Multicentre, randomized, multi-arm trial comparing the efficacy and safety of Adalimumab, Anakinra and Tocilizumab in Subjects with Non-infectious Refractory Uveitis

RUBI: Refractory Uveitis BIotherapies

BIOMEDICAL RESEARCH PROTOCOL RELATING TO A MEDICINAL PRODUCT FOR HUMAN USE

Version N°8.0 of 19/05/2021

Project Code P150945 / EUDRACT No 2016-002284-34

Coordinating Investigator: Pr David SAADOUN

Centre national de référence des maladies autoimmunes et systémiques rares
Department of Internal Medicine and Clinical Immunology
Hospital Pitie Salpetriere
Tel. : 01 42 17 80 88
Email : david.saadoun@aphp.fr

Scientific Director: Pr Bahram BODAGHI

Centre national de référence des uvéites
Department of Ophtalmology
Hospital Pitie Salpetriere
Tel.: 01 42 16 37 28
Email: bahram.bodaghi@aphp.fr

Sponsor:

AP-HP
and by delegation: Clinical Research and Innovation Department (DRCI)
Hôpital Saint-Louis
1, avenue Claude Vellefaux
DRCI-Siège project referent: Elodie SOLER
Tel.: 01 44 84 17 35
Email: elodie.soler@aphp.fr

Entity responsible for monitoring research:

URC du GH saint Louis Lariboisière, site Saint Louis
Hôpital Saint Louis
1 avenue Claude Vellefaux 75010 PARIS
DRCI-URC (Clinical Research Unit) project referent:

Dr Mathieu RESCHE RIGON
Tel. 01 42 49 97 42
Email : Matthieu.resche-rigon@univ-paris-diderot.fr
Nabil RAKED (CEC)
Tel.: 01 42 49 97 49

Email: nabil.raked@paris7.jussieu.fr

Clinical Trial Department of EP-HP AGEPS

Pharmacist: Dr Jean-Roch FABREGUETTES
Assistant: Florence CAPELLE
Département Essais Cliniques AGEPS – AP-HP
7, rue du fer à Moulin
75005 Paris
Tel: 01 46 69 92 44 / 90 73
E-mail: jean-roch.fabreguettes@aphp.fr
florence.capelle@aphp.fr

SIGNATURE PAGE FOR A BIOMEDICAL RESEARCH PROTOCOL

Research Research Code: P150945

Title: **Multicentre, randomized, multi-arm trial comparing the efficacy and safety of Adalimumab, Anakinra and Tocilizumab in Subjects with Non-infectious Refractory Uveitis**

Version N°8.0 of 19/05/2021

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

Coordinating Investigator:
Pr David SAADOUN
Centre national de référence des maladies autoimmunes et systémiques rares
Department of Internal Medicine and Clinical Immunology
Hospital Pitie Salpetriere

Date: 30/08/2021
Signature:

Professeur David SAADOUN
Département de Médecine Interne
et d'Immunologie Clinique DMU 3ID
Centre de Référence Maladies Auto-immmunes Systématiques rares
Maladies Auto inflammatoires et Amylose
RRPS 10005176275
FINESS 750100125
APHP - Sorbonne Université
Site Pitié-Salpêtrière
47/83 Bd de l'Hôpital - 75651 PARIS CEDEX 13
Tél. 01 42 16 10 51
Fax 01 42 16 10 53

Sponsor
Assistance Publique – Hôpitaux de Paris
Clinical Research and Innovation Department
Hôpital Saint Louis
1 avenue Claude Vellefaux
75010 PARIS

Date: 07 SEP. 2021
Signature:

P. YVACHER
~~Florence Favrel Feuillade~~
Director of DRCI
Stéphanie DECOOPMAN

The research received a favourable opinion from the CPP IDF IV on 05/10/2016 and authorisation from the ANSM on 02/08/2016.

TABLE OF CONTENTS

SUMMARY

Full title	**A multicenter, randomized, multi-arm trial comparing the Efficacy and Safety of Adalimumab, Anakinra and Tocilizumab in Subjects with Non-infectious Refractory Uveitis**
Acronym	**RUBI : Refractory Uveitis BIotherapies**
Coordinating Investigator	**Pr David SAADOUN** Centre national de référence des maladies autoimmunes et systémiques rares Department of Internal Medicine and Clinical Immunology, Hospital Pitie Salpetriere Tel.0142178088 / Email david.saadoun@psl.aphp.fr
Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	**RUBI**, is the first prospective randomized, head to head study, comparing Adalimumab to either anakinra, or tocilizumab in refractory NIU. There is no firm evidence or randomized controlled trials directly addressing the best biologic agent in severe and refractory NIU. NIU can cause devastating visual loss and up to 20% of legal blindness. Corticosteroids and immunosuppressants failed to demonstrate sustainable remission over 70 % of refractory/relapsing severe uveitis. The incidence of blindness in NIU has been dramatically reduced in the recent years with the use of biologics, raising the question of whether these compounds should be used earlier in the treatment of severe non infectious uveitis. Contrasting with immunosuppressors, biotherapies act rapidly and are highly effective in steroid's sparing thus preventing occurrence of cataract and/or glaucoma. Despite a strong rationale, these compounds are not yet approved in uveitis, which guarantees the innovative nature of this study that aims selecting or dropping any arm when evidence of efficacy already exists.
Primary objective and assessment criterion	**Primary Objective** • To evaluate the efficacy of Adalimumab (80mg then 40mg/14 days) compared to anakinra (100mg/day) and tocilizumab (162mg/7 days) in subjects with refractory non-infectious intermediate, posterior, or pan-uveitis (NIU) and with a prednisone dose $\leq$ 0.1 mg/kg/day of prednisone (or equivalent oral corticosteroid) at Week 16. **Primary Endpoint** • Efficacy measured by the Percentage of patients with at least 2-step reduction in Vitreous Haze (according to Miami 9-step Scale) and with a dose $\leq$ 0.1 mg/kg/day of prednisone (or equivalent oral corticosteroid) at W16.
Secondary objectives and assessment criteria	**Secondary Objectives** • To evaluate the change in best corrected visual acuity (BCVA). • To evaluate the safety of Adalimumab, anakinra and tocilizumab in patients with NIU. • To evaluate the change in macular edema.

