, the data collected about the study subjects and sent to the sponsor by the investigators (or any other specialised parties) will be made non-identifying.

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

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

11.3 Data processing and storage of documents and data

11.3.1 Data entry

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

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

11.3.3 This research is governed by the CNIL (French Data Protection Agency) “Reference Methodology for processing personal data used within the scope of health research” (amended MR-001). AP-HP, as sponsor of the research, has signed a declaration of compliance with this “Reference Methodology” Archiving

Specific documents for biomedical study 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 study.

This indexed archival includes, in particular:

- A sealed envelope containing the original copies of all information sheets and consent forms signed for all individuals at the centre that participated in the study for the investigator
- A copy of all the information notes and consent forms signed for all subjects at the centre that participated in the study for the sponsor
- "study" binders for the Investigator and the sponsor, including:
  - the successive versions of the protocol (identified by the version no. and date), and the appendices
  - the ANSM authorisations and CPP favourable opinions
  - letters of correspondence
  - the inclusion list or register
  - the appendices specific to the study
  - the final study report
- The data collection documents

11.3.4 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.

12 STATISTICAL ASPECTS

12.1 Description of statistical methods to be used including the timetable for the planned interim analyses

Characteritics at in clusion will be described within each arm as medians (interquartile ranges) for continuous variables and proportions for categorical variables.

- Primary criterion: Proportion at 6 months post-treatment of patients with prednisone (or the prednisolone) ≤ 0.1mg/kg per day and sustained inactive disease from M3 to M6.

This open randomized clinical trial is based on a Simon's two-stage design (Simon, 1989) that will be used separately, in both arms. The randomization and thus allocation concealment between both arms will insure the absence of selection bias in allocating the experimental treatments to the patients, with no between-arm comparison test. Only estimates of difference in the end points between treatment arms will be provided.

All the patients randomized in the trial will be analysed in the arm to which he (she) has been allocated to, so-called intention to treat analysis.

- Secondary criteria

All the secondary criteria will be estimated within each arm and described either by proportions for categorical variables and means for continuous variable. 95% Confidences intervals will be given.

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

For each arm, the null hypothesis (response rate 0.40) will be tested against a one-sided alternative (response rate 0.70) with 0.0248 type I error rate and power 0.8061. The first stage includes 10 patients. If 5 or fewer responses are observed in these patients, the arm is stopped. Otherwise, 15 additional patients are accrued. The null hypothesis will be rejected if 14 or more responses are observed in the 25 patients.

12.2 Specify if subjects who leave the study prematurely will be replaced and in what proportion.

All patient withdrawls will be considered as treatment failures. Lost of follow-up patients will be considered as treatment failure. A sensitivity analysis will be performed considering the reason of withdrawal or lost of follow-up: if the reason of the withdrawl or lost of follow-up is not link to the treatment multiple imputation aprraoch will be considered to impute the missing outcomes.

12.3 Statistical criteria for termination of the study.

The first stage includes 10 patients in each arm. If 5 or fewer responses are observed in these patients, the arm is stopped. Otherwise, 15 additional patients are accrued.

12.4 Method for taking into account missing, unused or invalid data

All the efforst will be done to avoid missing data in the outcomes. All causes of study dropouts will consider the patients as failures.

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

All modifications of the initial plan will be submitted.

12.6 Selection of populations

All the patients randomized in the trial will be analysed in the arm to which he(she) has been allocated to. This is the main principle of intent-to-treat analysis to avoid treatment selection biases in the estimation of treatment effect.

13 QUALITY CONTROL AND ASSURANCE

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

13.1 General organisation

The sponsor must be responsible for the safety and respect of those subjects who have agreed to participate in the study. The sponsor must implement a quality assurance system to best monitor the conduct of the study 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 study locations, after having carried out initial visits.

The objectives of monitoring the study, as defined in the French Good Clinical Practices (Décision du 24 novembre 2006 fixant les règles de bonnes pratiques cliniques pour les recherches biomédicales portant sur des médicaments à usage humain, section 5.18.1), are to verify that:

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

13.1.1 Strategy for opening the centres

The strategy for opening the centres established for this study is determined using the appropriate monitoring plan.

13.1.2 Level of centre monitoring

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

13.2 Quality control

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

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 study 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

13.3 Case Report Form

<u>eCRF</u>

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

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

When the investigators complete the case report via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data

entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. Thus, the investigator must validate any changes to the values in the case report form. These modifications will be subject to an audit trail. A justification can be added when applicable, as a comment. A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the study. The investigator must archive a copy of the authenticated document that was delivered to the sponsor.

13.4 Management of non-compliances

Any events that occur as a result of non-compliance, by the investigator or any other individual involved in conducting the study, with the protocol, with the standard operating procedures, with the good clinical practices or with the legislative and regulatory provisions in force must be noted in a declaration of non-compliance addressed to the sponsor.

As a first step, major or critical non-compliances will be reviewed and processed by the DRCI's medical coordinator in order to implement the necessary corrective or preventive actions.

