"Randomized controlled multicenter study comparing efficacy and safety of adalimumab to that of mycophenolate mofetil in steroid dependent non-infectious uveitis"

FOCUS: treatment FOr Corticosteroid dependent UveitiS

CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE

Version N°1.0 dated 03/07/2023
Project Code: APHP211032 / EU CT number: **2023-505112-38-00**

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SIGNATURE page for a research PROTOCOL

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Title: **Randomized controlled multicenter study comparing efficacy and safety of adalimumab to that of mycophenolate mofetil in steroid dependent non-infectious uveitis.**

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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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1. SUMMARY

Full title	Randomized controlled multicenter study comparing efficacy and safety of adalimumab to that of Mycophenolate mofetil in steroid dependent non-infectious uveitis
Acronym/reference	**FOCUS /** APHP211032 / **EU no: 2023-505112-38-00**
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Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	**FOCUS**, is the first prospective randomized study comparing standard of care (mycophenolate mofetil) to adalimumab in recently active non infectiuous uveitis (NIU) with steroid dependency. There is no firm evidence or randomized trials that compared classical immunosuppressive compounds to biological agents; or identified the best treatment in this condition. The burden of NIU has been reduced with the use of immunosuppressive agents and biologics, raising the question of which of these compounds should be preferentially used in recently active NIU with steroid dependency.

Main objective and primary endpoint	**Primary Objective** The objective is to compare the efficacy of adalimumab (80mg at day 0, then 40mg/14 days from W1 to W35 subcutaneously) with that of standard of care (mycophenolate mofetil [2g/day orally] for 36 weeks) in recently active non-infectious intermediate, posterior uveitis, and pan-uveitis with steroid dependency. **Primary endpoint** The primary efficacy endpoint is the treatment failure rate at 36 weeks. Treatment failure is defined by any of the following in at least one eye: - new active, inflammatory chorioretinal or retinal vascular lesions; - worsening of best corrected visual acuity (BCVA) by>3 lines; - 2- step increase in anterior chamber cell grade and/or in vitreous haze relative to baseline - Noabsence of and with steroid discontinuation between week 13 and week 19 (as per protocol) and without any- aor any additional immunosuppressive drug or injectable steroids – Study treatment permanent discontinuation
Secondary objectives and endpoints	**Secondary Objectives:** Comparing adalimumab (80mg at day 0, then 40mg/14 days from W1 to W35 subcutaneously) to standard of care (mycophenolate mofetil [(2g/day orally)] for 36 weeks): - To evaluate the cumulative incidence of treatment failure up to W55 after inclusion - To evaluate the change in best corrected visual acuity (BCVA, logMAR) from baseline to week W55 ; - To evaluate the change in ocular inflammation in the anterior chamber and vitreous from baseline to week W55; - To evaluate the change in other signs including vessel leakage, from baseline to week W55; - To evaluate the presence of macular edema from baseline to week W55; - To evaluate the quality of life related to uveitis, from inclusion to W55; - To evaluate steroid sparing effect from baseline to W55; - To evaluate the number and time to relapse of uveitis; and the characteristics of uveitis at worsening from baseline to W55; - To evaluate the effect on underlying systemic disease when appropriate from baseline to W55; - To evaluate the safety of adalimumab and mycophenolate mofetil (up to W55; **Secondary Endpoints,** - Time to treatment failure up to W55; - logMAR BCVA in each eye, at W4, W8, W12, W16, W20, W24, W30, W36 and W55; - Anterior chamber cell grade in each at W4, W8, W12, W16, W20, W24, W30, W36 and W55; - Vitreous haze grade (SUN criteria) in each eye at W4, W8, W12, W16, W20, W24, W30, W36 and W55; - Central retinal thickness in each eye from baseline at W4, W8, W12, W16, W20, W24, W30, W36 and W55; - Proportion of patients with central macular thickness< 300 microns at W4, W8, W12, W16, W20, W24, W30, W36 and W55; - Time to optical coherence tomographic (OCT) evidence of macular

	edema in at least one eye, up to W55; - NEI Visual Functioning Questionaire-25 (VFQ-25) composite score, at W12, W24, and W36; - Measures of corticosteroid sparing (e.g., percent meeting targets [<0.1 mg/kg/day prednisone], mean change, mean dose at week 55, and cumulative dose); - Cumulative incidence of relapse and number of relapses up to W55; - Other clinical manifestations of underlying disease (depending on the underlying disease) will be evaluated up to W55 - Safety and tolerability of treatments as assessed by the frequency and severity of adverse events and treatment discontinuation from baseline to Week 55
Design of the study	This is a prospective phase III clinical trial, multicenter, open-label, two-arm randomized (1:1) clinical trial comparing the efficacy and safety of adalimumab and standard of care (mycophenolate mofetil) in subjects with recently active intermediate posterior uveitis or pan-uveitis despite steroid use [i.e oral prednisone > 7 mg/day (or if no prednisone is available use ~~oral corticosteroid~~ as a replacement for prednisone (equivalent prednisone dose))]. Oral corticosteroids should be at a stable dose at least 2 weeks prior to the first study drug administration on Day 0.
Category	*Cat 2*
Population of study participants	**Adult patients with recently active Non-infectious Uveitis (NIU) despite oral prednisone > 7 mg/day (or equivalent prednisone doseoral corticosteroid at equivalent dose, only if prednisone is out of stock in the market if no prednisone is available use oral corticosteroid as a replacement for prednisone (equivalent dose)~~or oral corticosteroid equivalent~~)** **Recently active disease**: defined by the presence of at least 1 of the following parameters in either eye within the 3 months prior to inclusion visit: - Active chorioretinal or retinal vascular lesion - Presence of macular edema by optical coherence. - ≥ 2+ anterior chamber cells (Standardization of Uveitis Nomenclature [SUN] criteria) ≥ 2+ vitreous haze (National Eye Institute [NEI]/SUN criteria);
Inclusion criteria	The eligibility criteria will be checked at the screening visit (which takes place four weeks maximum prior to inclusion visit) and at the inclusion/randomization visit. Adult patients meeting the following criteria may be included in the study: 1. Provide written, informed consent prior to the performance of any study-specific procedures 2. ≥18 years of age 3. Diagnosis of non-infectious intermediate, posterior-, or pan-uveitis in at least one eye fulfilling the International Study Group Classification Criteria (Standardization of Uveitis Nomenclature [SUN] criteria) of posterior, or pan- uveitis confirmed by documented medical history 4. Recent activity of NIU as defined by the presence of at least 1 of the following parameters in either eye within the 3 months prior to inclusion visit despite >7mg/day of oral prednisone: ▪ Active chorioretinal or retinal vascular lesion

- Presence of macular edema by optical coherence.
- ≥ 2+ anterior chamber cells (Standardization of Uveitis Nomenclature [SUN] criteria)
- ≥ 2+ vitreous haze (National Eye Institute [NEI]/SUN criteria)

5. Chest X-ray (postero-anterior and lateral) or CT-scanner results within 12 weeks prior to inclusion with no evidence of active Tuberculosis, active infection, or malignancy
6. A potential subject with a positive interferon-gamma release assay (IGRA) (e.g., QuantiFERON®-TB Gold or T-spot TB® Test) at inclusion is eligible if:
    a. Her/his chest X-ray does not show evidence suggestive of active TB disease
    b. And there are no clinical signs and symptoms of pulmonary and/or extra-pulmonary TB disease.
    c. And these subjects with a latent TB infection who have not already received a prophylactic TB treatment must agree in advance to complete such a treatment course.
7. For female subjects of child-bearing potential: a negative pregnancy test at inclusion
8. 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 and 3 months and 5 months after stopping therapy for MMF and adalimumab, respectively, unless sterility is confirmed. The simultaneous use of two complementary methods of contraception is preferable. Methods which may be considered as highly effective methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods (according to CTFG recommendations). Such methods include:

    <u>For Female subjects :</u>

    a. combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation 1:
        - oral
        - intravaginal
        - transdermal

    [b.] progestogen-only hormonal contraception associated with inhibition of ovulation ~~1~~:
        - oral
        - injectable
        - implantable

    b.[c.] intrauterine device (IUD)
    c.[d.] intrauterine hormone-releasing system (IUS)
    d.[e.] bilateral tubal occlusion
    e.[f.] vasectomised partner
    f.[g.] sexual abstinence (In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject).

    <u>For male subjects :</u>

    a. use of condoms
    b. vasectomy (with documentation of azoospermia)

	c. sexual abstinence 9. Affiliated to a social security system
Exclusion criteria	Subjects will not be included in the study if they meet any of the following criteria: 1. Infectious uveitis, masquerade syndromes (idiopathic uveitis is permitted) 2. Isolated anterior uveitis 3. Monocular patient 4. Active tuberculosis 5. Positive HIV serology or HCV HBs Ag test 6. History of malignancy within 5 years prior to Inclusion other than carcinoma in situ of the cervix, non-metastatic squamous or basal cell carcinoma of the skin. 7. History of severe allergic or anaphylactic reactions to monoclonal antibodies, mycophenolate mofetil, rifampicin, isoniazid or fluorescein 8. Infection requiring treatment with intravenous antibiotics within 3 weeks prior to inclusion 9. History of multiple sclerosis and/or demyelinating disorder 10. Laboratory values assessed during inclusion: • Hemoglobin < 8g/dL • WBC < 2.0 x 10^3/mm^3 • Platelet count < 80 x 10^3/mm^3 • Glomerular filtration rates (GFR) <30ml/min. • Transaminases > 3 times upper normal value 11. Use of the following systemic treatments during the specified periods: • Treatment with any systemic alkylating agents within 12 months prior to inclusion (e.g., cyclophosphamide, chlorambucil) • Any live (attenuated) vaccine within 4 weeks prior to inclusion. 12. Stage III and IV New York Heart Association (NYHA) cardiac insufficiency 13. Pregnancy or breastfeeding 14. Under legal protection 15. Participation in another interventional study involving human participants or in the exclusion period at the end of a previous study involving human participants, if applicable
Investigational medicinal product(s)	Eligible patients with recently active NIU will be randomized at 1:1 ratio between: **Arm 1:** Adalimumab (80mg at day 0, then 40mg/14 days from W1 to W35 subcutaneously) **Arm 2**: standard of care defined by Mycophenolate mofetil 2 g/day orally for 36 weeks The 2 treatment groups will receive the same corticosteroid regimen. All patients with NIU will receive oral prednisone ≥ 10 mg/day (or oral corticosteroid equivalent) with a maximum of 35 mg/day of prednisone (or ~~oral corticosteroid at~~ equivalent prednisone dose, only if prednisone is out of stock in the marketif ~~no prednisone is available use oral corticosteroid as a replacement for prednisone (equivalent dose)~~)equ~~ivalence.~~ A common prednisone-tapering programme will be applied to both groups with a decrease until discontinuation between week 13 and week 19, as long as the disease is inactive.
Comparator	**Arm 2:** Standard of care defined by Mycophenolate mofetil 2 g/day orally

treatment	for 36 weeks
Interventions added for the study	- Adalimumab (80mg at day 0, then 40mg/14 days from W1 to W35 subcutaneously) - Visit at week 4, 8, 16, 20 and 30 weeks - βHCG plasmatic or urine pregnancy test at inclusion, and urine pregnancy test at 4, 8, 12, 16, 20, 24, 30, 36 and 55 weeks, and monthly until 6 weeks after stopping Mycophenolate mofetil therapy, and until 5 months after stopping Adalimumab therapy, unless menopause or sterility is confirmed. - Fundoscopy, Optical Coherence Tomography (OCT) at 4, 8, 16, 20 and 30 weeks - Retinal angiography at 36 weeks - QOL questionnaires at D0, W12, W24 and 36 weeks
Expected benefits for the participants and for society	Refractory non-infectious uveitis is a serious ocular pathology, accounting for 10-15% of total blindness cases. Reliable clinical data are required for the treatment of uveitis and more particularly in the use of biotherapies. Corticosteroids and immunosuppressants have shown a sustained remission rate of 70% in severe refractory/relapsing uveitis. The incidence of blindness in UNI has been reduced in recent years with the use of biotherapies, raising the question of whether these therapies should be prescribed earlier in the management of patients with severe non-infectious uveitis. Compared to conventional immunosuppressants, biotherapies are fast acting and highly effective in corticosteroids sparing, thus limiting the risk of cataract and/or cortico-induced glaucoma. FOCUS is the first randomized trial comparing the efficacy and safety of adalimumab to standard of care (mycophenolate mofetil) in the maintenance treatment of corticosteroid-dependent UNI. This study will validate and optimize the treatment of hard-to-treat patients with uveitis. It may also confirm whether or not adalimumab is superior to mycophenolate mofetil in terms of efficacy. It will allow a direct comparison of the safety profiles of these treatments. It could significantly improve the management of patients with corticosteroid-dependent UNI and finally help in the selection of the best treatment to prevent the onset of blindness and side effects in these difficult to treat cases. The expected benefit is both individual, by reducing morbidity for patients with non-infectious uveitis, and collective, by reducing the costs of unemployment, disability and hospitalization caused by UNI.
Risks and burdens added by the study	Risks associated with the toxicities of the investigational drugs Risks associated with use of concomitant medication The risk level of the study : **Risk C**
Practical implementation	After the collection of their free and informed consent, eligible patients will be randomized into one of 2 groups at the randomization visit (D0) **Arm 1:** Adalimumab (80mg at day 0, then 40mg/14 days from W1 to W35 subcutaneously) **Arm 2:** Mycophenolate mofetil 2 g/day orally for 36 weeks All patients will receive the same corticosteroid regimen at inclusion. All patients will receive corticosteroids (10-35 mg/day) at inclusion. The following schedule of reduction of prednisone will apply to both groups with a decrease until discontinuation between week 13 and week 19 as long as the disease is inactive:

		Prednisone dose at study entry (Or equivalent prednisone dose, if prednisone is out of stock in the market) **Dose (mg/day)** / **35** / **30** / **25** / **20** / **15** / **12.5** / **10** 35 / Day 0 - Week 1 30 / 2 / Day 0 - Week 1 25 / 3 / 2 / Day 0 - Week 1 20 / 4 / 3 / 2 / Day 0 - Week 1 15 / 5 / 4 / 3 / 2 / Day 0 - Week 1 12.5 / 6 / 5 / 4 / 3 / 2 / Day 0 - Week 1 10 / 7 / 6 / 5 / 4 / 3 / 2 / Day 0 - Week 1 7.5 / 8 / 7 / 6 / 5 / 4 / 3 / 2 5 / 9 / 8 / 7 / 6 / 5 / 4 / 3 4 / 11 / 10 / 9 / 8 / 7 / 6 / 5 3 / 13 / 12 / 11 / 10 / 9 / 8 / 7 2 / 15 / 14 / 13 / 12 / 11 / 10 / 9 1 / 17 / 16 / 15 / 14 / 13 / 12 / 11 Discontinue / 19 / 18 / 17 / 16 / 15 / 14 / 13 Prednisone dose at study entry (Or equivalent prednisone dose, if prednisone is out of stock in the market) **Dose (mg/day)** / **35** / **30** / **25** / **20** / **15** / **12.5** / **10** 35 / Day 0 - Week 1 30 / 2 / Day 0 - Week 1 25 / 3 / 2 / Day 0 - Week 1 20 / 4 / 3 / 2 / Day 0 - Week 1 15 / 5 / 4 / 3 / 2 / Day 0 - Week 1 12.5 / 6 / 5 / 4 / 3 / 2 / Day 0 - Week 1 10 / 7 / 6 / 5 / 4 / 3 / 2 / Day 0 - Week 1 7.5 / 8 / 7 / 6 / 5 / 4 / 3 / 2 5 / 9 / 8 / 7 / 6 / 5 / 4 / 3 4 / 11 / 10 / 9 / 8 / 7 / 6 / 5 3 / 13 / 12 / 11 / 10 / 9 / 8 / 7 2 / 15 / 14 / 13 / 12 / 11 / 10 / 9 1 / 17 / 16 / 15 / 14 / 13 / 12 / 11 Discontinue / 19 / 18 / 17 / 16 / 15 / 14 / 13
Number of participants included	120 patients (60 in each arms)	
Number of centres	- Multicenter national study including 27 centers (26 recruitment centres)	
Duration of the study	Duration of inclusions: 30 months	

	Duration of participation of each patient: 13 months and 3 weeks (55 weeks) Total duration of the study: 44 months
Number of enrolments expected per site and per month	0.15 patient/month/center
Statistical analysis	This is a prospective, two-arm randomized, open-label, phase III trial comparing Adalimumab to Standard of care (mycophenolate mofetil) based on a binary primary endpoint (treatment failure at week 36 of treatment). Randomization will be stratified on ~~retinal vasculitis~~, ~~-~~presence or not of macular oedema~~, underlying disease~~ (idiopathic uveitis or underlying disease associated~~)~~ and steroid dose at inclusion (<20mg/d vs. ≥ 20mg/d). This trial will be conducted using a group sequential design with one interim analysis after 50% of primary observations have been completed, with efficacy and futility early stopping rules. Specifically, assuming a probability of treatment failure (primary endpoint) of 50% in the SoC control population versus 20% under the alternative hypothesis with adalimumab, a total number of 106 patients (53 per randomization arm) is required to ensure 90% power with a 2.5% one-sided type I error risk, accounting for one interim analysis after 50% of primary observations have been completed and using Lan & DeMets O'Brien & Fleming-type risk-spending functions to define efficacy and futility (non-binding) early stopping rules. Moreover, we plan to include a total of 120 patients (60 per randomization arm) to account for potential 10% of lost-to-follow-up.
Funding sources	PHRC 2020
Study will have a Data Safety Monitoring Board	Yes

2. SCIENTIFIC JUSTIFICATION FOR THE STUDY

1.1[2.1] Hypothesis for the study

This study will evaluate the **efficacy and safety of adalimumab and the immunosuppressant (mycophenolate mofetil) in subjects with non-infectious uveitis** with steroid dependency**.**

Uveitis is a term referring to inflammation affecting structures in the eye including the iris, ciliary body, and choroid. The inflammation may affect only one eye structure or multiple structures. In many cases, both eyes are involved and symptoms may include decreased vision, eye pain, ocular redness, tearing, photophobia (pain and/or sensitivity to light), elevated intraocular pressure, intraocular scarring, macular edema, and even vascular occlusion. The International Uveitis Study Group (IUSG) has classified uveitis into four major categories based on the anatomic location of the inflammation: anterior (iris and ciliary body), intermediate (peripheral retina and pars plana of the ciliary body), posterior (choroid and retina), and panuveitis. The IUSG anatomic classification scheme was endorsed by the First International Workshop on Standardization of Uveitis Nomenclature (SUN) held in 2004 in the US[1]. In 2008, the IUSG updated this classification system to include etiological criteria[2]. The updated classification includes three main categories of uveitis: infectious, non-infectious (including idiopathic/unknown etiology, as well as systemic autoimmune disorders), and masquerade syndromes (neoplastic, drug induced).