	• To evaluate the change in other signs of ocular inflammation. • To evaluate the effect on retinal vessel leakage. • To evaluate the effect of Adalimumab, anakinra and tocilizumab on steroid sparing. • To evaluate the change in ocular inflammation in the anterior chamber. • To evaluate the effect on underlying systemic disease when appropriate. • To evaluate the effect on ocular disease. • To evaluate the number and time to relapse of uveitis and the characteristics of uveitis at worsening. • To evaluate the time to treatment failure **Secondary Endpoints, all measured at 16 weeks** • Best corrected visual acuity (BCVA). • Change in macular edema. • Change in other signs of ocular inflammation. • Retinal vessel leakage. • Steroid sparing. • Ocular inflammation in the anterior chamber. • Underlying systemic disease when appropriate. • Ocular disease. • Number and time to relapse of uveitis and the characteristics of uveitis at worsening. • Adverse events • Time to treatment failure
Experimental design	This is a prospective phase II clinical trial, multicenter, multi-arm, randomized (1:1:1) clinical trial comparing the efficacy and safety of Adalimumab, anakinra and tocilizumab in subjects with active and refractory non-infectious intermediate, posterior, or pan-uveitis. Oral corticosteroids should be at a stable dose 30 days prior to the first study drug administration on Day 0. All systemic immunosuppressants must have been discontinued 30 days prior to the first study drug administration on Day 0. Patients will have access to oral corticosteroids if needed before Day 0.
Population involved	Adult patients with **active and Refractory Non-infectious Uveitis (NIU)** 1. **Active disease:** either the presence of VH ≥4 on the Miami 9-step scale, and/or macular edema (CRT ≥300 microns), and/or other signs of intraocular inflammation (eg, perivascular sheathing of retinal vessels or leakage of retinal vessel on FA). 2. **Recently active disease:** evidence of activity within the 3 months prior to inclusion visit as per VH ≥4 on the Miami 9-step scale (or VH >1+ according to SUN classification), and/or macular edema (CRT ≥300 microns), and/or other signs of intraocular inflammation (e.g., perivascular sheathing of retinal vessels or leakage of retinal vessels on FA). The activity status (active disease or recently active disease) has to be confirmed for all patients before the randomization by the Reading Center evaluation of VH, OCT and FA assessments.

	3. **Refractory disease:** At inclusion, subjects must be receiving oral corticosteroids (≥10 mg/day prednisone equivalent and <80mg/day) and at least one other immunosuppressive (azathioprine, methotrexate, mycophenolate mofetyl, cyclosporine, leflunomide, cyclophosphamide); or interferon (IFN)-α; or being intolerant to such immunosuppressive therapies.
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. 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 3. Currently uncontrolled uveitic disease. Uncontrolled uveitic disease is defined as fulfilling 1 of the two following criteria within 4 weeks prior to inclusion: a. Active inflammatory chorioretinal and/or inflammatory retinal vascular lesions and/or macular edema (CRT ≥300 microns), OR b. Vitreous haze grade ≥4 on the Miami 9-step scale (or VH >1+ according to SUN/NEI classification) 4 a. Patient who are receiving prednisone ≥10 mg/day and <80mg/day (or equivalent dose of another corticosteroid) at stable dose 30 days prior to the first study drug administration on Day 0 and who received at least 1 other systemic immunosuppressant (*All systemic immunosuppressants must have been discontinued 30 days prior to the first study drug administration on Day 0)*, or, b. Patient who received IFNα (*All systemic immunosuppressants must have been discontinued 30 days prior to the first study drug administration on Day 0)*, or, c. To be intolerant to immunosuppressant 5. Best corrected visual acuity (BCVA) by ETDRS ≥ to 20/400 in either eye 6. Stable dose for two weeks prior to inclusion of topical corticosteroids and/or NSAIDs 7. Male or female, Age ≥ 18 years at Inclusion 8. Weight 40 – 120 kg (88.2 – 264 lbs) at Inclusion 9. Chest X-ray or thoracic CT scan results (postero-anterior and lateral) within 12 weeks prior to Inclusion with no evidence of active Tuberculosis, active infection, or malignancy 10. For female subjects of child-bearing age, a negative serum or urine pregnancy test 11. 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 and 5 months after stopping therapy for roactemra and adalimumab,