Next, the non-compliances will be sent to the Quality - Risk Management Division of the DRCI for verification and analysis. These verifications could result in the investigator in charge of the study location in question being asked for information or could lead to compliance or audit visits.

13.5 Audits/inspections

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

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

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

The audit may be applicable to all stages of the study, 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 study.

13.6 Primary investigator's declaration of responsibility

Before starting the study, 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 study 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 DRCI document) which will be sent to the sponsor's representative.

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

14 ETHICAL AND LEGAL CONSIDERATIONS

14.1 Methods for informing and obtaining consent from research participants

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

The subject will be granted a reflection period of 2 weeks between the time when the subject receives the information and the time when he or she signs the consent form.

The free and informed consent, in writing, of the subject is obtained by the investigator, or by a doctor representing the investigator, before the inclusion of the subject in the study**.**

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

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

Special case: If it is physically impossible for the subject being recruited to consent in writing, his or her consent will be confirmed by a third party. This third party must have no association with the investigator or with the sponsor.

At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

Information of the holders of parental authority and their consent in the case of a study protocol involving a minor

In accordance with Article L.1122-2 of the Code de la santé publique (French Public Health Code), when an interventional study involving human participants is conducted on a non-emancipated minor, consent must be given by the holders of parental authority.

A reflection period of of 2 weeks is given to those with parental authority between the time when they are informed and when they sign the consent form.

The freely-given written informed consent of the holders of parental authority is obtained by the investigator, or by a physician representing the investigator, before definitive inclusion of the minor in the study.

Information for minors participating in the research

Minors receive the information specified in Article L. 1122-1 of the *Code de la Santé Publique* (French Public Health Code), appropriate to their level of understanding, both from the investigator and from the holders of parental authority.

Minor’s personal endorsement is sought regarding their participation in the study involving human participants. In any cases, the investigator cannot override their refusal or the revocation of their acceptance.

One copy of the signed and dated consent form is given to the holders of parental authority. The principal investigator or a physician representing him/her will keep one copy.

At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

Information recorded in the minor’s medical file

The investigator will record the minor’s participation in the clinical study in the minor’s medical file, along with the procedure for informing and obtaining consent from the holders of parental authority as well as the procedure for informing the minor and a record of the minor’s non-rejection to take part.

Special circumstances: the minor reaches the age of majority during his or her participation in the study

Minors who reach the age of majority during their participation in the study will be given new, relevant information at that time. After they have been given this information, they will be asked to confirm their consent.

Subjects whose consent is sought	Who informs the subject and collects their consent?	When is the subject informed?	When is the subject's consent collected?
The patient and the holders of parental authority if applicable	Patient's study doctors inform their patients and the holders of parental authority if applicable and collect the consent form	At inclusion visit	At inclusion visit

14.2 Legal obligations

14.2.1 The sponsor's role

Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this study and by delegation, the Delegation of Clinical Research and Innovation (DRCI) carries out the study'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 study at any time for medical or administrative reasons. In this case, notification will be sent to the investigator

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

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

14.2.3 Request for authorisation to ANSM

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

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

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

14.4 Modifications to the trial

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 study, 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 study or if adverse reactions occur.

14.5 Final study report

The final study 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 study, meaning the end of the participation of the last study participant.

15 FUNDING AND INSURANCE

15.1 Funding source

Dr Tristan Mirault, the Principal Investigator is competing for the French PHRC 2016 funding plan.

15.2 Insurance

For the duration of the study, 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 study. The sponsor will also provide full compensation for all harmful consequences of the study for the study subjects and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any agent. The act of a third party or the voluntary withdrawal of the person who initially consented to participate in the study 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 study period, covering its own civil liability and that of any agent (doctor or study staff), in accordance with Article L.1121-10 of the French Public Health Code.

16 PUBLICATION RULES

16.1 Mention of the affiliation of AP-HP for projects sponsored or managed by AP-HP

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

"The sponsor was Assistance Publique – Hôpitaux de Paris (Délégation à la Recherche Clinique et à l'Innovation, Delegation of Clinical Research and Innovation)"

16.3 Mention of the financier in the acknowledgements of the text

If the money for the INTOReTAK study is coming from the French PHRC 2016 funding plan, acknowledgements will mention: "The study was funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC 2016 (Ministère de la Santé)"

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18 LIST OF ADDENDA

18.1 Appendix 1. Diagnostic criteria for Takayasu arteritis

Classification criteria proposed by the ACR in 1990. 3 simultaneous or successive criteria are necessary for the diagnosis of Takayasu's disease (sensitivity 90.5%, specificity 97.8%):

1. Age at disease onset ≤ 40 years: development of symptoms or findings related to Takayasu arteritis at age ≤ 40 years

2. Claudication of extremities: development and worsening of fatigue and discomfort in muscles of 1 or more extremity while in use, especially the upper extremities

3. Decreased brachial artery pulse: decreased pulsation of 1 or both brachial arteries

4. BP difference >10 mm Hg: difference of >10 mm Hg in systolic blood pressure between arms

5. Bruit over subclavian arteries or aorta: bruit audible on auscultation over 1 or both subclavian arteries or abdominal aorta

6. Arteriogram abnormality: arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia, or similar causes; changes usually focal or segmental

Source: Arend WP, BA Michel, DA Bloch, GG Hunder, LH Calabrese, SM Edworthy, et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum 1990; 33: 1129-34.