FOCUS is the first prospective randomized, head-to-head study, comparing Adalimumab to immunosuppressant (Mycophenolate mofetil) in non-infectious uveitis (NIU) with steroids dependency. There is no firm evidence or randomized controlled trials directly addressing the best biologic or immunosuppressive agent in NIU with steroids dependency to maintain remission. NIU can cause devastating visual loss and up to 20% of legal blindness.[3] The incidence of blindness in NIU has been dramatically reduced in the recent years with the use of efficient immunosuppressive treatments or biologics, raising the question of which treatments (immunosuppressants such as Mycophenolate mofetil or biologics such as adalimumab) are the most efficient in steroid dependent active NIU.

Despite a strong rationale, the place of each compound is not yet well defined in the strategy to maintain remission in uveitis, which guarantees the innovative nature of this study. In this study we will be able to evaluate and compare the efficacy and safety of these different drugs (immunosuppressants and biologic agents) in the treatment of non-infectious intermediate, posterior, or pan- uveitis with steroid dependency.

1.2[2.2] Description of knowledge relating to the condition involved

1.2.1[2.2.1] Morbidity of NIU

Inflammation localized to the posterior segment of the eye (behind the lens) is classified as intermediate or posterior, as described above. Non-infectious uveitis affecting the posterior segment of the eye is not a life-threatening disease but is a chronic debilitating condition, with a high risk of permanent vision loss. Uveitis and associated complications are the fifth most common cause of vision loss in the developed world, accounting for about 10% of all cases of total blindness[3].

Behçet's disease uveitis can be considered as a very severe form at one end of a large spectrum of ocular inflammatory events pooled under the term chronic non-infectious uveitis. The inflammation in non-infectious uveitis other than Behçet's disease may affect only one structure or multiple structures. In many cases, both eyes are involved and symptoms may

include decreased vision, eye pain, ocular redness, tearing, strabismus, and/or leukocorea. While the cause of the inflammation can sometimes be associated with underlying systemic diseases or reactions to systemic medications, the cause of uveitis is unknown in about 35% to 57% of all cases.[4]

Patients with uveitis reported markedly reduced general and vision-related quality of life compared with normal subjects[5] and the vision-related quality of life is worse in non-infectious uveitis patients than in infectious uveitis patients due to the often chronic, relapsing course of non-infectious disease[6].

1.2.2[2.2.2] Disease Prevalence

The US National Organization for Rare Diseases (NORD) lists posterior uveitis in its rare disease database. Two prevalence estimates for general uveitis (anterior, intermediate, and posterior) in the US are reported. The highest estimated prevalence of the two is 115/100,000[7], followed by a reported prevalence of 69/100,000[8]. Callanan estimated that 15 to 22 percent of the cases of general uveitis involve posterior uveitis (Callanan, 2011), and the American Academy of Ophthalmology Website estimates that at least 13% of general uveitis cases involve infectious uveitis[9]. Calculations taking account of these sources yield an estimated US range of 14/100,000 to 22/100,000 for the prevalence of documented non-infectious intermediate, posterior, and pan- uveitis, which falls within the reported prevalence range of 10 to 50/100,000 from the EU's Orphanet. Orphanet has classified non-infectious uveitis as an orphan disease, number ORPHA98715.

1.2.3[2.2.3] Treatment Options

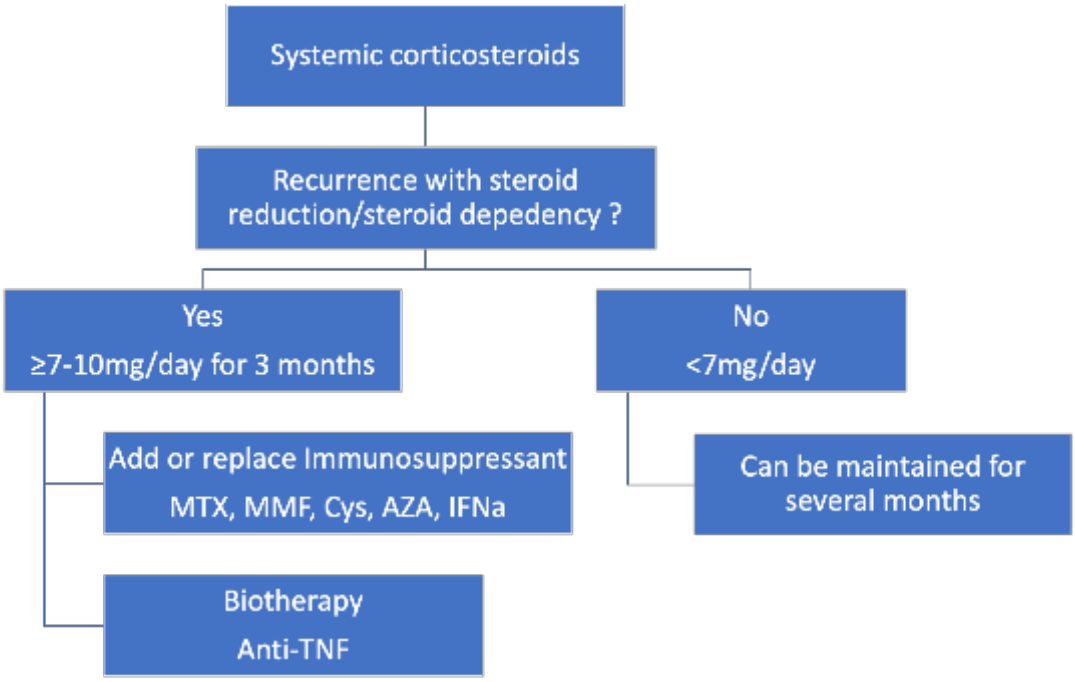
Uveitis treatment aims to quickly control the inflammatory response to minimize tissue damage and scarring.

Cycloplegia and topical corticosteroids are the first line of treatment, particularly for anterior manifestations, and there are many such FDA- and EMA-approved drugs for use in treating uveitis. However, an important risk related to the local use of corticosteroids is the development of intraocular pressure increases/glaucoma. Corticosteroids can also be given locally as periocular or intravitreal injections. However, topical ocular corticosteroid administration has limitations, as delivery to the posterior segment of the eye is very limited. Periocular corticosteroid injections are used regularly in clinical practice; however, use in this indication is unlicensed and the effect is short-term. This leads to the need for more frequent administration with its associated complications, such as globe perforation, conjunctival or, strabismus, proptosis, fibrosis of extraocular muscles, and increased risk of endophthalmitis.

In case of intermediate or posterior uveitis, moreover in case of bilateral uveitis, usefulness of local cortisteroids is limited and systemic (usually orally or intravenously) corticosteroids should be use. The use of systemic corticosteroids is associated with a number of safety concerns including systemic hypertension, hyperglycemia, increased susceptibility to infection, and peptic ulcers.

Immunomodulatory/immunosuppressive therapy is discussed for corticosteroid-dependent uveitis, with the aim of cortisone sparing and to prevent inflammatory recurrences. It is acknowledged that a long-term corticoid dose of more than 7 mg may cause side effects and requires the introduction of cortisone sparing treatment (**Figure 1**)[10].

Figure 1 : Algorithm for the systemic treatment of severe intermediate, posterior or non-infectious panuveitis in adults (adapted from PNDS Uvéites chroniques non infectieuses de l'enfant et l'adulte)[10]



Antimetabolites such as mycophenolate mofetil (2 g/day in adults), are the most commonly used immunomodulators/immunosuppressants in corticosteroid dependant NIU.

Adalimumab has recently been shown to be more effective than placebo in active and inactive non-infectious uveitis in phase 3 clinical trials and is approved in uveitis in France[11,12].

However, no head-to-head study compared adalimumab to classic immunosuppressive therapy.

1.3[2.3] Summary of relevant pre-clinical experiments and clinical trials

1.3.1[2.3.1] Immunosuppressants

Among immunosuppressants, mycophenolate mofetil is one of the most commonly used treatment for sparing corticosteroids in chronic non-infectious uveitis.

Mycophenolate mofetil (MMF) is a selective inhibitor of T and B cell proliferation, with a stronger cytostatic effect on lymphocytes than on other cell types. In inflammatory ocular diseases, many experts published data on the efficacy of MMF in controlling ocular inflammation with minimum side effects[13]. In a retrospective cohort of 84 patients treated with mycophenolate mofetil more than 80% of the patients were considered a treatment success (i.e the ability to control the inflammation and taper prednisone to < or =10 mg daily) with a median time to treatment success of 3.5 months[14]. In another retrospective cohort obtained from the case notes of 100 consecutive non-infectious chronic, recurrent uveitis patients treated with MMF[15], there was an 84.6% probability of achieving a prednisone dose of < or =10 mg daily after one year of MMF treatment. Alternative second-line immunosuppressive

therapy was introduced at a rate of 0.18 per patient-year (PY) and MMF was discontinued because of intolerance at a rate of 0.09/PY, predominantly because of gastrointestinal upset. MMF was also shown to be effective in maintaining remission in a long-term period. In a retrospective cohort of 60 patients with NIU, control of intraocular inflammation by MMF, defined as inactive disease under prednisolone dose of ≤ 10 mg daily, was achieved in 72% of patients after 1 year of MMF treatment and in 82% after 2 years therapy[16].

1.3.2[2.3.2] Anti-TNF

A better understanding of the mechanisms involved in the inflammatory response and regulation of adaptive immunity led to the development of biotherapies. Under this term are grouped interferons, intravenous and monoclonal antibodies. These were first developed in the field of rheumatology and then used in the treatment of systemic diseases and inflammatory eye diseases.

Several teams have reported on the efficacy of anti-TNF alpha in severe refractory non-infectious uveitis. Petropoulos et al. reported 15 patients with chronic refractory noninfectious posterior uveitis treated with anti-TNF alpha[17]. An improvement was observed in all cases associated with a stabilization or improvement of visual acuity within 2 months following the initiation of anti-TNFalpha. Of the 33 cases of cystoid macular edema treated with adalimumab reported by Diaz-Llopis et al, 54.5% regressed completely and 31% had improvement in visual acuity[18]. Diaz-Lopis et al. evaluated adalimumab therapy in a prospective cases series of 131 patients with refractory uveitis and intolerance or failure to prednisone and at least 1 other systemic immunosuppressive drugs[19]. Ocular inflammation, macular thickness, dose of corticosteroids significantly decreased while visual acuity improved. Six months after the initiation of the study, 111 patients (85%) were able to reduce at least 50% of their baseline immunosuppression load. An open-label phase II clinical trial has recently assessed adalimumab in 31 patients with non-infectious refractory uveitis to corticosteroids and at least one immunosuppressive medication[20]. Adalimumab was safe and effective in 68% patients and maintained in 39% after one year. A recent study have evaluated 91 patients with refractory uveitis in the context of juvenile idiopathic arthritis treated with systemic anti-TNF [infliximab (n=48) and adalimumab (n=43)]. Fifty-five percent of patients achieved remission, 33% relapsed and 12% were not improved. Remission rate with adalimumab were higher to that obtained with infliximab (67.4% vs 42.8%, respectively, p=0.025)[21]. A small open-label prospective study including 33 childhood-refractory uveitis patients compared the efficacy and safety of adalimumab (n=16 children, including 12 juvenile idiopathic arthritis) versus infliximab (n=17 children, including 10 AIJ)[22] . At 40 months of follow-up, 9 children (60%) receiving adalimumab compared to 3 (18.8%) receiving infliximab were still in remission on therapy. Several ongoing trials evaluate the efficacy and safety of adalimumab, either for the treatment active intermediate, posterior, or panuveitis, uveitis refractory to conventional therapy, inactive uveitis and uveitis in JIA. Artornsombudh et al. recently showed that infliximab was effective for controlling inflammation in 19 of 22 (88.9%) Birdshot retinochoroidopathy refractory to conventional immunomodulatory therapy[23].

A first multicenter, randomized, double-blind, multicenter study evaluated effectiveness of adalimumab against placebo in non-infectious, non-anterior, active uveitis (VISUAL 1)[12]. Among the 217 patients in the intention-to-treat population, those receiving adalimumab were significantly less likely than those in the placebo group to have treatment failure (defined as an increase in vitreous inflammation or previous inflammation, the appearance of a new chorioretinal lesion or vasculitis or decreased visual acuity). Outcomes with regard to three secondary end points (change in anterior chamber cell grade, change in vitreous haze grade, and change in best corrected visual acuity) were significantly better in the adalimumab group than in the placebo group. In VISUAL 2, among the 226 patients analyzed in intention-to-treat, the failure rates were 39% and 55% respectively in the

adalimumab-treated group and the placebo-treated group[11]. Adalimumab significantly reduces the risk of relapse and visual acuity decline with decreasing corticosteroid therapy, while having a good short-term safety profile.

In the VISUAL 1 (active uveitis) and VISUAL 2 studies (inactive uveitis), the time to relapse is doubled for patients on adalimumab versus placebo[11,12]. Thus, adalimumab was granted marketing authorization in 2017 in treatment of intermediate, posterior and adult non-infectious uveitis and panuveitis with insufficient response to corticosteroid therapy alone, and also for patients with requiring cortisone sparing, or for those for whom corticosteroid therapy is contraindicated.

1.4[2.4] Description of the population to be studied and justification for theis choice of participants

Adult patients with recently active Non-infectious Uveitis (NIU) despite oral prednisone > 7 mg/day (or ~~oral corticosteroid at~~ equivalent prednisone dose, only if prednisone is out of stock in the market ~~or if no prednisone is available use oral corticosteroid as a replacement for prednisone (equivalent dose)or oral corticosteroid equivalent~~).

Recently active disease: as defined by the presence of at least 1 of the following parameters in either eye within the 3 months prior to inclusion visit:

- Active chorioretinal or retinal vascular lesion;
- Presence of macular edema by optical coherence;
- ≥ 2+ anterior chamber cells (Standardization of Uveitis Nomenclature [SUN] criteria);
- ≥ 2+ vitreous haze (National Eye Institute [NEI]/SUN criteria).

1.5[2.5] Identification and description of the investigational medication or medications

Arm 1: Adalimumab (80mg at day 0, then 40mg/14 days from W1 to W35 subcutaneously)

Arm 2: Mycophenolate mofetil 2 g/day orally for 36 weeks

All patients will receive the same corticosteroid regimen at inclusion. All patients will receive corticosteroids (10-35 mg/day) at inclusion. A common prednisone tapering programme will be applied to both groups with a decrease until discontinuation between week 13 and week 19 as long as the disease is inactive.

Prednisone dose at study entry							
Dose (mg/day)	35	30	25	20	15	12.5	10
35	Day 0 - Week 1						
30	2	Day 0 - Week 1					
25	3	2	Day 0 - Week 1				
20	4	3	2	Day 0 - Week 1			
15	5	4	3	2	Day 0 - Week 1		
12.5	6	5	4	3	2	Day 0 - Week 1	
10	7	6	5	4	3	2	Day 0 - Week 1
7.5	8	7	6	5	4	3	2
5	9	8	7	6	5	4	3
4	11	10	9	8	7	6	5
3	13	12	11	10	9	8	7
2	15	14	13	12	11	10	9
1	17	16	15	14	13	12	11
Discontinue	19	18	17	16	15	14	13

Prednisone dose at study entry (Or equivalent prednisone dose, if prednisone is out of stock in the market)							
Dose (mg/day)	35	30	25	20	15	12.5	10
35	Day 0 - Week 1						
30	2	Day 0 - Week 1					
25	3	2	Day 0 - Week 1				
20	4	3	2	Day 0 - Week 1			
15	5	4	3	2	Day 0 - Week 1		
12.5	6	5	4	3	2	Day 0 - Week 1	
10	7	6	5	4	3	2	Day 0 - Week 1
7.5	8	7	6	5	4	3	2
5	9	8	7	6	5	4	3
4	11	10	9	8	7	6	5
3	13	12	11	10	9	8	7
2	15	14	13	12	11	10	9
1	17	16	15	14	13	12	11
Discontinue	19	18	17	16	15	14	13

1.6[2.6] Description and justification of the dosage, route of administration, administration schedule and treatment duration

Eligible patients with active and refractory NIU will randomized at 1:1 ratio after they have given free and informed consent between:

Arm 1: Adalimumab (80mg at day 0, then 40mg/14 days from W1 to W35 subcutaneously)

Arm 2: standard of care: Mycophenolate mofetil 2 g/day orally for 36 weeks

All treatment arms will receive the same corticosteroid regimen at inclusion.

At randomization (Day 0), patients receive treatment allocated by randomization. The schedule of reduction of prednisone (or ~~or oral corticosteroid at~~ equivalent prednisone dose, only if prednisone is out of stock in the market ~~if no prednisone is available use oral corticosteroid as a replacement for prednisone (equivalent dose)~~) presented above (table 1) will apply to both groups as long as the disease is inactive.

All patients will be followed at week W4, W8, W12, W16, W20, W24, W30, W36 and W55. Patients with uncontrolled, worsening and/or flare of uveitis at any time of the study will be considered as non-responders, and will be treated according to the best standard of care by their physician.

1.7[2.7] Summary of the known and foreseeable benefits and risks for the Clinical Trial participants

Refractory non-infectious uveitis is a serious ocular pathology, accounting for 10-15% of total blindness cases[3]. Reliable clinical data are required for the treatment of uveitis and more particularly in the management of biotherapies. Corticosteroids and immunosuppressants have not shown a sustained remission rate of more than 70% in severe refractory/relapsing uveitis[10]. The incidence of blindness in NIU has been reduced in recent years with the use of biotherapies, raising the question of whether these therapies should be prescribed earlier in the management of patients with severe non-infectious uveitis. Compared to conventional immunosuppressants, biotherapies are fast acting and highly effective in cortisone sparing, thus limiting the risk of cataract and/or cortico-induced glaucoma[10]. Despite a scientific justification and a strong clinical rationale, most of these treatments are not yet approved in the management of uveitis.

FOCUS is the first randomized trial comparing the efficacy and safety of adalimumab to standard of care (mycophenolate mofetil) in the maintenance treatment of corticosteroid-dependent NIU. This study will validate and optimize the treatment of hard-to-treat patients with uveitis. It may also confirm whether or not adalimumab is superior to mycophenolate mofetil in terms of efficacy. It will allow a direct comparison of the safety profiles of this treatment. It could significantly improve the management of patients with corticosteroid-dependent NIU and finally help in the selection of the best treatment to prevent the onset of blindness and side effects in these difficult to treat cases. The expected benefit is both individual, by reducing morbidity for patients with non-infectious uveitis, and collective, by reducing the costs of unemployment, disability and hospitalization.

Main side effects of mycophenolate mofetil are diarrh~~o~~ea, leukopenia, sepsis and vomiting. There is also evidence of a higher frequency of certain types of infections (most frequently candida mucocutaneous, CMV viraemia/syndrome and Herpes simplex)[24].

Common side effects of adalimumab include injection site reactions (pain, redness, rash, swelling, itching, or bruising), upper respiratory infections (sinus infections), headaches, rash, and nausea. Rare but severe side effects include tuberculosis reactivation, neoplasia, or demyelinating disorder[25].

3. OBJECTIVES

1.8[3.1] Primary objective

The objective is to compare the efficacy of adalimumab (80mg at day 0, then 40mg/14 days from W1 to W35 subcutaneously) with that of standard of care (mycophenolate mofetil [2g/day orally]) for 36 weeks in recently active non-infectious intermediate and posterior uveitis or pan-uveitis with steroid dependency.