	respectively. Birth control 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: - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation 1: o oral o intravaginal o transdermal - progestogen-only hormonal contraception associated with inhibition of ovulation 1: o oral o injectable o implantable - intrauterine device (IUD) - intrauterine hormone-releasing system (IUS) - bilateral tubal occlusion - vasectomised partner - 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). 12. A QuantiFERON®-Tuberculosis (TB) test within 6 months prior to Screening
Non-inclusion 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. Presence of cataract or posterior capsular opacification so severe that an assessment of the posterior segment of either eye is inadequate or impossible 4. Contraindication to mydriasis in either eye or presence of posterior synechiae in the study eye such that mydriasis is inadequate for posterior segment examination 5. Intraocular pressure ≥ 25mmHg by Goldmann tonometry or advanced glaucoma in either eye 6. Monocular patient 7.Active tuberculosis 8. Known positive syphilis serology, HIV antibody, hepatitis B surface antigen and/or anti-nucleocapsid antibody of hepatitis B virus and/or Hepatitis C virus, within 1 month prior to inclusion. 9. 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. 10. History of severe allergic or anaphylactic reactions to monoclonal antibodies 11. Infectious disease: a. Fever or infection requiring treatment with antibiotics within 3 weeks prior to Inclusion b. History of recurrent infection or predisposition to infection 12. Known immunodeficiency 13. History of multiple sclerosis and/or demyelinating disorder 14. Laboratory values assessed during Inclusion: a. Hemoglobin < 8g/dL b. WBC < $2.0 \times 10^3/mm^3$ c. Platelet count < $80 \times 10^3/mm^3$ d. Glomerular filtration rates (GFR) <30ml/min. e. Transaminases > 3 times upper normal value 15. Use of the following systemic treatments during the specified periods: a. Any previous systemic biologic therapy b. Treatment with any systemic alkylating agents within 12 months prior to Inclusion or between Inclusion and Day 0 (e.g., cyclophosphamide, chlorambucil) c. Any live (attenuated) vaccine within 3 months prior to Inclusion. 16. Use of the following ocular treatments during the specified periods: a. Previous anti-VEGF intravitreal therapy (applies to both eyes) within 3 months prior to Inclusion, or anticipated use during the study period b.Treatment with dexamethasone intravitreal implant [Ozurdex®]) within 6 months prior to Inclusion c. Intravitreal corticosteroids within 3 months prior to Inclusion. Previous Subtenon's corticosteroid injections are permitted if administered at least 2 months prior to Inclusion 17. Stage III and IV New York Heart Association (NYHA) cardiac insufficiency
Treatment being tested	Eligible patients with active and refractory NIU will randomized at 1:1:1 ratio between • **Arm 1:** Adalimumab (80mg then 40mg/14 days subcutaneously) (n=40) for 16 weeks • **Arm 2:** Anakinra (100 mg/day subcutaneously) (n=40) for 16 weeks • **Arm 3**: Tocilizumab (162 mg/7 days subcutaneously) (n=40) for 16 weeks. The three treatment groups will receive the same corticosteroid regimen. All patients with NIU will receive oral prednisone 0.5 mg/kg/day with a maximum of 40 mg/day of prednisone or equivalence. The following schedule of reduction of prednisone will apply to both groups as long as the disease is inactive: - 0.5 mg/kg/day of prednisone until week 4.

	- 0.4 mg/ kg/day of prednisone from week 4 to week 6 - 0.3 mg/ kg/day of prednisone from week 6 to week 8. - 0.2 mg/ kg/day of prednisone from week 8 to week 12 - - ≤0.1 mg/ kg/day of prednisone from week 12 to week 16. Due to the CSI recommendation of the 18/06/2019, inclusion in the Anakinra arm has been stopped and the investigational medicinal product Anakinra has been discontinued in patients undergoing follow-up. Thus we modified the planned analyses and the randomisation accordingly. After the inclusion and randomisation of 54 patients, the next patients will be randomized 1:1 either in the 2 remaining arms: • Arm 1: Adalimumab (80mg then 40mg/14 days subcutaneously) (n=40) for 16 weeks • Arm 3: Tocilizumab (162 mg/7 days subcutaneously) (n=40) for 16 weeks. In practice, it means that the remaining 66 planned patients will be randomized (33 in arm 1 and 33 in arm 3).
Other procedures added by the research	- Ophthalmologic visit at weeks 8 and 16 - Fluorescein and indocyanine green angiogram (FA/ICG) at week 16 and ocular coherence tomography (OCT) at weeks 8 and 16
Risks added by the research	Risk C
Practical procedure	The randomization will be stratified by retinal vasculitis, macular oedema and underlying disease. At randomization, the patient will be under treatment with prednisone. One study eye will be selected. If both eyes are eligible for the study (as per inclusion/exclusion criteria) the following rules will be respected: • The eye with active disease will be selected versus the eye with recently active disease, as defined by the protocol. • If both eyes present active disease documented by the same unique parameter, the eye with the worse score will be selected. • If both eyes present active disease defined by several parameters, the eye with the worse score ranked as follows will be selected: 1 Vitreous Haze; 2 cystoid macular edema (CME); 3 retinal vascular leakage and 4 best corrected visual acuity (BCVA). If both eyes have an equivalent score, the right eye will be selected. All patients will receive ocular coherence tomography (OCT) at enrolment, month 1, 2, 3, 4 and 6 and a fluorescein and indocyanine green angiogram (FA/ICG) at enrolment, month 2 and 4 or at all visits in case of vasculitis or worsening.
Number of subjects chosen	120
Number of centres	37 departments of 17 French public hospitals
Research period	Duration of inclusions: 56 months Duration of participation of each patient: 7 months maximum