Ishikawa diagnostic criteria for Takayasu arteritis modified by Sharma (1995)

Presence of two major or one major and two minor criteria or four minor criteria suggests a high probability of Takayasu arteritis

Three major criteria:

1. **Left Mid subclavian artery lesion**: The most severe stenosis or occlusion present in the mid portion from the point 1 cm proximal to the vertebral artery orifice up to that 3 cm distal to the orifice determined by angiography

2. **Right Mid subclavian artery lesion**: The most severe stenosis or occlusion present in the mid portion from the right vertebral artery orifice up to that 3 cm distal to the orifice determined by angiography

3. **Characteristic signs and symptoms of at least one month duration**: these include limb claudication, pulselessness or pulse differences in limbs, an unobtainable or significant blood pressure difference (> 10 mmHg systolic blood pressure difference in limbs), fever, neck pain, transient amaurosis, blurred vision, syncope, dyspnea or palpitations

Ten minor criteria:

1. **High ESR**: unexplained persistent high ESR > 20 mm/h (Westergren) at diagnosis or presence of the evidence in patient's history

2. **Carotid artery tenderness**: unilateral or bilateral tenderness of common arteries on palpation. Neck muscle tenderness is unacceptable.

3. **Hypertension**: Persistent blood pressure > 140/90 mmHg brachial or > 160/90 mmHg popliteal

4. **Aortic regurgitation or Annuloaortic ectasia**: by auscultation or echocardiography or angiography

5. **Pulmonary artery lesion**: lobar or segmental arterial occlusion or equivalent determined by angiography or perfusion scintigraphy, or presence of stenosis, aneurysm, luminal irregularity or any combination in pulmonary trunk or in unilateral or bilateral pulmonary arteries determined by angiography.

6. **Left mid common carotid lesion**: presence of the most severe stenosis or occlusion in the mid portion of 5 cm in length from the point 2 cm distal to its orifice determined by angiography.

7. **Distal brachiocephalic trunk lesion**: presence of the most severe stenosis or occlusion in the distal third determined by angiography.

8. **Descending thoracic aorta lesion**: narrowing, dilation or aneurysm, luminal irregularity or any combination determined by angiography: tortuosity alone is unacceptable.

9. **Abdominal aorta lesion**: narrowing, dilation or aneurysm, luminal irregularity or aneurysm combination.

10 **Coronary artery lesion**: documented on angiography below the age of 30 years in the absence of risk factors like hyperlipidemia or diabetes mellitus

Source: Sharma BK, Iliskovic NS, Singal PK. Takayasu arteritis may be underdiagnosed in North America. Can J Cardiol 1995;11:311–316

18.2 Appendix 2. Disease activity criteria

Criteria of the National Institutes of Health (NIH) (1994)

The activity of Takayasu's disease will be evaluated according to the following criteria established by the NIH in 1994. Takayasu's disease is considered active if there is new onset or worsening of at least two of the following four criteria:

1. Systemic features, such as fever, musculoskeletal (no other cause identified)

2. Elevated erythrocyte sedimentation rate

3. Features of vascular ischemia or inflammation, such as claudication, diminished or absent pulse, bruit, pain (carotidodynia), asymmetric blood pressure in either upper or lower limbs (or both).

4. Typical angiographic features

Source: Kerr GS, CW Hallahan, J Giordano, RY Leavitt, AS Fauci, M Rottem, et al. Takayasu arteritis. Ann Intern Med 1994; 120: 919-29.

18.3 Appendix 3: Patient monitoring card

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CARTE PATIENT

Merci de garder cette carte avec vous en permanence

Nom :…… Prénom : ……..

Je participe à la recherche *titre abrégé : INTOReTAK / P160909*

***Evaluation de* l'infliximab ou du tocilizumab dans la maladie de Takayasu**

☐ ***Bras A :*** **Infliximab** ☐ ***Bras B :*** **Tocilizumab**

dont le promoteur est l'Assistance Publique – Hôpitaux de Paris

Date de début de ma participation : __ __ /__ __ /__ __ __ __

Je suis suivi(e) par le Dr……
A l'Hôpital ……..
☎……

18.4 Appendix 4: Temporary recommendations of use (RTU) protocol

RTU remicade_V3_ 11-2018.

18.5 Appendix 5: Serious Adverse Events report form (in appendix)

18.6 Appendix 6: Pregnancy notification form (in appendix)

18.7 Appendix 7: List of Investigators (in appendix)