1.9[3.2] Secondary objectives

Comparing adalimumab (80mg at day 0, then 40mg/14 days from W1 to W35 subcutaneously) to standard of care (mycophenolate mofetil [(2g/day orally)]):

- To evaluate the cumulative incidence of treatment failure up to W55 after inclusion
- To evaluate the change in best corrected visual acuity (BCVA, logMAR) from baseline to week W55 ;
- To evaluate the change in ocular inflammation in the anterior chamber and vitreous from baseline to week W55;
- To evaluate the change in other signs including vessel leakage, from baseline to week W55;
- To evaluate the presence of macular edema from baseline to week W55;
- To evaluate the quality of life related to uveitis, from inclusion to W55;
- To evaluate steroid sparing from baseline to week W55;
- To evaluate the number and time to relapse of uveitis and the characteristics of uveitis at worsening at week from baseline to week W55;
- To evaluate the effect on underlying systemic disease when appropriate from baseline to week W55;
- To evaluate the safety of adalimumab and standard of care (mycophenolate mofetil) up to W55;

4. STUDY DESIGN

1.10[4.1] Study endpoints

1.10.1[4.1.1] Primary endpoint

The primary efficacy endpoint is the treatment failure rate at 36 weeks. Treatment failure is defined by any of the following in at least one eye:

- new active, inflammatory chorioretinal or retinal vascular lesions;
- worsening of best corrected visual acuity (BCVA) by >3 lines;
- 2-step increase in anterior chamber cell grade and/or in vitreous haze relative to baseline

~~and with steroid discontinuation between week 13 and week 19 (as per protocol) and without any additional immunosuppressive drug or injectable steroids~~

- ~~–~~ ~~N~~othe absence of steroid discontinuation between week 13 and week 19 (as per protocol)
- ~~–~~or ~~a~~any additional immunosuppressive drug or injectable steroids

~~- Study treatment permanent discontinuation~~

1.10.2 Secondary endpoints

- Time to treatment failure, up to W55;
- logMAR BCVA in each eye, at W4, W8, W12, W16, W20, W24, W30, W36 and W55;
- Anterior chamber cell grade in each at W4, W8, W12, W16, W20, W24, W30, W36 and W55;
- Vitreous haze grade (SUN criteria) in each eye at W4, W8, W12, W16, W20, W24, W30, W36 and W55;
- Central retinal thickness in each eye from baseline at W4, W8, W12, W16, W20, W24, W30, W36 and W55;
- Proportion of patients with central macular thickness < 300 microns at W4, W8, W12, W16, W20, W24, W30, W36 and W55;
- Time to optical coherence tomographic (OCT) evidence of macular edema in at least one eye, up to W55;
- NEI Visual Functioning Questionaire-25 (VFQ-25) composite score, at W12, W24, and W36;
- Measures of corticosteroid sparing (e.g., percent meeting targets [<0.1 mg/kg/day prednisone], mean change, mean dose at week 55, and cumulative dose);
- Cumulative incidence of relapse and number of relapses up to W55;
- Other clinical manifestations of underlying disease (depending on the underlying disease) will be evaluated up to W55
- Safety and tolerability of treatments as assessed by the frequency and severity of adverse events and treatment discontinuation from baseline to Week 55

1.11[4.2] Description of research methodology

1.11.1[4.2.1] Design of the study

This is a prospective phase III, multicenter, Bayesian, multi-arm multi-stage, randomized (1:1), clinical trial, comparing the efficacy and safety of Adalimumab to standard of care (mycophenolate mofetil) in subjects with recently active non-infectious intermediate, posterior, or pan-uveitis despite steroids use (oral prednisone > 7 mg/day or ~~oral corticosteroid at~~ equivalent prednisone dose, only if prednisone is out of stock in the market~~or if no prednisone is available use oral corticosteroid as a replacement for prednisone (equivalent dose)or equivalent~~).

For the purposes of this study, recently active Non-infectious Uveitis (NIU) is defined by the presence of at least 1 of the following parameters in either eye within the 3 months prior to inclusion visit:

- Active chorioretinal or retinal vascular lesion

- Presence of macular edema by optical coherence.

- ≥ 2+ anterior chamber cells (Standardization of Uveitis Nomenclature [SUN] criteria)

- ≥ 2+ vitreous haze (National Eye Institute [NEI]/SUN criteria);

The activity status (recently active disease) has to be confirmed for all patients before the randomization by ophtalmologic assessments.

All patients will be followed at week 4, W8, W12, W16, W20, W24, W30, W36 and W55. Patients with uncontrolled, worsening and/or flare of uveitis at any time of the study will be considered as non responders and will be treated at the discretion of their physician according to the best standard of care. The final visit will be at week 55.

The design is an open-label two-arm randomized clinical trial owing to the different frequency of administration of the 2 compared treatments.

We will use a group sequential design, with one interim analysis after 50% of primary observations have been completed, with efficacy and futility (non-binding) stopping rules. Lan&DeMets risk-spending functions will be used to define stopping boundaries (O'Brien&Fleming-like boundaries).

Randomization will be stratified by presence or not of macular oedema, ~~underlying disease (idiopathic uveitis or underlying disease associated)~~ and steroid dose at the time of inclusion (<20mg/d vs. ≥ 20mg/d). At randomization, the patient may be under treatment with prednisone as single therapy (10- 35 mg/day). All systemic immunosuppressants must have been discontinued prior to the first study drug administration on Day 0.

Day -30 to Day 0: Eligibility for enrollment is determined.

Day 0: Inclusion and randomization in a 1:1 ratio will be stratified by presence or not of macular oedema~~, underlying disease~~ and steroid dose at inclusion between 2 arms:

Arm 1: Adalimumab (80mg at day 0, then 40mg/14 days from W1 to W35 subcutaneously)
Arm 2: Standard of care: Mycophenolate mofetil 2 g/day orally for 36 weeks

Oral corticosteroids should be at a stable dose at least 2 weeks prior to the first study drug administration on Day 0. All patients will receive the same corticosteroid regimen at inclusion that is 10-35 mg/day at inclusion.

The following schedule of reduction of prednisone (or ~~oral corticosteroid at~~ equivalent prednisone dose, only if prednisone is out of stock in the market~~or if no prednisone is available use oral corticosteroid as a replacement for prednisone (equivalent dose)~~) will apply to both groups (discontinuation between W13 and W19) as long as the disease is inactive:

Table *1*: schedule of prednisone reduction (or ~~oral corticosteroid at~~ equivalent prednisone dose only if prednisone is out of stock in the market~~or if no prednisone is available use oral corticosteroid as a replacement for prednisone (equivalent dose)~~)

Dose (mg/day)	Prednisone dose at study entry						
	35	30	25	20	15	12.5	10
35	Day 0 - Week 1						
30	2	Day 0 - Week 1					
25	3	2	Day 0 - Week 1				
20	4	3	2	Day 0 - Week 1			
15	5	4	3	2	Day 0 - Week 1		
12.5	6	5	4	3	2	Day 0 - Week 1	
10	7	6	5	4	3	2	Day 0 - Week 1
7.5	8	7	6	5	4	3	2
5	9	8	7	6	5	4	3
4	11	10	9	8	7	6	5
3	13	12	11	10	9	8	7
2	15	14	13	12	11	10	9
1	17	16	15	14	13	12	11
Discontinue	19	18	17	16	15	14	13

Dose (mg/day)	Prednisone dose at study entry (Or equivalent prednisone dose, if prednisone is out of stock in the market)						
	35	30	25	20	15	12.5	10
35	Day 0 - Week 1						
30	2	Day 0 - Week 1					
25	3	2	Day 0 - Week 1				
20	4	3	2	Day 0 - Week 1			
15	5	4	3	2	Day 0 - Week 1		
12.5	6	5	4	3	2	Day 0 - Week 1	
10	7	6	5	4	3	2	Day 0 - Week 1
7.5	8	7	6	5	4	3	2
5	9	8	7	6	5	4	3
4	11	10	9	8	7	6	5
3	13	12	11	10	9	8	7
2	15	14	13	12	11	10	9
1	17	16	15	14	13	12	11
Discontinue	19	18	17	16	15	14	13

Week 4, 8, 12, 16, 20, 24, 30: Evaluation of secondary assessment criteria

Week 36: Evaluation of primary and secondary assessment criteria

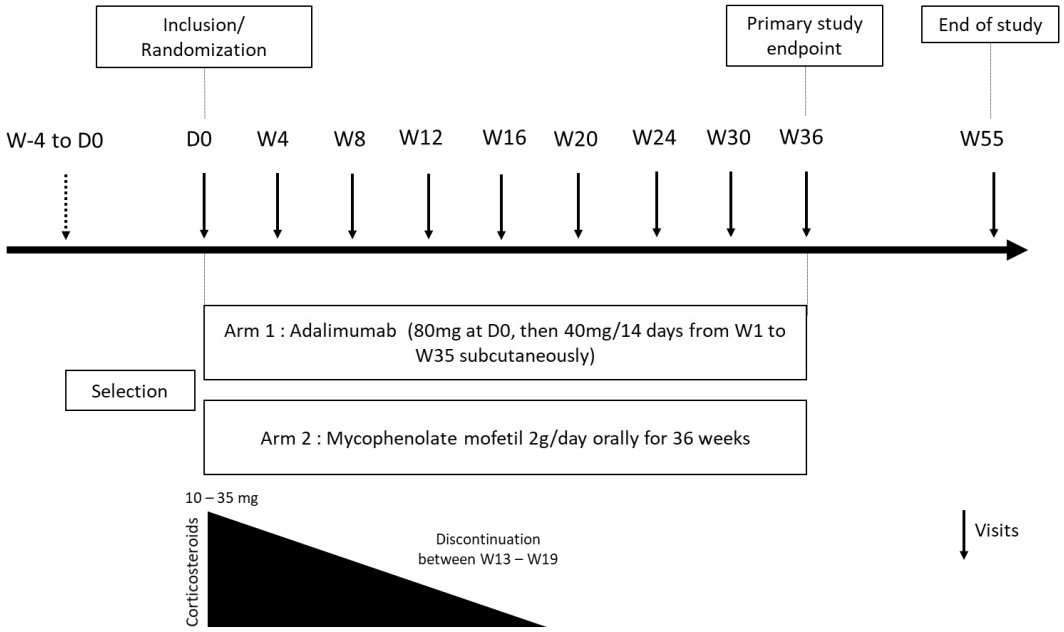
Patients with uncontrolled, worsening and/or flare of uveitis at any time of the study will be considered as non responders and will be treated at the discretion of their physician

according to the best standard of care. The final visit will be at week 55. Additional visits will take place in case of any clinical or laboratory findings suggestive of a flare-up of the disease.

The point of time for the primary analysis is at week 36.

Given the expected recurrence rate of the disease in the different treatment groups, 36 weeks is considered a sufficient period of time to do a statistically adequate comparison between the three medications as usually required in study relative to treatment of uveitis.

Figure 2: Scheme of the study



1.11.2[4.2.2] Number of participating sites

This national multicenters study, involving at least 27 clinical centers. Participating centers will be Internal medicine, or rheumatology, CIC, CRC and Opthalmology departments of public hospitals located in France.

Visits of Selection and Follow-up will be conducted by investigators of internal medicine or rheumatology and ophtalomology centers.

Patient's inclusion and randomization (D0) will be performed by an investigator of internal medicine center or rheumatology.

- **Recruitment centres**

Internal medicine, or rheumatology departments of public hospitals located in France.

- **Non-recruitment centres**

CIC, CRC and Opthalmology departments of public hospitals located in France.

1.11.3[4.2.3] Identification of participants

The participants in this Clinical Trial will be identified as follows:
Site number. (3 digits) - Sequential enrolment number for the site (4 digits) - surname initial - first name initial
This reference number is unique and will be used for the entire duration of the study.

1.11.4[4.2.4] Randomisation

When selected, the patient eligibility will be evaluated from inclusion and non-inclusion criteria and consent will be signed by the patient and investigator. The “Patient Inclusion Form” will be registered by connecting the centralized web-based electronic CRF (eCRF). The patient identification number will be allocated.

Randomization of patients will be centralized and carried out using a computerized system in the eCRF website according to a predefined randomization list. Distribution in the 2 groups will be balanced in a 1:1 ratio.

The randomization list will be designed by an independent statistician within the Sponsor/designee organization, and stratified on presence or not of macular oedema, ~~underlying disease vs idiopathic uveitis~~ and steroid dose at inclusion (<20mg/d vs. ≥20mg/day) between 2 arms. Each list will be based on permutation blocks, the size of which will be unknown to practitioners involved in patient accrual.

All inclusion and non-inclusion criteria will be checked before inclusion.

1.11.5[4.2.5] Blinding methods and measures put in place to protect blinding

This trial will be comparative, randomized and open-label.

5. IMPLEMENTATION OF THE STUDY

Before any examination or intervention related to the study may be carried out, the investigator must obtain the *freely given, informed and written consent of the participant, or of his/her legal representative* where applicable.

Individuals liable to participate in studies benefit from a preliminary medical examination adapted to the study.

The start of the clinical trial is the inclusion of the first patient.

1.12[5.1] Screening visit

The selection visit takes place within 4 weeks before the baseline visit, during a consultation or a hospitalization of the usual medical follow-up of patients with investigator of internal medicine, or rheumatologist, (depending on the hospital) or ophtalmology.

whose consent must be obtained	**Who informs the individual and collects their consent**	**When is the individual informed**	**When is the subject's consent collected**
Patient	*Internists or rheumatologist,*	*Screening visit*	*Inclusion visit*

During this visit, the investigator 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 (vital signs, extra ophthalmologic manifestations)
- perform an ocular examination by ophthalmologist which include fundoscopy, Vitreous Haze, (Tyndall and flare, BCVA (SNELLEN score), Optical Coherence Tomography (OCT) and fluorescein angiography.
- arrange the following usual laboratory tests: complete blood count with platelets, serum electrolytes, liver function tests (AST, ALT, GGT, PAL, total bilirubin, albumin), LDH, ESR, CRP, fibrinogen, haptoglobin, orosomucoid, urea, creatinine, glucose, Triglyceride and cholesterol, quantiferon test, HIV, HBV, HCV serologies and TPHA-VDRL.
- ECG
- Chest X-ray
- inform the patient about the protocol and give them the information and consent form.
- **Inform the unit of clinical research or notify via CleanWeb as soon as a selection of a patient in the center (at least 5 working days before inclusion/randomization) is validated. This will allow during the next visit (baseline visit) to be able to prescribe and dispense the treatments.**

Oral corticosteroids should be at a stable dose at least 2 weeks prior to the first study drug administration on Day 0. All patients will receive the same corticosteroid regimen at inclusion (see table 1)

1.13[5.2] Inclusion/randomisation visit (Day 0)

The baseline visit takes place at Day 0 and allows the verification of inclusion and exclusion criteria.

At this visit, the internist (or rheumatologist) investigator will:

- Review the results of the following laboratory tests: complete blood count with platelets, serum electrolytes, liver function tests (AST, ALT, GGT, PAL, total bilirubin, albumin), LDH, ESR, CRP, fibrinogen, haptoglobin, orosomucoid, urea, creatinine, glucose, triglycerides, cholesterol, quantiferon test, HIV, HBV, HCV serologies, and TPHA-VDRL and chest xray, ECG,
- Perform a physical examination (vital signs, extra ophthalmologic manifestations)
- Review the results of the ocular exams.
- Collect the free and informed written consent of the patient.
- Perform and review the result of a ßHCG or urine pregnancy test for women of child-bearing potential.
- When the patient is considered eligible, investigator will insure the inclusion and randomization via the centralized randomization/eCRF web site (CleanWeb).
- Assure the prescription of study treatment by using eCRF
- Assess baseline Quality of life (using the National Eye Institute Visual Functioning Questionnaire-25)
- Provide the first treatment and patient card to patient

A subject who meets all eligibility requirements will be randomized to one of 2 treatment groups:

- **Arm 1:** Adalimumab (80mg at day 0, then 40mg/14 days from W1 to W35 subcutaneously)
- **Arm 2:** Mycophenolate mofetil 2 g/day orally for 36 weeks

The first administration of Adalimumab will be done in the service by a nurse who will train the patient to the modalities of injection to enable him/her to carry out the subsequent injections.

A patient diary will be given to the patients during the treatment period. It contains practical information to help them take their treatment at home and will allow them to keep track of their treatment. Patients should be instructed to bring the patient diary and all treatment packs, including empty packs and unused treatments with them at each visit to allow assessment of the trial compliance. The investigator will review the subject's diary at each subject's hospital visit. At that time, a new diary will be given to the subject if necessary. All subject diaries should be stored with the medical file of the subject for reconciliation with the trial drug accountability.

A common prednisone-tapering (~~or oral corticosteroid at~~ equivalent prednisone dose only if prednisone is out of stock in the market ~~or if no prednisone is available use oral corticosteroid as a replacement for prednisone (equivalent dose)~~) program will be applied to both groups

with a decrease until discontinuation between week 13 and week 19, as long as the disease is inactive.

1.14[5.3] Follow-up visits

Monitoring should continue for all patients until the end of the Study according to the schedule, even if they discontinue treatment (provided a patient does not withdraw consent to participate). Consultations at these visits will be conducted by the patient's usual Study investigator. Patients will be reviewed at 4, 8, 12, 16, 20, 24, 30, 36 and 55 weeks and will have:

- Ophthalmic examination by ophthalmologist to follow the efficacy will take place before the internist visit and include:
    - fundoscopy, Vitreous Haze, (Tyndall and flare), change from baseline in BCVA (SNELLEN score), Optical Coherence Tomography (OCT) at 4, 8, 12, 16, 20, 24, 30, 36 and 55 weeks
    - Retinal angiogram at selection, and week 36, and at W12 and W24 in case of vascularitis and/or chorioretinal lesions
- A physical examination will be performed by the patient's Study internist or rhumatologist at each visit to dispensiate the treatment and follow tolerance (neurological exam to detect demyelinating disorders, infections, skin cancer, lymphoma, and autoimmune disorder)
- Blood count, platelets, serum electrolytes, creatinine, ESR, CRP, LDH, fibrinogen, haptoglobin, orosomucoid, , liver function tests (AST, ALT, GGT, PAL, total bilirubin, albumin), urea, triglycerides, cholesterol, and glucose will be measured at 4, 8, 12, 16, 20, 24, 30, 36 and 55 weeks.
- For women with reproductive potential, a urine pregnancy test will be performed at each visit and monthly until 3 months after the Mycophenolate mofetil last dose, and until 5 months after the Adalimumab last dose, unless menopause or sterility is confirmed.
- Quality of life Assessment (National Eye Institute Visual Functioning Questionnaire-25 (VFQ-25) composite score; VFQ-25 distance vision subscore; VFQ-25 near vision subscore; and VFQ-25 ocular pain subscore) at W12, W24 and W36

Additional visits will take place if there are clinical signs indicating a possible flare up of the disease. The primary endpoint will be at week 36. All patients will be followed at 4, 8, 12, 16, 20, 24, 30, 36 and 55 weeks. Patients with uncontrolled, worsening and/or flare of uveitis at any time of the study will be considered as non responders and will be treated at the discretion of their physician according to the best standard of care. The final visit will be at week 55.