	Total duration of the study: 63 months
Number of inclusions expected per centre and per month	0.4 patient/month/centre
Statistical analysis	We will use a Bayesian Multi-Arm Multi-Stage (MAMS) design that aim at comparing several new treatments (multi-arm), in order to select or drop any treatment arm to move forward when such evidence already exists based on interim analyses The randomization will be stratified by retinal vasculitis, macular oedema and underlying disease. At randomization, the patient will be under treatment with prednisone as single therapy.
Funding source	PHRC 2015
Data Safety Monitoring Board anticipated	Yes

LIST OF ABBREVIATIONS

ADA	Anti-drug antibodies
ADCC	Antibody dependent cell-mediated cytotoxicity
AE	Adverse event
ALT	Alanine amino transferase
Anti-VEGF	Anti-vascular endothelial growth factor
AST	Aspartate amino transferase
ATC	Anatomical-Therapeutic-Chemical classification
AUC	Area under the curve
AZA	Azathioprine
BCVA	Best corrected visual acuity
BRB	Blood-retinal barrier
BUN	Blood urea nitrogen
CBC	Complete blood count
CHO	Chinese hamster ovary
CINCA	Chronic Infantile Neurological Cutaneous Articular Syndrome
CRF	Case Report Form
CSA	Cyclosporine A
CTCAE	Common Terminology Criteria for Adverse Events
dL	Deciliter
EAU	Experimental autoimmune uveitis/uveoretinitis

EC	Ethics Committee
ECG	Electrocardiogram
ECL	Electrochemiluminescence
EDC	Electronic data capture
eCRF	Electronic case report form
EIU	Endotoxin-induced uveitis
EMA	European Medicines Agency
ETDRS	Early treatment diabetic retinopathy study
FFA	Fundus Fluorescein Angiography
g/day	Grams per day
g/dL	Grams per deciliter
GCP	Good Clinical Practice
GLP	Glucagon-like peptide or Good Laboratory Practice (note context)
H1N1	Hemagglutinin type 1 and neuramimidase type 1
HIV	Human immunodeficiency virus
hs-CRP	High sensitivity C-reactive protein
IC_{50}	Half maximal inhibitory concentration
ICH	International Conference on Harmonization
ID	Identification
INH	Isonicotinylhydrazine (also known as isoniazid)
IRS	Interactive response system
IUD	Intrauterine device
IUSG	International Uveitis Study Group
IV	Intravenous
KD	Equilibrium dissociation constant
kg	Kilograms
Ltd	Limited
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mm	Millimeter
mm3	Cubic millimeter
MMF	Mycophenolate mofetil
MPS	Mycophenolate sodium
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
NEI	National Eye Institute
nM	Nanomolar

NOAEL	No-observed-adverse-effect-level
OCT	Optical coherence tomography
OUD	Occurrence of uveitic disease
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamic
pH	Hydrogen ion concentration
PK	Pharmacokinetic
pM	Picomolar
PO_2	Oxygen pressure
PPD	Purified protein derivative
Q4W	Every 4 weeks
QOL	Quality of life
RA	Rheumatoid arthritis
rHu	Recombinant human
rMu	Recombinant mouse
SAE	Serious adverse event
SC	Subcutaneous
SPR	Surface Plasmon Resonance
SUN	Standardization of Uveitis Nomenclature
TB	Tuberculosis
TBD	To be determined
TH1	T helper 1 cell
TH17	T helper 17 cell
TLR	Toll-like receptor
TNFα	Tumor necrosis factor alpha
T2D	Type 2 diabetes
ULN	Upper limit of normal
WBC	White blood cell (count)
WHODD	World Health Organization Drug Dictionary
WMA	World Medical Association

1. BACKGROUND INFORMATION

1.1 Overview

This study will evaluate the **Efficacy and Safety of Adalimumab, Anakinra and Tocilizumab in Subjects with Non-infectious Refractory Uveitis.**

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, druginduced).

RUBI, is the first prospective randomized, head to head study, comparing Adalimumab to either anakinra, or tocilizumab in refractory NIU. There is no firm evidence or randomized controlled trials directly addressing the best biologic agent in severe and refractory NIU. NIU can cause devastating visual loss and up to 20% of legal blindness. Corticosteroids and immunosuppressants failed to demonstrate sustainable remission over 70 % of refractory/relapsing severe uveitis. The incidence of blindness in NIU has been dramatically reduced in the recent years with the use of biologics, raising the question of whether these compounds should be used earlier in the treatment of severe non infectious uveitis. Contrasting with immunosuppressors, biotherapies act rapidly and are highly effective in steroid's sparing thus preventing occurrence of cataract and/or glaucoma.

Despite a strong rationale, these compounds are not yet approved in uveitis, which guarantees the innovative nature of this study that aims selecting or dropping any arm when evidence of efficacy already exists.

Morbidity

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, 4).

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 (5).

Patients with uveitis reported markedly reduced general and vision-related quality of life compared with normal subjects (6) 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 (7,8).

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 (9), followed by a reported prevalence of 69/100,000 (10). 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 (11) estimates that at least 13% of general uveitis cases involve infectious uveitis. 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 **Disease Pathophysiology**

A better understanding of the mechanisms involved in the inflammatory response and regulation of adaptive immunity led to the development of biotherapy. Under this term are grouped interferons, intravenous and monoclonal antibodies. These were first developed in

the field of rheumatology and then used for the treatment of systemic diseases and inflammatory eye dieseases.

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, or systemically (usually orally or intravenously). The use of systemic corticosteroids is associated with a number of safety concerns including systemic hypertension, hyperglycemia, increased susceptibility to infection, and peptic ulcers. Furthermore, 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 corneo-scleral melting, strabismus, proptosis, fibrosis of extraocular muscles, and increased risk of endophthalmitis.

Biologic agents under investigation include mAbs and recombinant forms of natural inhibitory molecules. Infliximab, adalimumab, etanercept, certolizumab, and golimumab are inhibitors of the inflammatory cytokine, TNF-α. Limited studies have shown them to be active in the treatment of uveitis (3,12) (13,14)(15). Adalimumab has recently been shown to be superior to placebo in NIU in phase 3 clinical trials and should be approved in uveitis in France within few months.Infliximab is currently approved for the treatment of Behçet’s uveitis, though only in Japan. Anakinra and Tocilizumab, are inhibitors of IL-1 and IL-6, respectively, approved for rheumatoid arthritis (RA) that has also been used for the treatment of uveitis in a small number of patients. Interferon in several forms has been studied for the treatment of uveitis. Abatacept is a T cell modulator approved for RA and juvenile idiopathic arthritis that is starting early-phase trials for uveitis (16)

There are several topical and systemic corticosteroids approved for the treatment of uveitis or intraocular inflammation. However, there are only two therapies currently approved for the treatment of chronic non-infectious intermediate, posterior, and pan- uveitis: Retisert (Bausch & Lomb) fluocinolone acetonide intravitreal implant registered in the US and

Ozurdex (Allergan) dexamethasone intravitreal implant registered both in the US and in Europe. Both are extended-release corticosteroid implants that have been shown to improve vision and decrease inflammation, and in the case of Retisert to decrease the frequency of recurrent uveitis attacks. As with any corticosteroid, both carry an increased risk of cataracts, elevated intraocular pressure, glaucoma, and potential for increased or enhanced ocular infections due to bacteria, fungi, or viruses.

1.3 **Overview of different drugs**

Anti-TNF

Several teams have reported on the efficacy of anti-TNFα in severe refractory non-infectious uveitis. Petropoulos et al. reported 15 patients with chronic refractory noninfectious posterior uveitis treated with anti-TNFα (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-TNFα. 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).

Although head-to-head studies are not available, several explorative analyses showed that infliximab was more effective than etanercept in the treatment of refractory uveitis. 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(18). 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(19) Adalimumab was safe and effective in 68% patients, and maintained in 39% after one year.

Several studies have also shown that anti-TNF antibodies could be useful in the treatment of non-infectious scleritis, whether idiopathic or associated with a systemic disease, such as rheumatoid arthritis or granulomatosis with polyangeitis (Wegener polyangiitis).

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) (20). 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) (20). 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 (21).

Although one randomized clinical trial with etanercept did not report any improvement, several case-reports have shown the efficiency of humanized monoclonal antibodies targeted against TNFα for the treatment of refractory ocular sarcoidosis (22). Erckens et al recently reported an improvement in intraocular signs in 22 of 25 (85%) sarcoidosis patients with refractory chronic non-infectious disease (23). Most of these patients (n=20) did not response to the original therapy with immunosuppressive drugs (both prednisone and methotrexate). In our own experience, refractory uveitis in sarcoidosis is unusual and clinicians must first eliminate noncompliance, infectious uveitis or lymphoma before starting infliximab or adalimumab. Moreover, infliximab in the treatment of sarcoidosis is accompanied by a larger number of adverse effects, especially serious infections (22.1 per 100 patients-years), than in other approved indications. Clinicians should be aware that de novo uveitis under anti-TNF therapy, although uncommon (<1%) is possible. It occurs mainly in spondylarthritis, seems more frequent under etanercept and is self-limited without discontinuation of the TNF-blocker. Based on these data, the ASAS/EULAR recommendations for the management of ankylosing spondylitis do not suggest a difference in efficacy of the various TNF inhibitors on anterior uveitis (24).