1.15[5.4] Last study visit

After the study is completed at week 55, all subjects will be followed after the study according to their usual routine hospital care, usually every 3 months.

1.16[5.5] Expected length of participation and description of the chronology and duration of the study.

Duration of enrolment period : 30 months

Maximum duration between screening and enrolment : 4 weeks

The length of participation for each participant : 55 weeks of which:

- Treatment duration: 36 weeks
- Duration of follow-up period: 20 weeks (patient with adalimumab) et 19 weeks (patient with Mycophenolate mofetil)

Total study duration: 44 months

1.17[5.6] Table or diagram summarising the chronology of the study

	Selection visit	**Inclusion/ randomization visit**	**Follow-up visits**								**End of study**
	W-4 to D0	D0	W4 +/- 3 days	W8 +/- 3 days	W12 +/- 3 days	W16 +/- 3 days	W20 +/- 3 days	W24 +/- 3 days	**W30** +/- 3 days	**W36§** +/- 3 days	W55 +/- 3 days
Oral and written Information about the protocol	®										
Verification of inclusion and non inclusion criteria	®	®									
signature of informed consent		®									
Clinical examination	C	C	®	®	C	®	®	C	®	C	C
Ophthalmological examination* ***including Optical Coherence Tomography (OCT)***	C		®	®	C	®	®	C	®	C	C
Retinal angiography **	C				C			C		®	
Biological tests***	C		C	C	C	C	C	C	C	C	C
Quantiferon, HIV, HBV, HCV serologies and TPHA-VDRL,	C										
Pregnancy urinary test ** (blood ßHCG test for D0 only)**		®	®	®	®	®	®	®	®	®	®
ECG	C										
Chest X Ray	C										
QOL questionnaires		®			®			®		®	
Dispensing of investigational drugs		® + diary	®	®	®	®	® + diary	®	®		
Compliance		®	®	®	®	®	®	®	®	®	
Adverse events		®	®	®	®	®	®	®	®	®	

C= care / ® = research

§ Primary study endpoint

* Ophtalmic examination will include fundoscopy, Vitreous Haze, (Tyndall and flare according to the Standardization of Uveitis Nomenclature (SUN) classification), change from baseline in BCVA (SNELLEN score) and Optical Coherence Tomography (OCT).

**Retinal vasculitis will be determined by the investigator using clinical examination and/or ancillary testing such as fluorescein angiography. Retinal angiography will be performed at selection and week 36, and at W12 and W24 in case of vascularitis and/or chorioretinal lesions

*** Complete blood count with platelets, serum electrolytes, liver function tests (AST, ALT, GGT, PAL, total bilirubin, albumin), LDH, ESR, C-reactive protein, urea, creatinine, glucose, triglyceride and cholesterol, fibrinogen, haptoglobin, orosomucoid.

**** For women with reproductive potential urinary ßHCG at each visit and monthly until 3 months after Mycophenolate mofetil last dose, and until 5 months after Adalimumab last dose, unless menopause or sterility is confirmed.

1.18[5.7] Distinction between standard care and study

Interventions, procedures and treatments carried out for research purposes	**Interventions, procedures and treatments associated with standard care**	**Interventions, procedures and treatments added for research purposes**
Treatments	- Mycophenolate mofetil 2g/day orally - Oral Prednisone (or oral ~~corticosteroid at e~~quivalent prednisone dose only if prednisone is out of stock in the market) and Reduction of corticosteroid regimen - Supportive treatment to reduce the adverse effects associated with the use of steroids	- Adalimumab (80mg at day 0, then 40mg/14 days from W1 to W35 subcutaneously)
Consultations	- Visit at D0, W12, 24, 36 and 55	- Visit at week 4, 8, 16, 20 and 30 weeks
Blood samples	- Blood sampling every 4 weeks	- βHCG plasmatic or urine pregnancy test at inclusion and Urine pregnancy test at each visit, and monthly until 6 weeks after Mycophenolate mofetil last dose, and until 5 months after Adalimumab last dose, unless menopause or sterility is confirmed.
Imaging	- ECG: before starting treatment - Chest X Ray before starting treatment - Fundoscopy, Optical Coherence Tomography (OCT) before starting treatment and at W12, 24, 36, and 55 - Retinal angiography before starting treatment and at W12 and W24 in case of vascularitis and/or chorioretinal lesions	- Fundoscopy, Optical Coherence Tomography (OCT) at 4, 8, 16, 20 and 30 weeks - Retinal angiography at 36 weeks
Others		- QOL questionnaires at D0, W12, W24 and 36 weeks

TABLE: "Standard care" vs. "additional interventions" required specifically for the study

6. ELIGIBILITY CRITERIA

1.1[6.1] *Inclusion criteria*

The eligibility criteria will be checked at the selection visit (which takes place four weeks maximum prior to inclusion visit) and at the inclusion/randomization visit. Adult patients meeting the following criteria may be included in the study:

1. Provide written, informed consent prior to the performance of any study-specific procedures

2. >18 years of age

3. Diagnosis of non-infectious intermediate, posterior-, or pan-uveitis in at least one eye fulfilling the International Study Group Classification Criteria (Standardization of Uveitis Nomenclature [SUN] criteria) of posterior, or pan- uveitis confirmed by documented medical history

4. Recent activity of NIU as defined by the presence of at least 1 of the following parameters in either eye within the 3 months prior to inclusion visit despite >7mg/day of oral prednisone

    a. Active chorioretinal or retinal vascular lesion

    b. Presence of macular edema by optical coherence.

    c. ≥ 2+ anterior chamber cells (Standardization of Uveitis Nomenclature [SUN] criteria)

    d. ≥ 2+ vitreous haze (National Eye Institute [NEI]/SUN criteria)

5. Chest X-ray (postero-anterior and lateral) or CT-scanner results within 12 weeks prior to Inclusion with no evidence of active Tuberculosis, active infection, or malignancy

6. A potential subject with a positive interferon-gamma release assay (IGRA) (e.g., QuantiFERON®-TB Gold or T-spot TB® Test) at inclusion is eligible if:

    a. Her/his chest X-ray does not show evidence suggestive of active TB disease

    b. And there are no clinical signs and symptoms of pulmonary and/or extra-pulmonary TB disease.

    c. And these subjects with a latent TB infection who have not already received a prophylactic TB treatment must agree in advance to complete such a treatment course.

7. For female subjects of child-bearing potential, a negative serum pregnancy test at inclusion

8. 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 and 3 months and 5 months after stopping therapy for MMF and adalimumab, respectively, unless sterility is confirmed. The simultaneous use of two complementary methods of contraception is preferable.

   Methods which may be considered as highly effective methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods (according to CTFG recommendations). Such methods include:

   For female subjects:

   a. combined (estrogen and progestogen containing) hormonal contraceptionassociated with inhibition of ovulation 1:
      - oral
      - intravaginal
      - transdermal

   b. progestogen-only hormonal contraception associated with inhibition of ovulation 1:
      - oral
      - injectable
      - implantable

   c. intrauterine device (IUD)

   d. intrauterine hormone-releasing system (IUS)

   e. bilateral tubal occlusion

   f. vasectomised partner

   g. sexual abstinence (In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject).

   For male subjects:

   a. use of condoms
   b. vasectomy (with documentation of azoospermia)
   c. sexual abstinence

9. Affiliated to a social security system

1.2[6.2] Exclusion criteria

1.Subjects will not be included in the study if they meet any of the following criteria:
Infectious uveitis, masquerade syndromes (idiopathic uveitis is permitted)
2.Isolated anterior uveitis

3.Monocular patient
4.Active tuberculosis
5. Positive HIV serology or HCV HBs Ag test.
6.History of malignancy within 5 years prior to Inclusion other than carcinoma in situ of the cervix, non-metastatic squamous or basal cell carcinoma of the skin.
7.History of severe allergic or anaphylactic reactions to monoclonal antibodies, mycophenolate mofetil , rifampicin, isoniazid or fluorescein
8.Infection requiring treatment with intravenous antibiotics within 3 weeks prior to inclusion
9.History of multiple sclerosis and/or demyelinating disorder
10.Laboratory values assessed during inclusion:
- Hemoglobin < 8g/dL
- WBC < 2.0 $\times$ 10^3/mm^3
- Platelet count < 80 $\times$ 10^3/mm^3
- Glomerular filtration rates (GFR) <30ml/min.
- Transaminases > 3 times upper normal value

11.Use of the following systemic treatments during the specified periods:
- Treatment with any systemic alkylating agents within 12 months prior to inclusion (e.g., cyclophosphamide, chlorambucil)
- Any live (attenuated) vaccine within 4 weeks prior to inclusion.

12.Stage III and IV New York Heart Association (NYHA) cardiac insufficiency
13.Pregnancy or breastfeeding
14.Under legal protection
15.Participation in another interventional study involving human participants or in the exclusion period at the end of a previous study involving human participants, if applicable

1.3[6.3] ***Recruitment procedure***

The dynamism of the French national reference center for inflammatory ocular diseases and the French uveitis network, both of which sharing a strong experience as investigation centers for clinical studies regarding the treatment of inflammatory ocular conditions, together with the expected level of recruitment by these centers ensure the feasibility of this study. The French uveitis network (GMIO - Groupe français d'étude des Maladies Inflammatoires de l'Œil) conducted a recent study that evaluated the efficiency of anti-TNF therapy in NIU and recruited 250 patients in 1 year. We have enrolled more than 100 patients in a controlled randomized study in NIU (PHRC RUBI).

	Number of subjects
Total number of participants to be included	*120*
Number of ***recruitment centers***	*26*
Inclusion period (months)	*30*
Number of participants/center	*4.6*
Number of subjects/centre/month	***0.15***

[6.4] Termination rules

1.18.1[6.4.1] Criteria and procedures for prematurely terminating the study treatment

Several situations are possible
- Temporary suspension of treatment: the investigator must document the reason for suspending and resuming the treatment in the participant's source file and the case report form (CRF)
- Premature discontinuation of treatment, but the participant remains enrolled in the study until the end of their participation
- Premature discontinuation of treatment and withdrawal from the study

The investigator must:
- Document the reason(s)
- Collect the assessment criteria at the time of ending participation in the study, if the participant agrees
- Schedule a follow-up for the participant, particularly in case of a serious adverse event.

In the case of severe adverse events, the investigator must notify the sponsor and follow up the participant after the premature discontinuation of treatment for the duration of participation according to the research schedule. Notification of a serious adverse event must be sent by email (eig-vigilance.drc@aphp.fr) to the sponsor. The serious adverse event will be monitored until it is resolved. Since a Data Safety Monitoring Board has been created, the committee can specify and/or validate the follow-up methods.

If, during the course of his/her participation in the study, the participant presents one of the following exclusion criteria, then the study product/ must be discontinued but the participant will continue to be monitored for the study.

A subject must permanently discontinue the study treatment for any of the following criteria,:
- Pregnancy.
- During the study: Active tuberculosis TB, or positive IGRA results indicating latent TB and absence of compliance to a prophylactic TB treatment.
- Serious allergic (≥ grade 3) reaction to the study drug including anaphylactic reactions.
- Stevens Johnson syndrome.
- Increase of ALT and/or AST> grade 3
- Disease flare or worsening of ocular inflammation requiring another immunosuppressant and/or immunomodulator.
- Interruption of treatment > 30 days.
- Serious infections (grade > 3) .
- Anemia grade > 3, neutropenia grade >3, thrombocytopenia grade > 3
- Malignancy other than in situ cervix carcinoma, or adequately treated non-metastatic squamous cell or basal cell skin carcinoma.
- Multiple sclerosis or any other demyelinating disorder.
- HIV/AIDS, viral hepatitis (B or C) diagnosed during the study period.
- Consent withdrawal.

- Any condition that would place the subject at risk in case of treatment continuation.

1.18.2[6.4.2] Temporary interruption of the study treatment

Non-injection of Adalimumab (HUMIRA®) is permitted in the event of an intercurrent event requiring suspension of treatment, at the investigator's discretion. The continuation of the protocol treatment by Adalimumab (HUMIRA®) is possible if 1 injection have not been performed in this case.
The reason for interruption should be documented in the patient's study record.

1.18.3[6.4.3] Criteria and procedure for premature withdrawal of a participant from the study

- Participants may exit the study at any time and for any reason.
- The investigator can temporarily or permanently withdraw a participant from the study for any safety reason or if it is in the participant's best interests.
- Participant lost to follow-up: the participant cannot be located. The investigator must make every effort to reconnect with the participant (and document his attempts in the source file), at least to determine whether the participant is alive or dead

If a participant exits the study prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used.

- If a participant exits the study prematurely, and if the participant agrees, state the procedure and schedule for collecting the data required by the protocol (primary endpoint, secondary endpoints, safety assessment) (NB: this must be stated in the information and consent form)
- State how premature exit from the study will affect the participant's ongoing care (state exactly what the participant will be offered).
- In case of serious adverse events, see the corresponding section on vigilance

The case report form must list the various reasons why the participant has discontinued the study:

- ☐ Lack of efficacy
- ☐ Adverse reaction
- ☐ Another medical issue
- ☐ Personal reasons of the participant
- ☐ Explicit withdrawal of consent
- ☐ Lost to follow-up

1.18.4[6.4.4] Follow-up of participants following premature termination of study treatment

If a participant discontinues the study, this will in no way affect their usual care for their condition.
In the event of serious adverse events following premature discontinuation of treatment and participation of the patient in the study; see section 6.4.1

In case of premature treatment termination, the reason(s) must be clearly specified in the participant's medical records and on the appropriate page of the eCRF and follow up visits will take place according to the pre established protocol calendar until week 55 except in case of consent withdrawal and lost to follow-up.

The participant will receive the most appropriate care in all cases by his/her physician. Ending a participant's participation does not affect his/her normal management of the participant's illness in any way.

The adverse event reporting period for safety surveillance begins when the participant is included in the trial (date of inclusion and of the first administered of treatment) and continues through the trial's post treatment follow-up period, defined as week 55 (±3) days after last trial drug administration.

1.18.5[6.4.5] Follow-up of participants following premature withdrawal from the study

If a participant discontinues the study, this will in no way affect their usual care for their condition.
In the event of serious adverse events following premature discontinuation of treatment and participation of the patient in the study; see section 6.4.1.

1.18.6[6.4.6] Procedures for replacing participants

If a patient's consent is withdrawn, the data collected prior to the withdrawal will be used, except if the patient does not allow investigators to use the already collected data. If the study is still in the inclusion period and if the withdrawn implies that the primary outcome could not be analysed, a new patient will be included, otherwise all patients included will be analysed and not replaced (Intention to treat Analysis).

1.18.7[6.4.7] Full or partial discontinuation of the study

AP-HP as sponsor or the Competent Authority can prematurely discontinue all or part of the study, temporarily or permanently, further to the recommendations of the Data Safety Monitoring Board in the following situations:

- first of all, if suspected unexpected serious adverse reactions (SUSARs) are observed in one of the treatment arms or if there is a discrepancy in the serious adverse reactions between the two treatment arms, requiring a reassessment of the benefit-risk ratio for the study.

- if an interim analysis confirms the efficacy of one of the treatment arms or, alternatively, the lack of efficacy.

Similarly, AP-HP, as the sponsor, or the Competent Authority may decide to prematurely discontinue the study due to unforeseen issues or new information about the product, in light of which the objectives of the study or clinical programme are unlikely to be achieved.

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

In case the study is discontinued, the participants included in the study will be monitored until the end of their participation, as set forth in the protocol

If the study is prematurely discontinued for safety reasons, the decision and justification will be provided by the sponsor (AP-HP) to the Competent Authority and to the Ethics Committee without undue delay but not later than in 15 days of the date of the temporary halt or early termination. It shall include the reasons for such action and specify follow-up measures, along with recommendations from the Data Safety Monitoring Board in the case of substantial modification.

7. TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

1.4[7.1] Description of the investigational medicinal product(s)

Treatments will be labelled for this study according to the Good Manufacturing Practices by and under the responsibility of the DEC-AGEPS.

1.18.8[7.1.1] Investigational medicinal product 1 : Adalimumab - HUMIRA®

Presentation: The experimental drug administered will be Adalimumab (HUMIRA®) 40 mg solution for injection in pre-filled pen. Each 0.4 ml single dose pre-filled pen contains 40 mg of adalimumab.

Posology : The dose to be administered is 80mg at Day 0, then 40mg every 14 days from W1 to W35 subcutaneously (19 injections per patient).

For the elderly: No dosage adjustment is necessary.

In case the patient forgets an injection, he/she must perform it as soon as he/she realizes it, and within a maximum of 7 days. Then inject the next dose on the date originally scheduled.

Storage condition: Store in a refrigerator (between 2 ° C and 8 ° C). Do not freeze. Keep the pre-filled syringe or pre-filled pen in the outer carton in order to protect from light. A pre-filled pen of Humira can be kept at temperatures up to 25 ° C for up to 14 days at the time of use. away from light. After this period, the medicine should be discarded.

1.18.9[7.1.2] Investigational medicinal product 2 - Mycophenolate mofetil

Presentation : The experimental drug 2 administered will be mycophenolate mofetil 500 mg, box of 50 tablets for oral use.

Posology : The dose to be administered orally is 2 g per day (4 tablets of 500 mg per day) for 36 weeks. As mycophenolate mofetil has shown teratogenic effects in rats and rabbits, the tablets should not be crushed.

Patients will be treated orally, with4 tablets of 500 mg per day (2g/day) for 36 weeks (1008 tablets per patient).

Storage conditions : Store in its original package at a temperature not exceeding 30 ° C. Keep the blister in the outer carton in order to protect from light.

1.5[7.2] Description of Auxiliary medicinal products (treatments required to conduct the study

According to the Regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014, an auxiliary medicinal product is a medicinal product used in the context of a clinical trial but not as investigational medicinal product.

NIMP will not be provided by the Sponsor. They will be prescribed on a non-specific research prescription.

1.18.10[7.1.3] Auxiliary medicinal product 1: Systemic steroid therapy

All patients will receive the same corticosteroid regimen at inclusion. All patients will receive corticosteroids (10-35 mg/day) at inclusion.

The following schedule of reduction of prednisone (or ~~oral corticosteroid at equivalent~~ prednisone dose only if prednisone is out of stock in the market~~or if no prednisone is available use oral corticosteroid as a replacement for prednisone (equivalent dose)~~) will apply to both groups with a decrease until discontinuation between week 13 and week 19 as long as the disease is inactive:

	Prednisone dose at study entry						
Dose (mg/day)	35	30	25	20	15	12.5	10
35	Day 0 - Week 1						
30	2	Day 0 - Week 1					
25	3	2	Day 0 - Week 1				
20	4	3	2	Day 0 - Week 1			
15	5	4	3	2	Day 0 - Week 1		
12.5	6	5	4	3	2	Day 0 - Week 1	
10	7	6	5	4	3	2	Day 0 - Week 1
7.5	8	7	6	5	4	3	2
5	9	8	7	6	5	4	3
4	11	10	9	8	7	6	5
3	13	12	11	10	9	8	7
2	15	14	13	12	11	10	9
1	17	16	15	14	13	12	11
Discontinue	19	18	17	16	15	14	13

Dose (mg/day)	Prednisone dose at study entry (Or equivalent prednisone dose, if prednisone is out of stock in the market) 35	30	25	20	15	12.5	10
35	Day 0 - Week 1						
30	2	Day 0 - Week 1					
25	3	2	Day 0 - Week 1				
20	4	3	2	Day 0 - Week 1			
15	5	4	3	2	Day 0 - Week 1		
12.5	6	5	4	3	2	Day 0 - Week 1	
10	7	6	5	4	3	2	Day 0 - Week 1
7.5	8	7	6	5	4	3	2
5	9	8	7	6	5	4	3
4	11	10	9	8	7	6	5
3	13	12	11	10	9	8	7
2	15	14	13	12	11	10	9
1	17	16	15	14	13	12	11
Discontinue	19	18	17	16	15	14	13

Side effects of corticosteroids

These are related to the cumulative administered dose, ie the total amount taken from disease onset. There are several steroid-related side effects, but there are ways to reduce their intensity:

- Weight gain. Low-fat, low-sugar (rapidly absorbed carbohydrates) and low-salt diet is usually recommended.