Anti-TNFα represent attractive therapeutic alternative in BD (Behcet's Disease). We treated with infliximab (5mg/kg at W0, W2, W6 and every 8 weeks) 21 eyes in 12 patients after failure of multiple lines of immunosuppressants. Infliximab was constantly and rapidly effective, but relapse occurred in one third of cases when the infusion was spaced every 10-12 weeks and only one patient has been weaned of anti-TNFα. Nicoli et al. reported 12 patients with posterior uveitis refractory to at least one immunosuppressant (azathioprine, ciclosporin, methotrexate and/or cyclophosphamide) (25). Nine out of twelve (75%) had a significant improvement in ocular inflammation after the first dose of infliximab (5mg/kg) associated with prednisone at a dose of 1mg/kg/j. The steroids were discontinued after 22 weeks of treatment in these 9 patients. At the week twenty-fourth, 7 of the 9 responders (78%) were still in remission. Tugal-Tutkun et al, reported 13 patients with at least two episodes of posterior uveitis and/or retinal vasculitis despite treatment with corticosteroids, azathioprine and cyclosporine (26). Infliximab (5 mg/kg) was administered at weeks 0, 2, 6,

and 14 in combination with corticosteroids and azathioprine. Four patients (30.8%) showed no uveitis flare and 9 had a total of 13 relapses between weeks 14 and 22. Tolerability was good in both studies without severe side effects. Tognon et al. also reported 7 cases of posterior uveitis refractory to immunosuppressants treated by infliximab (5mg/kg at W0, W2 and W4, then every 6 to 8 weeks) and low-dose prednisone, azathioprine or methotrexate (27). After 23 months of follow up, the number of relapses was of 6 compared to 21 flares before infliximab. Visual acuity was improved in 4 patients and stabilized in 9 cases. Doses of corticosteroids and immunosuppressants have been reduced but ocular relapses were recorded after stopping anti-TNFα and/or when the interval between infusions exceeded 8 weeks stressing. A literature review of published cases on the efficacy and safety of anti-TNFα in Behcet's disease has recently been conducted (28). The authors analyzed 88 articles including 369 patients, 83.3% received infliximab, 9.5% etanercept and 7.2% adalimumab. Only 11 cohort studies included more than 10 patients. The main indication for anti-TNFα was ocular inflammation. It mainly included severe posterior uveitis (sometimes associated with retinal vasculitis) and refractory to one or more lines of immunosuppressants. Infliximab was used either alone (5mg/kg at weeks 0, 2, 6 and every 8 weeks) with corticosteroids or more rarely in combination with azathioprine, cyclosporine or methotrexate. Early response as quick as 48 hours after the first injection of infliximab was observed. After a median follow-up of 15.9 months (28 days-3 years), 65% were complete responders (ie regression of ocular inflammation and improvement or stabilization of visual acuity). In long term follow-up, there were 60% of relapses after stopping or spacing infliximab that often responded to the reintroduction of treatment. Of the 20 patients resistant to previous treatment with IFN-α, 18 (90%) responded to infliximab.

Data on the efficacy of adalimumab (used subcutaneously at a dose of 40 mg every 15 days) and etanercept (used subcutaneously at a dose of 25mg twice weekly) are rare. Improvement of uveitis was observed in 16/16 (100%) patients on adalimumab and only 6/10 (60%) patients on etanercept. Replacement of infliximab by adalimumab was successful in some patients. Infliximab was also effective in cases of cystoid macular edema (29) or choroidal neovascularization associated with BD (30). Adalimumab has been recently shown to be superior to placebo in NIU in phase 3 clinical trials and should be approved in uveitis in France within few months.

Tocilizumab

Although as yet little used in ophthalmology, tocilizumab, a humanized anti-human IL-6 receptor antibody that inhibits the biological activities of IL-6 by blocking its receptor, could be used in the near future, for the treatment of uveitis. IL-6 is a pleiotropic pro-inflammatory cytokine with multiple functions and secreted by T cells, monocytes, macrophages and

synovial fibroblasts, involved in the immune response (induction of differentiation of Th17 cells) hematopoiesis and inflammation. This cytokine also increases vascular permeability and angiogenesis. The receptor for IL-6 is a complex formed of the signal transduction molecule gp130 and the membrane receptor for IL-6. It also exists as a soluble receptor of IL-6 which is released into the blood and inflamed tissues. IL-6 can bind to two receptor types; the IL6/soluble receptor of IL-6 complex can bind to the membrane molecule gp130 and induce signal transduction. Tocilizumab prevents the binding of IL-6 with its membrane and soluble receptors and also antagonizes its action. Tocilizumab is used for the treatment of active rheumatoid arthritis, moderate to severe (i) in combination with methotrexate, in case of inadequate response to at least one DMARD or in case of inadequate response or intolerance to at least one anti-TNF (ii) in monotherapy, in case of intolerance to methotrexate or when continued treatment is inadequate. More recently a marketing authorization has been granted for the treatment of active systemic juvenile idiopathic arthritis (JIA) in children aged 2 years and older who have had an inadequate response to treatment with NSAIDs and/or systemic corticosteroids, in combination with methotrexate or in case of intolerance or contraindication to it. Apart from these two pathologies, many retrospective or open studies have shown efficacy of tocilizumab in inflammatory and/or autoimmune diseases refractory to conventional therapy and/or other biologics (31). This mostly included series of large vessels vasculitis (Takayasu's arteritis, giant cell arteritis), BD, adult onset Still's disease, multicentric Castleman disease, relapsing polychondritis, Cogan's disease, inflammatory myositis and lupus.

Dysregulated production of IL-6 has been found in several chronic inflammatory disorders, such as rheumatoid arthritis or Behçet’s disease. It has been demonstrated that IL-6 is essential, in association with TGF-beta and IL23, for the differentiation of Th17 from naïve CD4+ T cells in vitro and that their inhibition leads to auto-immune diseases prevention. Experiments in mice suggested that IL6-R blocking antibody might improve ocular inflammation in autoimmune uveoretinitis, by inhibiting Th17 cells development and increasing Treg cells (32).