- Abnormal behavior such as nervousness, irritability, tremors, insomnia, and bulimia for the highest doses.

- Cushing's syndrome with moon facies, linked to a change in fat distribution is usually observed at high doses.

- Hypertension and leg edema. Low-salt diet can reduce their incidence.

- Muscle wasting and cramping. These can be reduced with a potassium-rich diet (bananas, dried fruit...), potassium and protein supplementation and regular muscular exercise.

- Small vessel and capillary fragility. Ecchymoses and hematomata are common and can occur after minimal injury.

- The skin may also be affected by acne and delayed healing.

- Osteoporosis can occur after prolonged treatment. Supplementation with calcium and vitamin D associated with bisphosphonates reduces the theoretical risk of fracture.

- Infections are more common.

- Steroids can induce diabetes.

1.18.11[7.1.4] Auxiliary medicinal product 2: Fluorescein and indocyanin green (Retinal angiography)

All patients will receive a fluorescein and indocyanine green angiogram (FA/ICG) at selection, and week 36, and at W12 and W24 in case of vascularitis and/or chorioretinal lesions Examination at W36 is added by the research.
Products will be used according to their respective marketing authorization and angiogram made following local usual procedure

1.18.12[7.1.5] Auxiliary medicinal product 3: Prophylactic TB treatment

Prophylactic TB treatment including Rifampicin (300mg/day) and isoniazid (150mg/day) or isoniazid (150mg/day) will be prescribed for 3 or 6 months, respectively, in patients treated by Adalimumab with a positive interferon-gamma release assay (IGRA) (e.g.,QuantiFERON®-TB Gold or T-spot TB® Test) at inclusion.

1.6[7.3] Description of traceability elements accompanying the investigational medicinal product(s)

1.18.13[7.1.6] Supply

Shipments of labelled commercial boxes containing experimental drugs will be made by the Clinical Trials Department (DEC) of AGEPS to the hospital pharmacies within 5 working days.

There will be no initial stock of treatment at site opening.

Shipment of investigational drugs will be made following the first patient's screening visit in the center. The quantities sent will allow the first dispensing for both treatment arms.

1.18.14[7.1.7] Re-supply

After the patient's inclusion/randomization visit, an automatic order will be sent by the eCRF. The remaining patient's allocated treatment will be sent to the hospital pharmacy.

When another patient is selected on the site (at least 5 working days before inclusion/randomization, for the supply time). The necessity of a resupply will be evaluated by the Clinical Research Unit after contact with the center hospital pharmacy. If needed (according to patient arm previously randomized/expiry date of treatments on site/local remaining stock), a re-supply demand will be sent to the DEC-AGEPS for a new shipment.

The hospital pharmacy will confirm their receipt by completing the acknowledgment of receipt provided by the sponsor.

1.18.15[7.1.8] Dispensing

A maximum of eight dispensations (D0, W4, W8, W12, W16, W20, W24, W30) will be required per patient.

For investigational medicinal product 1 – HUMIRA ®

- At D0:

The PUIs will dispense two boxes of two pre-filled pens HUMIRA with a cooler bag and a waste collector for each patient in accordance with the specific research prescription completed and duly signed by the investigator.

- At W4, W8,W12, W16, W20, W24 and W30:

The PUIs will dispense one or two boxes of two pre-filled pens HUMIRA with a cooler bag and a waste collector for each patient in accordance with the specific research prescription completed and duly signed by the investigator.

For investigational medicinal product 2 – Mycophenolate mofétil

The PUIs will deliver the boxes of mycophenolate mofetil in accordance with the specific research prescription completed and duly signed by the investigator.

1.18.16[7.1.9] Administration and compliance

For investigational medicinal product 1 – HUMIRA ®

Treatment with Humira should be started and supervised by a qualified medical practitioner. After proper training in injection technique, patients can self-inject Humira.

After the first injection of two pre-filled pens, properly trained subjects can self-administer all subsequent doses at home every 14 days (one pre filled pen every 14 days). After each administration, the patient must fill his patient diary.

⇨ Administration schedule for HUMIRA 40 mg

Week	Number of pre-filled pen for administration of HUMIRA 40 mg
D0	2
W1	1
W3	1
W5	1
W7	1
W9	1
W11	1
W13	1

W15	1
W17	1
W19	1
W21	1
W23	1
W25	1
W27	1
W29	1
W31	1
W33	1
W35	1
TOTAL	20

In case the patient forgets an injection, he/she must perform it as soon as he/she realizes it, and with ain a ~~maximum~~minimum of 7 days ~~with. Then inject~~till the next dose on the date originally scheduled.

For investigational medicinal product 2 – Mycophenolate mofétil .

The administrations will be carried out in accordance with the instructions present on the ordinances Tablets of mycophenolate mofetil can be taken orally once daily at any time (2 g / day (4 tablets 500mg) orally for 36 weeks).

As mycophenolate mofetil has shown teratogenic effects in rats and rabbits, the tablets should not be crushed.

During his treatment, the patient the patient must fill his patient diary.

In case the patient forgets to take the treatment, he/she must take it as soon as he/she realizes it, then continue taking it as usual. Do not take a double dose to make up for the missed dose.

1.18.17[7.1.10] Method of monitoring compliance

All patients will receive subject diaries before starting the experimental treatment and the diaries will be the only ones allowed to document self-administration.

Patients should be instructed to bring all treatment packaging with them to each visit, including opened, empty and unused (full) treatment packaging, to allow assessment of patient adherence. The investigator will review the subject's diary at each hospital visit. At S20, a new diary will be given to the subject as needed. The exact time of investigational drug administration will be documented in the CRF. Treatment compliance will also be assessed by treatment accountability. All subject diaries should be stored with the medical file of the subject for reconciliation with the trial drug accountability.

1.18.18[7.1.11] Accountability and destruction

The study medication must be stored in accordance with the manufacturer's instructions. Pharmacists will also keep accurate records of the quantities of study medication dispensed and used for each patient.

Returns:

- for the HUMIRA group : The box(es) of HUMIRA must be returned by the patient in the cooler bag, to the PUI

- for the control group : The boxes of mycophenolate mofetil must also be brought back by the patient, ~~at these visits to the hospital~~to a local pharmacy.

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

1.7[7.4] Authorised and prohibited treatments (medicinal, additional medicinal, surgical), including rescue medications

1.18.19[7.4.1] Authorized treatments

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

To reduce the adverse effects associated with the use of steroids, the following supportive treatments can be administered routinely starting day 0 if needed:

- potassium supplementation (DIFFU K, 1 capsule 3 times/day).
- calcium/vitamin D supplementation (CACIT D3, 1 g/day).
- a bisphosphonate, in the absence of contra-indications, either risedronate at 35 mg/week or alendronate at 70 mg/week to be taken on an empty stomach with a large glass of water then remaining sitting or standing for 30 minutes.
- Low-fat, low-sugar (rapidly absorbed carbohydrates) and low-salt diet
- Topical treatment for cycloplegia is permitted.

1.18.20[7.4.2] Prohibited treatments

All systemic immununosuppressive or immunomodulatory therapies or biotherapy must have been discontinued prior to the first study drug administration (Day 0) and are contraindicated for the duration of the treatment, as long as the disease is inactive.

It is recommended that mycophenolate mofetil not be co-administered with azathioprine, as such a combination has not been studied.

In the absence of compatibility studies, HUMIRA should not be mixed with other drugs.

Additional Precautions with mycophenolate mofetil:

- Patients treated with mycophenolate mofetil should be advised to contact their physician immediately for any infection, unexplained bruising, bleeding, or other symptoms of bone marrow failure.

- Patients should be cautioned that while taking mycophenolate mofetil vaccinations may be less effective and that live attenuated vaccines should be avoided. Influenza vaccination may be helpful. Prescribers should refer to national influenza vaccination guidelines.

- Patients should not donate blood during treatment and for at least 6 weeks after stopping mycophenolate

- Men should not donate sperm during treatment and for at least 90 days after stopping mycophenolate.

Additional Precautions with HUMIRA:

- Patients taking Humira can receive several vaccines at the same time, except vaccines living. Treatment with Humira may lead to the formation of autoimmune antibodies. The impact of long-term treatment with Humira on the development of autoimmune diseases is unknown. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Humira and has a positive anti-dsDNA reaction, treatment with Humira should not be continued.

8. EFFICACY ASSESSMENT

1.8[8.1] Description of efficacy endpoints assessment parameters

The primary endpoint will be the treatment failure rate within 36 weeks. Treatment failure is defined by any of the following in at least one eye occurring at any point between inclusion and week 36 (included):

- new active, inflammatory chorioretinal or retinal vascular lesions;

- worsening of BCVA by >3 lines;

- 2-step increase in anterior chamber cell grade and/or in vitreous haze relative to baseline ~~and with steroid discontinuation between week 13 and week 19 (as per protocol) and without any additional immunosuppressive drug or injectable steroids.~~

- ~~N~~the absence of steroid discontinuation between week 13 and week 19 (as per protocol)
- or additional immunosuppressive drug or injectable steroids
- ~~. Study treatment permanent discontinuation~~

F~~f~~or the secondary endpoints, the different aspects of clinical response will be evaluated monthly from day 0 to week 36 and in W55. See chapter (4.1.2).

All patients that will not meet the failure definition will be considered as responders to the treatment

1.9[8.2] Anticipated methods and timetable for measuring, collecting and analysing the efficacy data

Physical examination will be performed by the patient's study physician at each visit.

Ophthalmic examination will be performed at 4, 8, 12, 16, 20, 24, 30, 36 and 55 weeks and will include:

- Mean change from baseline BCVA (SNELLEN score).

- Mean change from baseline anterior chamber tyndall and flare.
- Percentage of patients with anterior chamber score = 0 or at least 2-step reduction in score (tyndall and flare according to the Standardization of Uveitis Nomenclature (SUN) classification)
- Mean change from baseline vitreous haze.
- Mean change from baseline central retinal thickness measured with OCT.
- Proportion of patients with CRT <300 microns.
- Percentage of patients without retinal vessel leakage on fluorescein angiography.
- Uveitis relapse with date
- Quality of life assessment, using the National Eye Institute Visual Functioning Questionnaire-25 (VFQ-25) composite score

At each visit ESR, CRP, fibrinogen, haptoglobin, orosomucoid, CBC, creatinine, liver function tests (AST, ALT, GGT, total bilirubin, albumin), and glucose will be measured.

Safety will be assessed at each visit by the following outcome measures:

- Adverse events.
- Clinically significant changes compared to baseline in: vital signs including systolic blood pressure, diastolic blood pressure, pulse rate, temperature, and body weight.
- Clinically significant abnormal changes in laboratory parameters (hematology, chemistry, and urinalysis) compared to baseline
- Standard 12-lead ECGs will be performed at *Screening visit* after 10 minutes rest with the subject in the supine position, relaxed and not talking.. ECG abnormalities will be reported as adverse events if they are considered clinically significant by the investigator and if they are not related to any pre-existing condition or considered as a deteriorating sign of a pre-existing condition.
- Chest X-rays (frontal and lateral) will be performed at selection (unless performed within 12 weeks of Day 0) and the results will be recorded in the appropriate section of the eCRF. Chest X-ray abnormalities will be reported as adverse events if they are considered clinically significant by the investigator and if they are not related to any pre-existing condition or considered as a deteriorating sign of a pre-existing condition.
- Clinically significant abnormalities observed on optical coherence tomography.
- Intraocular pressure.

9. SPECIFIC STUDY COMMITTEES

1.10[9.1] Steering Committee

Members of the committee:

Investigator Coordonator *Pr Bahram BODAGHI*	*Ophtalmologist*	*Hospital Pitie Salpetriere*	*Tel. 0142163728* *Email: bahram.bodaghi@aphp.fr*
Scientific director *Pr David SAADOUN*	*Internist*	*Hospital Pitie Salpetriere*	*Tel.0142178088* *Email: david.saadoun@aphp.fr*
Methodologist *Pr Mathieu RESCHE-RIGON*	*Methodologist*	*APHP, Hôpital Saint-Louis*	*Tel 01 42 49 97 47* *Email: matthieu.resche-rigon@univ-paris-diderot.frmatthieu.resche-rigon@univ-paris-diderot.fr*
Nabil RAKED	*Project manager*	*DRCI-URC du GH saint Louis Lariboisière, site Saint Louis* *Hôpital Saint Louis*	*Tel. 01 42 49 97 49* *Email: nabil.raked@univ-paris-diderot.fr*
Breno MELO, PhD	*Project manager*	*DRCI-Head Office. Promotion* *Hôpital Saint Louis*	*Tel. 01 40 27 18 40* *Email: breno.melolima@aphp.fr*

• Missions: Define the overall structure of the study, coordinate information, determine the initial methodology and oversee the trial.

• Operating procedures: Propose procedures to be followed every 6 months during the study, acknowledging any recommendations from the Data Monitoring Committee. The sponsor retains the decision-making authority.

1.11[9.2] Scientific Committee

This committee will consist of the Coordinating Investigator (Pr Bahram BODAGHI CHU Pitié-Salpétrière), the scientific director (Pr David SAADOUN, CHU Pitié-Salpétrière), and a representative of the sponsor (Pr Mathieu Resche Rigon, Hôpital Saint Louis, Clinical Research Unit).
The scientific committee will meet regularly to determine the objective, write the protocol, recommend changes to the protocol during the trial, 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.

10. SAFETY ASSESSMENT - RISKS AND BURDEN ADDED BY THE STUDY

1.12[10.1] Description of Safety endpoints assessment parameters

Safety endpoints will overlap with efficacy (see as per item 4.1).

1.13[10.2] Anticipated methods and timetable for measuring, collecting and analysing the safety endpoints

See as per item 4.1

1.14[10.3] Recording and reporting adverse events

1.18.21[10.3.1] Definitions

According to Article 2 of the Regulation (EU) No 536/2014:

- **Adverse event**

Any untoward medical occurrence in a subject, to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment. .

- **Serious adverse event**

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

- **Unexpected serious adverse reaction**

A serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information.

According to Article 53 of the Regulation (EU) No 536/2014:

- **Unexpected event**

An unexpected event which affect the benefit-risk balance of the clinical trial, but are not suspected unexpected serious adverse reactions as referred to in Article 42. That notification shall be made without undue delay but no later than 15 days from the date the sponsor became aware of this event.

According to Article 54 of the Regulation (EU) No 536/2014:

- **Urgent safety measure**

Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects.

The sponsor shall notify the Member States concerned, through the EU portal, of the event and the measures taken.
That notification shall be made without undue delay but no later than seven days from the date the measures have been taken.

1.18.22[10.3.2] The role of the investigator

The investigator must **assess the seriousness of each adverse event** and record all serious and non-serious adverse events in the case report form (eCRF).
The investigator must **document** serious adverse events **as thoroughly as possible** and provide a definitive medical diagnosis, if possible.

The investigator must **assess the intensity** of the adverse events:
- either by using a rating scale for adverse events : *Common Terminology Criteria for Adverse Events [National Cancer Institute]*/I

The investigator must **assess the causal relationship** between serious adverse events and the investigational medicinal product(s), or interventions/procedures added by the study.

The method used by the investigator is based on 2 causality terms (EVCTM method):
- Related
- Not related

.

1.18.22.1[10.3.2.1] Serious adverse events that require the investigator to notify the sponsor without delay

The investigator notifies the sponsor without undue delay but not later than within 24 hours on the day the investigator becomes aware of any serious adverse event which occurs during a study that meets the description in article 41 of Regulation (EU) N°536/2014, with the exception of any event which is listed in the protocol and, if applicable, in the investigator's brochure as not requiring notification.

A serious adverse event is any untoward medical occurrence that:

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

Medication errors, pregnancies and uses outside what is foreseen in the protocol, including misuse and abuse of the product, require the investigator to notify the sponsor without delay.

1.18.22.2[10.3.2.2] Specific features of the protocol

1.18.22.2.1[10.3.2.2.1] Other events that require the investigator to notify without delay the sponsor

- **Adverse events deemed "medically significant"**

The following events are of special interest with respect to the evaluation of study drug safety and should be closely monitored, documented, and notified immediately to the Sponsor:

- Serious allergic study drug reaction including anaphylactic reaction of grade 3 and 4 CTCAE.
- Neutropenia (defined as absolute neutrophil count [ANC] < 0.5 x 10^9/L).
- Autoimmune and demyelinating disorders regardless of the seriousness of the events.
- Malignancy.
- HIV/AIDS, viral hepatitis (B or C) diagnosed during the study.
- Tuberculosis diagnosed during the study.
- Skin cancer.
- Stevens Johnson syndrome.
- Increase of ALT and/or AST > 5N
- Gastro-intestinal perforation and diverticulitis.

The investigator must notify the sponsor **without delay** on the day the investigator becomes aware of these adverse events, in the same manner and within the same deadline as for serious adverse events (see above).

- ***In utero* exposure**

Pregnancy test for all childbearing women is performed at inclusion and throughout the follow-up.

The investigator must notify the sponsor without delay on the day the investigator becomes aware of any pregnancy that occurs during the study, even if it is not associated with an adverse event.
If the investigational medicinal product is genotoxic, every case of maternal or paternal exposure must be notified.

- Exposure **while breastfeeding**

Exposure while breastfeeding occurs if an infant or a child may have been exposed to a medicinal product *via* the breast milk of a mother being treated with an investigational medicinal product.
Even if it is not associated with an adverse event, the investigator must notify the sponsor without delay on the day the investigator becomes aware of the exposure while breastfeeding.

1.18.22.2.2[10.3.2.2.2] Serious adverse events that do not require the investigator to notify the sponsor without delay

These serious adverse events are only recorded in the case report forms.

- *Normal and natural course of the condition*:

- Scheduled hospitalization to monitor the disease being studied.

- hospitalization for routine treatment or monitoring of the disease being studied not associated with a deterioration of the subject status.

- *Special circumstances*

In some circumstances, investigators can delay the report of adverse events. For example: hospitalization for a preexisting condition, hospitalization for medical or surgical treatment before the research, emergency room assessment lower than 12 hours, hospitalization for a social or administrative reason.

- *Adverse events potentially related to authorized auxiliary medicinal products and related to treatments prescribed as part of the care provided during the study follow-up*

The investigator must report these adverse events to the relevant regional pharmacovigilance centre, Centre Régional de Pharmacovigilance (CRPV).