IL-6 is a cytokine involved in the pathogenesis of experimental autoimmune uveitis. This experimental model is to immunize rats against the S antigen of the retina or the binding protein of the retinal photoreceptors. Several studies in rats and mice have shown that IL-6 was involved in the genesis of the inflammatory process and that the invalidation of the gene for IL-6 or the blocking of this molecule by tocilizumab warned the onset of uveitis by the suppression of Th17 response, both locally and systemically (32). Haruta et al. have recently shown that tocilizumab also increased, in this context, Th1 cells specific regulatory binding protein of retinal photoreceptors (33). These data suggest that blocking the IL-6 with monoclonal antibodies could be effective for the treatment of refractory uveitis associated

with an inflammatory or autoimmune disease. To date, several case-reports have shown the interest of tocilizumab in the treatment of uveitis refractory to anti-TNF, including idiopathic uveitis, Birdshot's disease (34) and BD (35). More recently, Tappeiner et al. reported the efficacy of tocilizumab in three adult patients with uveitis associated with juvenile idiopathic arthritis refractory to immunosuppressants and anti-TNF(36). Our group recently reported 8 consecutive unselected patients with severe and refractory non-infectious uveitis (Birdshot's chorioretinopathy (n=1), Behçet's disease (n=1), idiopathic bilateral panuveitis (n=6)) treated with tocilizumab, including 7 patients who have been previously treated with anti-TNF-α agents. Six patients improved under tocilizumab while tolerance was satisfactory. An ongoing trial in United States evaluates the efficacy of tocilizumab for the treatment of uveitis in juvenile idiopathic arthritis in case of failure or intolerance of immunosuppressants (clinicaltrials.gov).

Anakinra

The importance of IL-1 has been documented in infections, tissue damages, and in a growing number of systemic autoinflammatory diseases. Recent advances in our understanding of the production of IL-1 by the inflammasome have increased interest in the signaling of IL-1 and therapeutic agents targeting IL-1. Excessive signaling of IL-1 as a result of overactive inflammasome occurs in a defined set of auto-inflammatory diseases commonly characterized by inflammation involving multiple organs, usually of the skin, joints and eyes. Anakinra (Kineret ®) is a soluble antagonist IL-1Ra), which proved to be effective in this group of diseases. In addition to these relatively rare diseases, genetic polymorphisms of the IL-1 group (IL1A, IL1B, IL1RN) or IL-1RII influence susceptibility to inflammatory diseases in which the most common uveitis and arthritis coexist, such as ankylosing spondylitis, sarcoidosis and Behcet's disease. If the use of anakinra in rheumatoid arthritis (RA) became anecdotal because of disappointing trials, its interest in some rarer inflammatory pathology is major. In adults, the therapeutic regimen is that of RA and is 100mg daily subcutaneously. We can recommend a pretherapeutic assessment close to that of anti-TNF, including the verification of the absence of active infection, exclusion of neoplasia and updated vaccines. Lequerré et al. retrospectively compared the efficacy and safety of anakinra in Still's disease, at a dose of 100 mg / day subcutaneously in 15 adults (38). All patients had active disease despite several lines of therapy including MTX, anti-TNF, thalidomide, intravenous immunoglobulin or cyclosporin. Eleven patients had a clinical and biological improvement (ACR 20), including 9 complete responses at the end of study, with the possibility of lower doses of corticosteroids or even stop in 2 patients. Lequerré et al. also reported data from 20 children who were treated with 1 to 2mg/kg/jour anakinra (100mg/day maximum). Fifteen children (75%) improved and 10 (50%) achieved pediatric response criteria of the ACR

(pedi30) at 6 months. Corticosteroids sparing effect was observed in all cases. Anakinra has also shown efficacy in hereditary autoinflammatory syndromes (familial Mediterranean fever, hyper IgD syndrome, the TNF-associated periodic syndrome, syndrome acne - Pyogenic arthritis - pyoderma gangrenosum, and cryopyrinopathies). Anakinra has been tested with some success in two other inflammatory diseases, Sweet syndrome, and chronic atrophic polychondritis. The most common side effect is injection site reaction, found in 72.6% of patients treated with anakinra versus 32.9% in the placebo group. When the pruritus is important, the application of a topical steroid derivative may be necessary. Discontinuation of treatment is rare. The overall risk of infection does not appear to be increased by anakinra compared with placebo (41.2% versus 43.5% in the placebo group), however, serious infections (pneumonia and infectious cellulitis especially) seem more frequent with the anakinra (2.1% versus 0.4% in the placebo group). The risk of infection appears to be increased with the combination of anakinra and etanercept with frequency of serious infections of 7.4%. This led to contraindication of concomitant administration of these two biotherapies. Unlike anti-TNF, there is no increased risk of tuberculosis. In addition, rare cases of neutropenia have been reported.