1.18.22.3[10.3.2.3] Period during which SAEs must be notified without delay by the investigator to the sponsor

The investigator must notify the sponsor without delay of any serious adverse events as defined in the corresponding section:
- from the date on which the participant signs the consent form
- throughout the whole follow-up period required for the trial
- until the end of the study for the participant
- indefinitely, if the SAE is likely to be due to the investigational medicinal product or to the study interventions (e.g. serious reactions that could appear long after exposure to the medication, such as cancers or congenital abnormalities)

1.18.22.4[10.3.2.4] Procedures and deadlines for notifying the sponsor

The initial notification of an SAE must be provided in a written report signed by the investigator using a SAE notification form specific to the study and intended for this purpose (in the case report form).

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

The initial notification to the sponsor of a serious adverse event must be quickly followed by an additional detailed written report (or reports) so that the case outcome may be monitored by the Safety Department or to provide further information.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results from additional examinations, etc.). These documents must be non-identifying. In addition, the documents must include the following: study acronym, number and participant's initials.

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 participant has left the study.

The initial notification, the SAE follow-up reports and all other documents must be sent to the sponsor's Safety Department by email (eig-vigilance.drc@aphp.fr). It should be noted that it is possible to send SAE reports to the Safety Department by fax to +33 (0)1 44 84 17 99 only in the event of a failed attempt to send the SAE report by email (in order to avoid duplication).

For studies which use e-CRFs
- the investigator completes the SAE notification form in the e-CRF, then validates, prints, and signs the form before sending it by email;
- if it is not possible to connect to the e-CRF, the investigator should complete, sign, and send the SAE notification form to the Safety Department. As soon as the connection is restored, the SAE notification form in the e-CRF must be duly completed.

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

For cases of ***in utero* exposure**, the investigator will complete the Notification and Follow-up form for a pregnancy occurring during participation in a study".
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 SAEs.
The initial pregnancy notification, the SAE follow-up reports, and any other documents will be sent to the sponsor according to the same procedures specified herein.
If it was the father who was exposed, the investigator must obtain the pregnant woman's permission before collecting information about the pregnancy.

1.18.23[10.3.3] Role of the sponsor

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

1.18.23.1[10.3.3.1] Analysis and declaration of serious adverse events

The sponsor assesses:
- the **seriousness** of all the adverse events reported
- the **causal relationship** between these events and each investigational medicinal product and any other treatments,
  All serious adverse events which the investigator and/or the sponsor reasonably believe may have a causal relationship with the investigational medicinal product are classed as suspected serious adverse reactions.
- the **expected or unexpected nature** of the serious adverse reactions
  Any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the summary of product characteristics, or in the investigator's brochure if the product is not authorised, is considered unexpected.
  The sponsor, represented by its Safety Department, assesses the expected/unexpected nature of a serious adverse reaction based on the information described below**.**

❖ For serious adverse events likely to be related to the investigational medicinal product(s):

- refer to the SmPC for Humira® (see EMEA website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000481/human_med_000822.jsp&mid=WC0b01ac058001d124; https://www.ema.europa.eu/en/documents/product-information/humira-epar-product-information_fr.pdf) and for Cellcept® (see EMEA website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000082/human_med_000688.jsp&mid=WC0b01ac058001d124 ; https://www.ema.europa.eu/en/documents/product-information/cellcept-epar-product-information_fr.pdf).

- For serious adverse events likely to be related to additional medicinal products (treatments required for the trial):
  - refer to the SmPC for the specialities of prednisone, isoniazid and rifampicin administered,

- For serious adverse events likely to be related to other study procedure
  - tapering-of corticosteroids: relapse of disease activity.
  - use of contrast medium : allergy . Refer to the SmPC of the contrast medium (such as Fluoresceine Sodique Faure® (fluorescein) and Infracyanine® (indocyanine green) for retinal angiography)

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs) via Eudravigilance, within the regulatory time frame, to the competent authority:
- in the case of fatal or life-threatening suspected unexpected serious adverse reactions, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction;
- in the case of non-fatal or non-life-threatening suspected unexpected serious adverse reactions, not later than 15 days after the sponsor became aware of the reaction;
- in the case of a suspected unexpected serious adverse reaction which was initially considered to be non-fatal or nonlife threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction being fatal or life-threatening
- in the uncompleted case of fatal or life-threatening suspected unexpected serious adverse reactions, all additional information to complete this case have to be reported as soon as possible and in any event not later than eight days after the initial report
- All additional, relevant information must be declared by the sponsor in the form of follow-up reports within a period of 15 days starting from when the sponsor had this information.

The sponsor must notify all the investigators involved about any information that could adversely affect the safety of the research participants.

1.18.23.2[10.3.3.2] Analysis and declaration of other safety data

This means any new information that prompts a reassessment of the risk/benefit ratio of the trial or of the product under investigation, or which could be sufficient to consider changes to the use of the product, the trial procedures or trial documentation, or the suspension, cancellation or amendment of the research trial or of other similar trials. For trials involving the first administration or use of a health product in healthy volunteers: any serious adverse reaction.

The sponsor will inform report in CTIS platform and to ANSM the competent authority and the Research Ethics Committee without delay upon knowledge of any emerging safety issue and, if applicable, describe what measures have been taken.

Following the initial declaration of any emerging safety issue, the sponsor will address to competent authorities any additional relevant information about the emerging safety issue in the form of a follow-up report, which must be sent no later than 8 days after learning of the information.

1.18.23.3[10.3.3.3] Annual safety report

Once a year for the duration of the clinical study, the sponsor must produce an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:
- a safety analysis for the research participants,
- a description of the patients included in the study (demographic profile etc.)
- a list of all the suspected serious adverse reactions that occurred during the period covered by the report,
- summary tables of all the serious adverse events that have occurred since the start of the study,

The sponsor produce one annual safety report (Development Safety Update Report - DSUR) for one clinical trial.

The report must be submitted in CTIS no later than 60 days after the anniversary of the date on which the competent authority authorised the trial.

1.18.24[10.3.4] Data Safety Monitoring Board (DSMB)

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

The DSMB must hold its first meeting before the first participant is enrolled and ideally before the protocol is submitted to the competent authority and the Ethics Committee.

The DSMB members are:
- Pr DE SMET Marc (Lausanne, mddesemet1@mac.com; doctors@retina-uveitis.eu)
- Dr DELLAL Azeddine (GHI Le Raincy - Montfermeil) : azeddine.dellal@ght-gpne.fr
- Dr BELFEKI Nabil (GH Sud Île de France - Melun) : nabil.belfeki@ghsif.fr
- Dr CAILLE Agnès (Méthodologiste:Univ Tours): agnes.caille@univ-tours.fr

All missions as well as the specific operating procedures of the DSMB are described in the study's DSMB charter.

The DSMB will operate in accordance with the sponsor's procedures. The DSMB works in an advisory capacity only and the sponsor retains all decision-making authority.

11. DATA MANAGEMENT

1.15[11.1] Identification of data recorded directly in the CRFs which will be considered as source data

Not applicable

1.16[11.2] Right to access source data and documents

1.18.25[11.2.1] Data access

In accordance with GCPs and appendix 1 of the European Regulation N°536-2014:
- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures or inspections by the competent authority
- the Sponsor declares that investigators and participating institution will ensure the persons in charge of monitoring, quality control and auditing or inspecting the interventional study involving human participants clinical trial have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

1.18.26[11.2.2] Source documents

Source documents are defined as any original document or item that can prove the existence or accuracy of a data or a fact recorded during the study study (medical file, original biological examination results, summary from imaging examinations, etc.). These documents will be kept in accordance with the regulations in force by the investigator or by the hospital in the case of a hospital medical file.

1.18.27[11.2.3] Data confidentiality

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the Code de la Santé Publique [French Public Health Code]) will take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular their identity and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the Code Pénal [French Criminal Code]).
During and after the research involving human participants clinical trial, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be rendered non-identifying.
Under no circumstances shall the names and addresses of the participants involved be shown.
Only the participant’s initials will be recorded, accompanied by an encoded number specific to the study indicating the order of enrolment.
The sponsor will ensure that each participant has given written permission for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

1.17[11.3] *Data processing and storage of research documents and data*

Data will be collected on an E-CRF, with data entry performed in each center by Clinical research assistants (CRA) and/or physicians. Monitoring of the data will be performed by

CRA under the supervision of the URC and DRCI. Statistical analysis will be performed by Pr Matthieu Resche-Rigon, Saint Louis hospital, Paris.

1.18[11.4] Data entry

Data will be entered electronically via a web browser. Non-identifying data will be entered electronically via a web browser.

1.19[11.5] Data ownership

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

12. STATISTICAL ASPECTS

We will use a group sequential two-arm randomized comparative design with one interim analysis at 50% of completed primary observations, with efficacy and futility (non-binding) early stopping rules (O'Brien & Fleming spending functions).

1.20[12.1] Description of statistical methods to be used including the timetable for the planned interim analyses

The following analysis sets will be considered:

- *Intent-to-treat*: Includes all randomized subjects. This will refer to the primary analyses.
- *Per protocol set*: Includes all subjects from the intent-to-treat set without any major violations which could affect the evaluation of the primary efficacy endpoint. This will be used as secondary, exploratory or sensitivity analyses.
- *Safety set*: Includes all subjects who take any amount of any study drug.

As a general strategy, continuous efficacy and safety endpoints will be summarized using summary measures (median and interquartile range). Frequency distributions (counts and percentages) will be used to summarize categorical endpoints. Similarly, characteristics of patients will be presented using summary measures (median and interquartile range for quantitative characteristics and counts and percentages for categorial characteristics). Analyses by treatment group will be presented according to the treatment to which subjects were randomized.

An interim analysis is planned at half of the inclusions, i.e. 60 patients.

Primary endpoint:

Primary endpoint will be compared based on the intent-to-treat set using fisher exact test. The critical values to conclude on efficacy or futility are given below (12.2)

Secondary endpoint

- Time to treatment failure up to W55 will be estimated using Kaplan Meier estimator compare between arms using Logrank test. Intent-to-treat set will be used.

- logMAR BCVA in each eye, at W4, W8, W12, W16, W20, W24, W30, W36 and W55 will be compare between arms using linear random effect model and Wald test. Intent-to-treat set will be used.

- Anterior chamber cell grade in each at W4, W8, W12, W16, W20, W24, W30, W36 and W55 will be compare between arms using linear random effect model and Wald test. Intent-to-treat set will be used.

- Vitreous haze grade (SUN criteria) in each eye at W4, W8, W12, W16, W20, W24, W30, W36 and W55 will be compare between arms using linear random effect model and Wald test. Intent-to-treat set will be used.

- Central retinal thickness in each eye from baseline at W4, W8, W12, W16, W20, W24, W30, W36 and W55 will be compare between arms using linear random effect model and Wald test. Intent-to-treat set will be used.

- Proportion of patients with central macular thickness< 300 microns at W4, W8, W12, W16, W20, W24, W30, W36 and W55 will be compare between arms using logistic random effect model and Wald test. Intent-to-treat set will be used.

- Time to optical coherence tomographic (OCT) evidence of macular edema in at least one eye, up to W55 will be estimated using Gray cumulative incidence estimator. It will be compared between arms with the Gray test to compare cumulative incidence.

- NEI Visual Functioning Questionaire-25 (VFQ-25) composite score, at W12, W24, and W36 will be compare between arms using linear random effect model and Wald test. Intent-to-treat set will be used.

- Measures of corticosteroid sparing (e.g., percent meeting targets [<0.1 mg/kg/day prednisone], mean change, mean dose at week 55, and cumulative dose) will be compare between arms using Fisher exact test and t-tests respectively. Intent-to-treat set will be used.

- Cumulative incidence of relapse and number of relapses up to W55 will be estimated using Gray cumulative incidence estimator. It will be compared between arms with the Gray test to compare cumulative incidence. Intent-to-treat set will be used.

- Other clinical manifestations of underlying disease (depending on the underlying disease) will be evaluated up to W55 will be described by arms.

- Safety and tolerability of treatments as assessed by the frequency and severity of adverse events and treatment discontinuation from baseline to Week 55 will be compared between arms using either Fisher exact test or Wilcoxon test according to the variables. Safetset will be used.

1.21[12.2] Calculation hypotheses for the number of participants required and the result

The study will use a group sequential two-arm randomized comparative design with one interim analysis at 50% of completed primary observations, with efficacy and futility early stopping rules.

Specifically, assuming a probability of treatment failure (primary endpoint) of 50% in the SoC control population versus 20% under the alternative hypothesis with adalimumab[11,12,] , a total maximum number of 106 patients (53 per randomization arm) is required to ensure 90% power with a 2.5% one-sided type I error risk, accounting for one interim analysis after 50% of primary observations are complete and using Lan & DeMets O'Brien & Fleming-type risk-spending functions[26,27] to define efficacy and futility (non-binding) early stopping rules. Moreover, we plan to include a total of 120 patients (60 per randomization arm) to account for potential 10% of lost-to-follow-up. Sample size calculation has been performed with the *rpact* R-package.

The corresponding critical values of the design for this design are given below. The first values correspond to the interim analysis that will be performed after inclusion of the first 60 patients.

```
Design parameters:

  Information rates                       : 0.500, 1.000

  Critical values                         : 2.963, 1.969

  Futility bounds (non-binding)           : 0.267

  Cumulative alpha spending               : 0.001525, 0.025000

  Local one-sided significance levels     : 0.001525, 0.024500

  Significance level                      : 0.0250

  Type II error rate                      : 0.1000

  Test                                    : one-sided
```

1.22[12.3] Anticipated level of statistical significance

The Anticipated level of statistical significance of the primary endpoint analysis is 0.025 for a one-sided test. All other tests will be performed with a 0.05 level of statistical significance and two-sided formulation.

1.23[12.4] Statistical criteria for termination of the study

An interim analysis is planned at half of the inclusions, i.e. 60 patients. The critical values to stop either for efficacy or futility are given above.

1.24[12.5] Method for taking into account missing, unused or invalid data

In case of missing data, complete case analyses will be performed. Confirmatory analyses will be performed by using multiple imputation by chained equation or using joint Bayesian modelling to impute outcome as well as missing characteristics.

13. QUALITY CONTROL AND ASSURANCE

Every clinical trial sponsored by AP-HP is ranked according to the projected risk incurred by study participants using the classification system specific to AP-HP sponsored clinical trial.

1.25[13.1] General organisation

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the study. The sponsor must implement a quality assurance system to best monitor the implementation of the study in the investigation centres.

For this purpose, the sponsor shall assign Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the study locations, after having carried out the initial visits.
The purpose of monitoring the study, as defined in Good Clinical Practices (GCP section 5.18.1), is to verify that:

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

1.18.28[11.2.4] Strategy for center opening

The strategy for opening the centers established for this study is determined using the appropriate monitoring plan.
The opening of the different participating center will be performed on site by the CRA from the URC-DRCI from Saint Louis hospital.

1.18.29[11.2.5] Scope of center monitoring

In the case of this C risk study the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Therefore, in agreement with the coordinating investigator, the sponsor has determined the logistical score and impact, resulting in a study monitoring level to be implemented: Intermediate Risk level

These various levels are defined in the monitoring charter for research involving human participants

1.18.30[11.2.6] Quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the good completion of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI (Clinical Research and Innovation Department) and in accordance with Good Clinical Practices as well as the statutory and regulatory requirements.

The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits carried out by the Clinical Research Associate. During these visits, the following elements will be reviewed depending on the monitoring level:

- 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

1.26[13.2] Case Report Form

All information required by 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. Any missing data must be coded.
Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given a document offering guidance on using this tool.
When the investigators complete the case report form 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. To this end, the investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment.
The investigator must archive a copy of the authenticated document that was issued to the sponsor.

1.27[13.3] Management of non-compliances

Any events that occur as a result of non-compliance – by the investigator or any other individual involved in running the study – with the protocol, standard operating procedures, good clinical practices or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.

These non-compliances will be managed in accordance with the sponsor's procedures.
The sponsor shall notify the Member States concerned about a serious breach of this Regulation or of the version of the protocol applicable at the time of the breach through the EU portal without undue delay but not later than seven days of becoming aware of that breach.

1.28[13.4] Audits/inspections

The investigators agree to consent to 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. These audits and inspections cannot be refused on the grounds of medical secrecy.
An audit can be carried out at any time by individuals appointed by the sponsor and independent of those responsible for the research. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage 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 encompass all stages of the study, from the development of the protocol to the publication of the results, including the storage of the data used or produced as part of the study.

1.29[13.5] Principal Investigator's commitment to assume responsibility

Before starting the study, each investigator will give the sponsor's representative a copy of his/her updated personal curriculum vitæ, signed and dated less than one year, with his/her RPPS number (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals). The CV must include any previous involvement in clinical research and related training.
Any conditions, such as economic interests and institutional affiliations that might influence the impartiality of the investigators shall be presented.

Each investigator will commit to comply with legislation and to conduct the study in line with GCP, in accordance with the Declaration of Helsinki. Each investigator will give the sponsor's representative a GCP certificate dated fewer than three years ago.

The Principal Investigator at each participating site will sign a commitment of responsibility (standard DRCI document) which will be sent to the sponsor's representative.
The investigators and their staff will sign a delegation of duties form specifying each person's role and will provide their CVs.

1.30[13.6] Suitability of the facilities

Before starting the study, each clinical trial sites will give the sponsor's representative a duly justified written statement on the suitability adapted to the nature and use of the investigational medicinal product and including a description of the suitability of facilities, equipment, human resources and description of expertise.

1.31[13.7] Commitment to the pharmacist's responsibilities

The DEC-AGEPS will ensure the purchase, packaging and distribution of the various research MEs and will put in place the traceability elements necessary to ensure the traceability of pharmaceutical activities (supply, dispensing and destruction).

The pharmacist of each center participating in the research will sign a delegation form specifying his role.

14. ETHICAL AND LEGAL CONSIDERATIONS

1.32[14.1] Methods for informing research participants and obtaining their consent

According to article 29 of European regulation N°536/2014, No clinical trials on medicinal products for human use can be carried out on a person without his/her freely given and informed consent, obtained in writing after the person has been given the information specified in article 29.2 of the European Regulation

A reflection period is given to the individual between the time he/she receives the information (at the screening visit) and the time he/she agrees to sign the consent form (at the baseline/inclusion/randomization visit).

The person's freely-given, written, informed consent will be obtained by the principal investigator or a physician representing the investigator before the person is enrolled in the study at the inclusion/randomization visit.

A copy of the information note and consent form, signed and dated by the research participant and by the principal investigator or the physician representing the investigator will be given to the individual prior to their participation in the study. The principal investigator or the physician representing him/her will keep a 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.

In addition, the investigator will specify in the person's medical file the person's participation in the research, the procedures for obtaining his/her consent as well as the methods used for providing information for the purpose of collecting it. The investigator will retain one copy of the signed and dated consent form.

1.33[14.2] Prohibition from participating in another clinical study or exclusion period set after the study

An exclusion period of participation after the participant has finished this study is defined in the context of this research. It will last for 3 months

The participant may not enrol in another interventional study protocol involving human participants for the duration of his or her participation without consulting with the physician monitoring him or her in the context of the study.

The participants can however participate in other non-interventional studies

1.34[14.3] Compensation for participants

Each participant will receive financial compensation for transportation costs for the 4, 8, 16, 20 and 30 weeks visits. A flat rate of 50 euros maximum (for the round trip) for patients included in Ile de France and 150 euros maximum (for the round trip) for patients included in the others districts.

1.35[14.4] Registration on the National Register of study participants to studies involving human participants concerning the products mentionned in Article L. 5311-1 of the Code de la santé publique

Not applicable.

1.36[14.5] Authorisation for the research location

In France, the study will be carried out in treatment units on individuals presenting a clinical condition for which the units are specialised and who require interventions that are routinely performed at those units. Therefore, the research location does not require specific authorisation.

1.37[14.6] Legal obligations

1.18.31[14.1.1] Role of the sponsor

Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this study and, by delegation, the DRCI (Clinical Research and Innovation Department) carries out the study's missions in accordance with regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014 and all national Laws. 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.

1.18.32[14.1.2] Request for approval from the CPP (Research Ethics Committee)

Prior to starting the study, AP-HP, as sponsor, must obtain for this interventional study involving human participants concerning a medicinal product for human use, approval from the appropriate CPP (Research Ethics Committee), within the scope of its authority and in accordance with in force legislation and regulatory requirements.

1.18.33[14.1.3] Request for authorisation

Prior to starting the study, AP-HP, as sponsor, must obtain authorisation from the Competent Authority and the Research Committee for this clinical trial on medicinal product for human use within the scope of its authority and in accordance with in force legislation and regulatory requirements.

1.18.34[14.1.4] Procedures relating to data protection regulations

The computer file used for this research is implemented in accordance with French (amended “Informatique et Libertés” law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.

- Commitment to comply with “Reference Methodology” MR-001

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”

1.18.35[14.1.5] Start of the Clinical Trial

The sponsor shall notify each Member State concerned of the start of a clinical trial and the start of the recruitment through the EU portal. That notification shall be made within 15 days from the start of the clinical trial.

1.18.36[14.1.6] Amendments to the Clinical 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 approval from the Ethics Committee) and authorisation from the competent authority within the scope of their respective authorities, before the amendment can be implemented.
The information note and the consent form can be revised if necessary, in particular in case of a substantial amendment to the study or if adverse reactions occur

1.18.37[14.1.7] End of the Clinical Trial

The end of the Clinical Trial corresponds to the end of the participation of the last person who participate to the Clinical Investigation.

The end of the recruitment of subjects for the clinical trial and the end of the clinical trial should be notified in CTIS. That notification shall be made within 15 days from the end of the clinical trial in relation to that Member State.

1.18.38[14.1.8] Summary of the results of the clinical trial

According to article 37.4 of the European regulation n°536/2014, irrespective of the outcome of a clinical trial, within one year from the end of a clinical trial in all Member States concerned, the sponsor shall submit to the CTIS a summary of the results of the clinical trial. This summary shall be accompanied by a summary written in a manner that is understandable to laypersons.

1.18.39[14.1.9] Archiving

Specific documents for a clinical trial on medicinal product for human use will be archived by the investigator and the sponsor for 25 years after the end of the research.
This indexed archiving includes, in particular:

- A sealed envelope for the investigator containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- A sealed envelope for the sponsor, containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- "Study" binders for the Investigator and the sponsor, including (non-exhaustive list):
  - the successive versions of the protocol (identified by the version number and its date), and any appendices
  - the competent authority authorisations and Research Ethics Committee decisions
  - any correspondence
  - the enrolment list or register
  - the appendices specific to the research
  - final study report
- The data collection documents

15. FUNDING AND INSURANCE

1.38[15.1] Funding sources

PHRC 2020 (Hospital Funding for Clinical Research)

1.39[15.2] Insurance

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own public liability, as well as the public liability for all the physicians involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the participant enrolled and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator. Compensation cannot be refused on the grounds of a third-party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique-Hôpitaux de Paris (AP-HP) has taken out insurance with HDI-GLOBAL SE through the insurance broker BIOMEDIC-INSURE for the full study period, which covers its own public liability and that of any collaborator (physician or research staff), in accordance with Article 76(1) of regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014 and Article L.1121-10 of the *Code de la Santé Publique* (French Public Health Code).

16. PUBLICATION RULES

The author(s) of any publication relating to this study must include the AP-HP among their affiliations and must name the sponsor AP-HP (DRCI) and the source of funding, if funded by a call for tenders (e.g. national or regional PHRC); a copy of the publication must be sent to the sponsor (see below for rules governing affiliation, and naming of the sponsor and funders.

1.40[16.1] Mention of AP-HP affiliation for projects sponsored by AP-HP

- If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is unimportant
- However, if the study is funded in the context of an internal AP-HP call for tender, the first affiliation must be "AP-HP"
- Each of these affiliations must be identified by an address and separated by a semicolon (;)
*- The AP-HP institution must feature under the acronym "**AP-HP**" first in the address, specifically followed by: **AP-HP**, hospital, department, city, postcode, France*

1.41[16.2] Mention of the sponsor AP-HP (DRCI) in the acknowledgements of the text

- "The sponsor was Assistance Publique – Hôpitaux de Paris (Direction de la Recherche Clinique et de l'Innovation)"

1.42[16.3] Mention of the financial backer in the acknowledgements of the text

The research was funded by a grant from Programme Hospitalier de Recherche Clinique – PHRC 2020 (Ministère de la Santé)

This study has been registered on the website http://clinicaltrials.gov/ under number *(add the registration number when the study is registered)*.

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18. LIST OF ADDENDA

1.43[18.1] List of Investigators

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1.44[18.2] Serious Adverse Events notification form

Direction de la Recherche Clinique et de l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS **Formulaire de notification d'un Evènement Indésirable Grave (EIG) survenant au cours d'une recherche impliquant la personne humaine portant sur un Médicament ou produit assimilé**	**PARTIE RÉSERVÉE AU PROMOTEUR** **REFERENCE VIGILANCE :** Référence GED : REC-DTYP-0192

Dès la prise de connaissance de l'EIG par l'investigateur, ce formulaire doit être dûment complété (4 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par mail (eig-vigilance.drc@aphp.fr)
Il est possible de transmettre les formulaires de notification d'EIG au secteur Vigilance par télécopie au +33 (0)1 44 84 17 99 uniquement en cas de tentative infructueuse d'envoi par mail afin d'éviter les doublons

Notification initiale ☐ **Suivi d'EIG** ☐ **N° du suivi** |__|__|

1. Identification de la recherche

Acronyme : **FOCUS**

Code de la recherche : **APHP211032**

Risque : C

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

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

Titre complet de la recherche :
"Randomized controlled multicenter study comparing efficacy and safety of adalimumab to that of mycophenolate mofetil in steroid dependent non-infectious uveitis" / **FOCUS:** treatment **FO**r Corticosteroid dependent **U**veiti**S**

2. Identification du centre investigateur

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

Investigateur (nom/prénom) : .....
Tél : ..... Fax : .....
E-mail : .....

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

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

Sexe : ☐ M ☐ F

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

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

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

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

Date d'inclusion/ randomisation : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

☐ Groupe adalimumab ☐ Groupe mycophenolate mofetil

4. Médicament(s) expérimental(aux) (ME) avant la survenue de l'EIG
(barrer l'encadré si traitement non débuté)

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie[1]	Posologie (préciser l'unité ex : mg/j)	Date de début *(jj/mm/aaaa)*	En cours[2]	Date de fin *(jj/mm/aaaa)*
☐ Humira® ☐ NA	.....	.....	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|
☐ Mycophénolate mofétil ~~Cellcept®~~ ☐ NA	.....	.....	|__|__| |__|__| |2|0|__|__|	☐	|__|__| |__|__| |2|0|__|__|

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser) (2) En cours au moment de la survenue de l'EIG

PARTIE RÉSERVÉE AU PROMOTEUR
RÉFÉRENCE VIGILANCE :
Référence GED : REC-DTYP-0192

Acronyme : **Erreur : source de la référence non trouvéeFOCUS**

Référence de la personne se prêtant à la recherche : |__|__|__| - |__|__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

5. Médicament(s) nécessaire(s) à la réalisation de la recherche ou produit(s) assimilé(s) avant la survenue de l'EIG *(barrer l'encadré si traitement non débuté)*					
Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie(1)	Posologie (préciser l'unité ex : mg/j)	Date de début *(jj/mm/aaaa)*	En cours(2)	Date de fin *(jj/mm/aaaa)*
CORTICOTHERAPIE					
Prednisone (ou équivalent si prednisone ~~non disponible~~en rupture de stock sur le marché) , nom de spécialité (à préciser s'il vous plait) : ………………………………………………	………	………	|__|__| |__|__| |2_|0_|__|__|	☐	|__|__| |__|__| |2_|0_|__|__|
	………	………	|__|__| |__|__| |2_|0_|__|__|	☐	|__|__| |__|__| |2_|0_|__|__|
	………	………	|__|__| |__|__| |2_|0_|__|__|	☐	|__|__| |__|__| |2_|0_|__|__|
	………	………	|__|__| |__|__| |2_|0_|__|__|	☐	|__|__| |__|__| |2_|0_|__|__|
	………	………	|__|__| |__|__| |2_|0_|__|__|	☐	|__|__| |__|__| |2_|0_|__|__|
	………	………	|__|__| |__|__| |2_|0_|__|__|	☐	|__|__| |__|__| |2_|0_|__|__|
	………	………	|__|__| |__|__| |2_|0_|__|__|	☐	|__|__| |__|__| |2_|0_|__|__|
	………	………	|__|__| |__|__| |2_|0_|__|__|	☐	|__|__| |__|__| |2_|0_|__|__|
PROPHYLAXIE ANTI-TB ☐ NA					
Rifampicine, nom de spécialité (à préciser s'il vous plait) : ………………………………………………	………	………	|__|__| |__|__| |2_|0_|__|__|	☐	|__|__| |__|__| |2_|0_|__|__|
Isoniazide, nom de spécialité (à préciser s'il vous plait) : ………………………………………………	………	………	|__|__| |__|__| |2_|0_|__|__|	☐	|__|__| |__|__| |2_|0_|__|__|
ANGIOGRAPHIE A LA FLUOROSCEINE ☐ NA					
Fluoresceine, nom de spécialité (à préciser s'il vous plait) : ………………………………………………	………	………	|__|__| |__|__| |2_|0_|__|__|	☐	|__|__| |__|__| |2_|0_|__|__|
Vert d'Indocyanine, nom de spécialité (à préciser s'il vous plait) : ………………………………………………	………	………	|__|__| |__|__| |2_|0_|__|__|	☐	|__|__| |__|__| |2_|0_|__|__|

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser) (2) En cours au moment de la survenue de l'EIG

6. Procédures et actes ajoutés par la recherche *(barrer l'encadré si procédures et actes non réalisés)*	Date de réalisation *(jj/mm/aaaa)*	Chronologie	
		Avant la survenue de l'EIG	Après la survenue de l'EIG
Angiographie à la fluoresceine	|__|__| |__|__| |2_|0_|__|__|	☐	☐
Angiographie à la fluoresceine	|__|__| |__|__| |2_|0_|__|__|	☐	☐
Angiographie à la fluoresceine	|__|__| |__|__| |2_|0_|__|__|	☐	☐

7. Médicament(s) concomitant(s) au moment de l'EIG, à l'exclusion de ceux utilisés pour traiter l'événement indésirable
(compléter le tableau ci-après et si nécessaire l'annexe relative aux médicaments concomitants ou barrer l'encadré si non applicable)

Annexe jointe au présent formulaire : ☐ Oui ☐ Non

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie(1)	Posologie (préciser l'unité ex : mg/j)	Dates d'administration *(du jj/mm/aa au jj/mm/aa)*	En cours (2)	Indication	***Action prise*** *0 : poursuite sans modification de la posologie 1 : arrêt 2 : diminution de la posologie 3 : augmentation de la posologie 4 : ne sais pas*	***Causalité de l'EIG*** *0 : non lié au médicament 1 : lié au médicament 2 : ne sais pas*
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser) (2) En cours au moment de la survenue de l'EIG

PARTIE RÉSERVÉE AU PROMOTEUR
RÉFÉRENCE VIGILANCE :

Référence GED : REC-DTYP-0192

8. Evènement indésirable grave [EIG]

Diagnostic : ☐ Définitif ☐ Provisoire

.....

.....

.....

Date de survenue des premiers symptômes : |__|__| |__|__| |_2_|_0_|__|__|

Préciser lesquels :

.....

Organe(s) concerné(s) :

.....

.....

.....

.....

.....

.....

Acronyme : **FOCUS**

Référence de la personne se prêtant à la recherche : |__|__|__| - |__|__|__|__| - |__| - |__|

n°centre - n° ordre de sélection - initiale nom - initiale prénom

Date d'apparition de l'EIG :

|__|__| |__|__| |_2_|_0_|__|__|

jj mm aaaa

Heure de survenue : |__||__| hh |__||__| min

☐ *donnée manquante*

Délai entre la date de la dernière administration du ME/produit assimilé ou la date de procédure/acte ajouté par la recherche et la date de survenue de l'EIG :

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

jj hh min

L'évènement a-t-il conduit à :

☐ aucune mesure prise concernant le ME

☐ diminution de la posologie du ME, nouvelle posologie à préciser : .....

le |__|__| |__|__| |_2_|_0_|__|__|

☐ augmentation de la posologie du ME, nouvelle posologie à préciser : .....

le |__|__| |__|__| |_2_|_0_|__|__|

☐ arrêt définitif du ME le |__|__| |__|__| |_2_|_0_|__|__|

☐ arrêt transitoire du ME, date de reprise : |__|__| |__|__| |_2_|_0_|__|__|

☐ ne sais pas

Récidive de l'EIG après ré-administration : O Non O Oui Date : |__|__| |__|__| |_2_|_0_|__|__|

O Non applicable

Des mesures symptomatiques ont-elles été prises ?

☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|Préciser : .....

L'évènement fait-il suite à :

- une erreur médicamenteuse ?	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|
- un surdosage ?	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|
- un mésusage ?	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|
- autre (préciser) :	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|

Critères de gravité :

☐ Nécessite ou prolonge l'hospitalisation :

du |__|__| |__|__| |_2_|_0_|__|__|

au |__|__| |__|__| |_2_|_0_|__|__| ☐ *en cours*

☐ Décès

☐ Mise en jeu du pronostic vital

☐ Incapacité ou handicap important ou durable

☐ Anomalie ou malformation congénitale

☐ Autre(s) critère(s) médicalement significatif(s), préciser :

.....

.....

Degré de sévérité :

☐ Léger ☐ Modéré ☐ Sévère

CTCAE :

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ NA

Evolution de l'événement

☐ **Décès**
O sans relation avec l'EIG
O en relation avec l'EIG
Date : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

☐ **Sujet non encore rétabli**, préciser :
O Etat stable O Amélioration O Aggravation

☐ **Résolu :**
O sans séquelles
O avec séquelles, préciser lesquelles :
Date : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa
|__|__| |__|__|
hh min

☐ **Evolution inconnue**

9. Autre(s) étiologie(s) envisagée(s)

☐ Non ☐ Oui Si oui, préciser : .....

.....

.....

10. Examen(s) complémentaire(s) réalisé(s)

☐ Non ☐ Oui Si oui, préciser date, nature et résultats : [joindre les bilans anonymisés].....

.....
.....

Acronyme : FOCUS Erreur : source de la référence non trouvée

Référence de la personne se prêtant à la recherche : |__|__|__| - |__|__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

11. Selon l'investigateur, l'événement indésirable grave est (plusieurs cases possibles)

Lié à la recherche :

☐ **Oui :** ☐ **au(x) médicament(s)/produit(s) assimilé(s) de la recherche**
☐ **Humira®** ☐ NA

☐ **Mycophénolate mofétil**
~~**Cellcept®**~~ ☐ NA

☐ **à la (aux) procédure(s)/acte(s) de la recherche ?**
☐ **Décroissance de la corticothérapie**

☐ **Prednisone (ou équivalent si prednisone ~~non disponible~~en rupture de stock sur le marché), nom de spécialité (à préciser s'il vous plait) : .....**

☐ **Fluoresceine, nom de spécialité (à préciser s'il vous plait) : .....**

☐ **Vert d'Indocyanine, nom de spécialité (à préciser s'il vous plait) : .....**

☐ **Non :** ☐ **à la progression de la maladie faisant l'objet de la recherche (à préciser s'il vous plait) : .....**
☐ **à un (ou plusieurs) médicament(s) concomitant(s) administré(s), le(s)quel(s) : .....**
☐ **à une maladie intercurrente, laquelle : .....**
☐ **autre, préciser : .....**

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

1.45[18.3] Pregnancy notification form

Direction de la Recherche Clinique et de l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS **Notification et suivi d'une grossesse apparue au cours d'une recherche portant sur un Médicament ou produit assimilé**	**PARTIE RÉSERVÉE AU PROMOTEUR** **RÉFÉRENCE INTERNE :** *Référence GED : REC-DTYP-0185*

Dès la prise de connaissance de l'EIG par l'investigateur, ce formulaire doit être dûment complété (3 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par mail (eig-vigilance.drc@aphp.fr)

Il est possible de transmettre les formulaires de notification d'EIG au secteur Vigilance par télécopie au +33 (0)1 44 84 17 99 uniquement en cas de tentative infructueuse d'envoi par mail afin d'éviter les doublons

1. Identification de la recherche

Acronyme : FOCUS
Code de la recherche : APHP211032

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

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

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

Titre complet de la recherche : "Randomized controlled multicenter study comparing efficacy and safety of adalimumab to that of mycophenolate mofetil in steroid dependent non-infectious uveitis" / **FOCUS:** treatment **FO**r Corticosteroid dependent **U**veiti**S**

2. Identification du centre investigateur

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

Investigateur (nom/prénom) : .....
Tél : Fax :
E-mail :

3. Identification de la personne présentant une grossesse

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

Date de naissance : |__|__| |__|__|__|__|

Date d'inclusion/randomisation : |__|__| |__|__| |2|0|__|__|

Groupe de randomisation :
☐ Groupe adalimumab ☐ Groupe mycophenolate mofetil

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

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

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

Date de naissance : |__|__| |__|__|__|__|
Date d'inclusion /randomisation: |__|__| |__|__| |2|0|__|__|
Groupe de randomisation :
☐ Groupe Adalimumab ☐ Groupe mycophenolate mofetil

Expositions au cours de la grossesse :

Tabac :	☐ non	☐ oui (préciser nombre de paquets/année) :	☐ arrêt (préciser date) :	☐ poursuite
Alcool :	☐ non	☐ oui (préciser unités OH) :	☐ arrêt (préciser date) :	☐ poursuite
Drogue :	☐ non	☐ oui (préciser substance) :	☐ arrêt (préciser date) :	☐ poursuite

Autre (préciser) :

4. Antécédents maternels

Médicaux :

Chirurgicaux :

Obstétricaux : |__|__| geste |__|__| pare

Préciser si fausse couche, grossesse extra-utérine, interruption de grossesse (médicale ou volontaire), mort *in utero*, malformation congénitale, pathologie congénitale/néonatale non malformative, … (*nombre, date et nature/raison si applicable).*

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

Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration Ou non administré	Date de dernière administration Ou en cours	Voie d'administration(1)	Posologie / 24h
Humira®	|__|__| |__|__| |2|0|__|__| ☐ Non administré	|__|__| |__|__| |2|0|__|__| ☐ En cours		
Mycophénolate mofétil~~Cellcept®~~	|__|__| |__|__| |2|0|__|__| ☐ Non administré	|__|__| |__|__| |2|0|__|__| ☐ En cours		

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

6. Médicament(s) nécessaire(s) à la réalisation de la recherche ou produit(s) assimilé(s) pendant la grossesse ou s'il s'agit une exposition paternelle *(barrer l'encadré si traitement non débuté)*

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie(1)	Posologie (préciser l'unité ex : mg/j)	Date de début *(jj/mm/aaaa)*	Date de fin *(jj/mm/aaaa)*
CORTICOTHERAPIE				
Prednisone **(ou équivalent si prednisone ~~non disponible~~en rupture de stock sur le marché)**,	.....	.....	|__|__||__|__||2|0|__|__|	|__|__||__|__||2|0|__|__|
	.....	.....	|__|__||__|__||2|0|__|__|	|__|__||__|__||2|0|__|__|
	.....	.....	|__|__||__|__||2|0|__|__|	|__|__||__|__||2|0|__|__|

nom de spécialité (à préciser s'il vous plait) : ……………………………………………..	………	………	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__|
	………	………	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__|
	………	………	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__|
	………	………	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__|
	………	………	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__|
PROPHYLAXIE ANTI-TB ☐ NA				
Rifampicine, nom de spécialité (à préciser s'il vous plait) : ……………………………………………..	………	………	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__|
Isoniazide, nom de spécialité (à préciser s'il vous plait) : ……………………………………………..	………	………	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__|
ANGIOGRAPHIE A LA FLUOROSCEINE ☐ NA				
Fluoresceine, nom de spécialité (à préciser s'il vous plait) : ………………………………………………..	………	………	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__|
Vert d'Indocyanine, nom de spécialité (à préciser s'il vous plait) : ………………………………………………..	………	………	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__|

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

7. Procédures et actes ajoutés par la recherche ***(Barrez l'encadré si procédures et actes non réalisés)***	Date de réalisation *(jj/mm/aaaa)*	Chronologie	
		Avant la grossesse	Au cours de la grossesse
Angiographie à la fluoresceine	|__|__| |__|__| |_2_|_0_|__|__|		
Angiographie à la fluoresceine	|__|__| |__|__| |_2_|_0_|__|__|		
Angiographie à la fluoresceine	|__|__| |__|__| |_2_|_0_|__|__|		

8. Médicament(s) concomitants administré(s) dans le cadre du soin

(Cf. annexe « Liste relative aux médicaments concomitants » complétée : ☐ Oui ☐ Non applicable)

Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration	Date de dernière administration Ou en cours	Voie d'administration(1)	Posologie / 24h
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		

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

9. Suivi de la grossesse

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

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

10. Grossesse en cours ☐ (envoyer par mail un nouveau formulaire complété à l'issue de la grossesse pour le suivi de la notification initiale)

ou issue de la grossesse ☐ (compléter ci-dessous)

Date : |__|__| |__|__| |_2_|_0_|__|__| Terme : |__|__| SA |__|__| J

☐ Fausse couche

→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Grossesse extra-utérine

→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Interruption de grossesse → Raison :

→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Accouchement : ☐ Spontané ☐ Provoqué ☐ Voie basse ☐ Césarienne

Naissance multiple : ☐ Non ☐ Oui, précisez le nombre :

Souffrance fœtale :	☐ Non	☐ Oui, précisez :		
Mort-né :	☐ Non	☐ Oui, précisez :		
Placenta normal :	☐ Oui	☐ Non, précisez :		
Liquide amniotique :	☐ Clair	☐ Autre, précisez :		
Anesthésie :	☐ Générale	☐ Péridurale	☐ Rachianesthésie	☐ Aucune

11. Nouveau-né (Si naissance multiple, compléter les parties 1, 2, 3, 10 et 11 d'un nouveau formulaire et l'envoyer par mail)

Sexe : ☐ Masculin ☐ Féminin

Poids : |__|__|__|__| grammes Taille : |__|__|__| cm Périmètre crânien : |__|__|__| cm

APGAR : 1 minute : _____ 5 minutes : _____ 10 minutes : _____

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

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

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

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

1.46[18.4] SmPC or Investigator's Brochure

Refer to the SmPC for Humira (see EMEA website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000481/human_med_000822.jsp&mid=WC0b01ac058001d124; https://www.ema.europa.eu/en/documents/product-information/humira-epar-product-information_fr.pdf) and for Mycophenolate mofetil (see EMEA website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000082/human_med_000688.jsp&mid=WC0b01ac058001d124 ; https://www.ema.europa.eu/en/documents/product-information/cellcept-epar-product-information_fr.pdf).

1.47[18.5] Description of the Clinical Trial in the AP-HP Trials Register

Etude multicentrique, randomisée et contrôlée, comparant l'efficacité et la tolérance de l'Adalimumab à celles du Mycophenolate Mofetil dans l'Uvéites non infectieuses cortico-dépendantes

1.48[18.6] Ophthalmologic Assessments

The following ophthalmologic assessments will be performed for both eyes. For a given subject and ophthalmologic assessment, all efforts will be made to use the same evaluator throughout the study. Unscheduled ophthalmologic assessments may be performed at the discretion of the investigator when medically indicated.

1.18.40[18.1.1] Assessment of Best Corrected Visual Acuity (BCVA) by the SNELLEN Method

Best corrected visual acuity (BCVA) will be assessed and graded using the SNELLEN method.

1.18.41[18.1.2] External and Anterior Segment Examination Pupils and Ocular Motility

Pupil reaction and extraocular eye movements will be assessed as per a site's usual practice.

Lids, Lashes, Conjunctiva:

Lids, lashes, and conjunctiva will be assessed as part of the external exam or with the slit lamp per the investigator's usual practice.

Cornea:

The cornea will be assessed with the slit lamp.

Anterior Chamber Cell and Flare:

Anterior chamber cell and flare will be assessed with slit-lamp biomicroscopy and scored using the SUN Working Group Grading Schema shown below. For the determination of anterior chamber cell and flare, the field consists of 1 x 1 mm beam. Grading should be performed in a darkened room with the brightest possible slit lamp illumination, a high slit lamp magnification, and a beam angle of 45°. On an individual subject, grading should be performed by the same investigator using the same slit lamp.

The SUN Working Group Grading

Scheme for Anterior Chamber Cells

Grade	Cells in Field[2]
0	< 1
0.5+	1 – 5
1+	6 – 15
2+	16 – 25
3+	26 – 50
4+	> 50

Source: Standardization of Uveitis Nomenclature (SUN) Working Group (Jabs et al., 2005).

If a hypopyon is present, evaluate it using a thin slit beam.

The SUN Working Group Grading

Scheme for Anterior Chamber Flare

Grade	Description
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

Source: Standardization of Uveitis Nomenclature (SUN) Working Group (Jabs et al., 2005).

Iris and Pupil:
The iris and pupil will be assessed by slit lamp biomicroscopy.

Lens, Capsule, and Cataract:
Lens status will be assessed by slit lamp biomicroscopy through a dilated (cyclopleged) pupil.

1.18.42[18.1.3] Assessment of Intraocular Pressure by Goldmann Tonometry

Goldmann Tonometry will be used to measure intraocular pressure. Intraocular pressure should be measured after the assessment of anterior chamber flare but prior to the installation of any dilating drops in addition to cycloplegics that a patient may already be taking.

1.18.43[18.1.4] Posterior Segment Examination

Assessment of vitreous cell, macula, posterior pole, and optic nerve should be performed at the slit lamp through a dilated pupil using appropriate lenses for high magnification stereoscopic viewing as needed. Assessment of vitreous haze and the peripheral retina should be performed through a dilated pupil with an indirect ophthalmoscope and appropriate lens for indirect ophthalmoscopy (e.g., 20D, 28 D, 2.2).

Vitreous Cell: Inflammatory vitreous cell in the anterior vitreous will be assessed at the slit lamp through a dilated pupil using a 1 x 3 mm beam at high magnification and high light intensity and scored using the scoring system in Opremcak**.** Only live active white blood cells are counted using the scheme below.

The SUN Working Group Grading

Scheme for Vitreous Cells

Grade	Cells in Field[1]

0	< 1
0.5+	1 – 10
1+	11 – 20
2+	21 – 30
3+	31 – 100
4+	> 100

[1] Field size is a 1 mm by 3 mm slit beam. Note if the condition is not evaluable.

Vitreous Haze:

Vitreous haze will be graded in a dimly lit room with a dilated pupil, binocular indirect ophthalmoscope with a large beam at mid-range brightness, and an appropriate lens for indirect ophthalmoscopy. The degree of retinal obscuration will be compared to the Nussenblatt photographic scale and scored (0, 0.5+, 1+, 2+, 3+, or 4+) using the SUN Working Group's adaptation of the National Eye Institute system for grading vitreous haze. For an individual subject, the same examiner, lens, and indirect ophthalmoscope should be used throughout the study.

Optic Nerve, Macula, and Posterior Pole:

The macula, posterior pole, and optic nerve will be assessed at the slit lamp through a dilated pupil using an appropriate lens for high-magnification stereoscopic viewing.

Peripheral Fundus Examination:

Assessment of the peripheral retina will be performed through a dilated pupil with an indirect ophthalmoscope and appropriate lens for indirect ophthalmoscopy (e.g., 20D, 28 D, 2.2).

1.18.44[18.1.5] Assessment of Macula Edema by Optical Coherence Tomography (OCT)

Spectral domain OCT will be performed through a dilated pupil to document macular thickness and presence of macular edema.

1.18.45[18.1.6] Fundus Photography

Fundus photography will be performed through a dilated pupil to document the appearance of the optic nerve, macula, and posterior retinal vessels.

1.49[18.7] NEI VFQ-25, version française

INSTRUCTIONS :

1. Nous vous demandons d'essayer de remplir ce questionnaire par vous-même. Mais si vous pensez avoir besoin d'aide, n'hésitez pas à vous adresser au personnel de l'étude qui vous aidera.

2. Veuillez répondre à toutes les questions (sauf quand on vous demande de sauter des questions qui ne vous concernent pas).

3. Répondez aux questions en entourant le chiffre correspondant à la réponse choisie.

4. Si vous ne savez pas quelle réponse choisir, choisissez celle qui se rapproche le plus de votre situation et inscrivez un commentaire dans la marge de gauche.

5. Veuillez remplir le questionnaire avant de partir et remettez-le à un membre du personnel de l'étude. Ne l'emportez pas chez vous.

6. Si vous avez des questions, n'hésitez pas à vous adresser à un membre du personnel de l'étude qui se fera un plaisir de vous aider

1ère PARTIE - ETAT DE SANTE GENERAL ET VUE

1. Dans l'ensemble, pensez-vous que votre santé est :

(Entourez un chiffre)

Excellente	1
Très bonne	2
Bonne	3
Médiocre	4
Mauvaise	5

2. Actuellement, lorsque vous regardez avec les deux yeux en même temps, vous diriez que votre vue (avec lunettes ou lentilles, si vous les portez) est excellente, bonne, moyenne, mauvaise, ou très mauvaise, ou bien êtes-vous complètement aveugle ?

(Entourez un chiffre)

Excellente	1
Bonne	2
Moyenne	3
Mauvaise	4
Très mauvaise	5
Complètement aveugle	6

3. Etes-vous inquiet(ète) au sujet de votre vue ?

(Entourez un chiffre)

Jamais	1
Rarement	2
Quelquefois	3
Très souvent	4
Tout le temps	5

4. Avez-vous eu des douleurs ou une gêne dans les yeux ou autour des yeux (par exemple : brûlures ou démangeaisons) ?

(Entourez un chiffre)

Aucune douleur ou gêne	1
Douleurs ou gêne légère(s)	2
Douleurs ou gêne modérée(s)	3
Douleurs ou gêne forte(s)	4
Douleurs ou gêne très forte(s)	5

2ème PARTIE - DIFFICULTES DANS VOS ACTIVITES

Les questions suivantes portent sur les difficultés que vous pouvez rencontrer dans certaines activités quand vous portez vos lunettes ou vos lentilles (si vous les utilisez pour ces activités).

5. Avez-vous du mal à lire les caractères d'imprimerie de taille normale dans les journaux ?

(Entourez un chiffre)

Pas du tout	1
Un peu	2
Moyennement	3
Enormément	4
Arrêté de le faire à cause de votre vue	5
Arrêté de le faire pour d'autres raisons ou par manque d'intérêt	6

6. Avez-vous du mal à faire certaines tâches ou certains passe-temps qui exigent de bien voir de près, comme faire la cuisine, de la couture, bricoler dans la maison ou utiliser des petits outils ?

(Entourez un chiffre)

Pas du tout	1
Un peu	2
Moyennement	3
Enormément	4
Arrêté de le faire à cause de votre vue	5
Arrêté de le faire pour d'autres raisons ou par manque d'intérêt	6

7. A cause de votre vue, avez-vous du mal à retrouver quelque chose sur une étagère encombrée ?

(Entourez un chiffre)

Pas du tout	1
Un peu	2
Moyennement	3
Enormément	4
Arrêté de le faire à cause de votre vue	5
Arrêté de le faire pour d'autres raisons ou par manque d'intérêt	6

8. Avez-vous du mal à lire les panneaux de circulation ou les enseignes de magasins dans la rue ?

(Entourez un chiffre)

Pas du tout	1
Un peu	2
Moyennement	3
Enormément	4
Arrêté de le faire à cause de votre vue	5
Arrêté de le faire pour d'autres raisons ou par manque d'intérêt	6

9. A cause de votre vue, avez-vous du mal à descendre des marches, un escalier ou les rebords de trottoirs la nuit ou quand l'éclairage est faible ?

(Entourez un chiffre)

Pas du tout	1
Un peu	2
Moyennement	3
Enormément	4
Arrêté de le faire à cause de votre vue	5
Arrêté de le faire pour d'autres raisons ou par manque d'intérêt	6

10. A cause de votre vue, avez-vous du mal à remarquer ce qui se trouve sur le côté quand vous marchez ?

(Entourez un chiffre)

Pas du tout	1
Un peu	2
Moyennement	3
Enormément	4
Arrêté de le faire à cause de votre vue	5
Arrêté de le faire pour d'autres raisons ou par manque d'intérêt	6

11. A cause de votre vue, avez-vous du mal à voir comment les gens réagissent à ce que vous dites ?

(Entourez un chiffre)

Pas du tout	1
Un peu	2
Moyennement	3
Enormément	4
Arrêté de le faire à cause de votre vue	5
Arrêté de le faire pour d'autres raisons ou par manque d'intérêt	6

12. A cause de votre vue, avez-vous du mal à choisir vos vêtements et à les assortir ?

(Entourez un chiffre)

Pas du tout	1
Un peu	2

Moyennement	3
Enormément	4
Arrêté de le faire à cause de votre vue	5
Arrêté de le faire pour d'autres raisons ou par manque d'intérêt	6

13. A cause de votre vue, avez-vous du mal à rendre visite à des gens, à aller dans des soirées ou au restaurant ?

(Entourez un chiffre)

Pas du tout	1
Un peu	2
Moyennement	3
Enormément	4
Arrêté de le faire à cause de votre vue	5
Arrêté de le faire pour d'autres raisons ou par manque d'intérêt	6

14. A cause de votre vue, avez-vous du mal à aller au cinéma, au théâtre, ou à assister à des rencontres sportives ?

(Entourez un chiffre)

Pas du tout	1
Un peu	2
Moyennement	3
Enormément	4
Arrêté de le faire à cause de votre vue	5
Arrêté de le faire pour d'autres raisons ou par manque d'intérêt	6

15. Conduisez-vous actuellement, au moins une fois de temps en temps ?

(Entourez un chiffre)

Oui 1 Passez à la question 15c

Non 2

15a. SI VOTRE REPONSE EST NON : est-ce parce que vous n'avez jamais conduit ou bien vous avez arrêté de conduire ?

(Entourez un chiffre)

Jamais conduit 1 Passez à la 3e partie, question 17

Arrêté de conduire 2

15b. SI VOUS AVEZ ARRETE DE CONDUIRE : c'était surtout à cause de votre vue ou surtout pour d'autres raisons, ou à la fois à cause de votre vue et pour d'autres raisons ?

(Entourez un chiffre)

Surtout à cause de votre vue 1 Passez à la 3e partie, question 17

Surtout pour d'autres raisons 2 Passez à la 3e partie, question 17

Pour les deux à la fois 3 Passez à la 3e partie, question 17

15c. SI VOUS CONDUISEZ ACTUELLEMENT : avez-vous du mal à conduire de jour dans des endroits familiers ?

(Entourez un chiffre)

Pas du tout	1
Un peu	2
Moyennement	3
Enormément	4

16. Avez-vous du mal à conduire de nuit ?

(Entourez un chiffre)

Pas du tout	1
Un peu	2
Moyennement	3
Enormément	4
Arrêté de le faire à cause de votre vue	5
Arrêté de le faire pour d'autres raisons ou par manque d'intérêt	6

3éme PARTIE &endash; VOS REACTIONS A VOS PROBLEMES DE VUE

Les questions suivantes portent sur ce qui vous arrive peut-être à cause de votre vue. Pour chaque question, entourez le chiffre qui indique si, dans votre situation, cette question est vraie en permanence, très souvent, quelquefois, rarement ou jamais.

(Entourez un chiffre sur chaque ligne)

	En permanence	Très souvent	Quelquefois	Rarement	Jamais
17. Faites-vous moins de choses que vous ne le voudriez à cause de votre vue ?	1	2	3	4	5
18. Etes-vous limité(e) dans le temps que vous pouvez consacrer à votre travail ou à vos activités à cause de votre vue ?	1	2	3	4	5
19. Les douleurs ou la gêne ressentie(s) dans ou autour des yeux, par exemple brûlures ou démangeaisons, vous empêchent-elles de faire ce que vous aimeriez faire ?	1	2	3	4	5

Pour chacune des phrases suivantes, entourez le chiffre qui indique si, dans votre situation, c'est entièrement vrai, plutôt vrai, plutôt faux, entièrement faux ou si vous n'en n'êtes pas certain(e).

(Entourez un chiffre sur chaque ligne)

	Entièrement vrai	Plutôt vrai	Pas certain(e)	Plutôt faux	Entièrement faux
20. Je reste chez moi la plupart du temps à cause de ma vue	1	2	3	4	5
21. Je me sens souvent contrarié(e) et insatisfait(e) à cause de ma vue	1	2	3	4	5
22. Je maîtrise beaucoup moins bien ce que je fais à cause de ma vue	1	2	3	4	5
23. A cause de ma vue, je dois trop compter sur ce que me disent les autres	1	2	3	4	5
24. J'ai beaucoup besoin de l'aide des autres à cause de ma vue	1	2	3	4	5
25. Je m'inquiète à l'idée de faire	1	2	3	4	5

des choses embarrassantes pour moi-même ou pour les autres, à cause de ma vue					