A pilot study was recently conducted by Gul et al. using XOMA 052 (gevokizumab) a humanized recombinant antibody anti-IL1β with only one injection of 0.3 mg/kg (6). This work focused on 7 patients with posterior uveitis or panuveitis severe and/or retinal vasculitis related to BD, resistant to first-line immunosuppressant including azathioprine and/or cyclosporine. Rapid improvement (median 14 days) was observed in all patients while the steroid dose was maintained at 10 mg/day or less, and with no association with an immunosuppressant. The duration of study follow-up was 120 days after the injection of XOMA 052. Six of the seven patients relapsed after a median of 49 days (21-97), two of which were treated with systemic or intraocular corticosteroids. The remaining 4 patients were effectively retreated by a second injection of XOMA 052. No relapse was observed after a median follow up of 115 days (41-197). No serious adverse event was reported except for an infection of the upper airways (37).

1.4 **Study Rationale**

Noninfectious refractory uveitis is a serious visual condition. It can cause devastating visual loss and is the fifth most common cause of visual loss in the developed world, accounting for about 10–15% of the cases of total blindness and up to 20% of legal blindness. There are important unmeet needs with respect to the treatment of this condition and more specifically in the management of biotherapies. Corticosteroids and immunosuppressants failed to demonstrate sustainable remission over 70 % of refractory/relapsing severe uveitis. The incidence of blindness in NIU has been dramatically reduced in the recent years with the use

of biologics, raising the question of whether these compounds should be used earlier in the treatment of severe non infectious uveitis. Contrasting with immunosuppressors, biotherapies act rapidly and are highly effective in steroid's sparing thus preventing occurrence of cataract and/or glaucoma. Despite a strong scientific and clinical rationale, these compounds are not yet approved in uveitis. This is the first randomized study comparing the efficacy and safety of infliximab to either anakinra, or tocilizumab in the treatment of refractory NIU. It will validate and optimize the treatment of difficult to treat uveitis patients.

This study could confirm or not the superiority of adalimumab relative to other agents (anakinra, and tocilizumab) in terms of efficacy. It will allow a direct comparison of the safety profiles of these biologic agents. It could really improve the management of patients with severe and refractory NIU and finally help to prevent the occurrence of blindness and side effects in these difficult to treat cases. The expected benefit is both individual, in reduced morbidity for patients with NIU, and collective, in reducing costs of unemployment, invalidity and hospitalization.

In summary, non-infectious uveitis is characterized by an inflammatory process resulting in breakdown of the blood-eye and blood-retinal barriers, where cytokines play a central role. Common treatments, including corticosteroids and immunosuppressive medications, rely on the control of inflammation. In this study we will be able to evaluate the efficay and safety of thoses differents drugs in order to demonstrate how they may improve the symptoms of non-infectious intermediate, posterior, or pan- uveitis refractory uveitis by reducing inflammatory mediators involved in the pathogenesis of the disease.

1.5 **Rationale for Study Design**

Randomized clinical trial: Open- Indeed, owing to the different frequency of administration of the three compared treatments, this open-label study appeared the only feasible design. We will use a Bayesian Multi-Arm Multi-Stage (MAMS) design that aim at comparing several new treatments (multi-arm), in order to select or drop any treatment arm to move forward when such evidence already exists based on interim analyses, derived from the Xie and Tremmel's Bayesian design (Xie 2012).

This is a multicenter, randomized (1:1:1 ratio), prospective study comparing the efficacy and safety of Adalimumab, anakinra, and tocilizumab in subjects with active and refractory NIU.

Randomization will be stratified by retinal vasculitis, macular oedema and underlying disease. At randomization, the patient will be under treatment with prednisone as single therapy at 0.5 mg/kg/day with a maximum of 40 mg/day.

All systemic immunosuppressants must have been discontinued 30 days prior to the first study drug administration on Day 0. Patients will have access to oral corticosteroids if needed before Day 0.

In patients with bilateral uveitis, the eye with the highest disease activity will be chosen as the study eye.

Study Scheme (**Figure 1**):

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

Day 0: Inclusion and randomization in a 1:1:1 ratio will be stratified by inclusion retinal vasculitis, macular oedema and underlying disease; between three arms:

- **Arm 1: Adalimumab (80mg then 40 mg/14 days subcutaneously) (n=40) for 16 weeks**
- **Arm 2: Anakinra (100 mg/day subcutaneously) (n=40) for 16 weeks**
- **Arm 3: Tocilizumab (162 mg/7 days subcutaneously) (n=40) for 16 weeks.**

All patients will receive the same corticosteroid regimen at inclusion. All patients will receive corticosteroids at 0.5 mg/kg/day with a maximum of 40 mg/day at inclusion.

The following schedule of reduction of prednisone will apply to both groups as long as the disease is inactive:

- 0.5 mg/kg/day of prednisone until week 4.
- 0.4 mg/ kg/day of prednisone from week 4 to week 6
- 0.3 mg/ kg/day of prednisone from week 6 to week 8.
- 0.2 mg/ kg/day of prednisone from week 8 to week 12
- ≤0.1 mg/ kg/day of prednisone from week 12 to week 16

Week 4, 8, 12: Evaluation of secondary assessment criteria

Week 16: Evaluation of primary assessment criteria

Week 24: Evaluation of 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 24. Treatment between week 16 and 24 will be left at the discretion of the physician in charge of the patient. Physicians who decide to prescribe off protocol treatment with Adalimumab, anakinra or tocilizumab, beyond week 16 should monitor blood count and platelets at week 20.

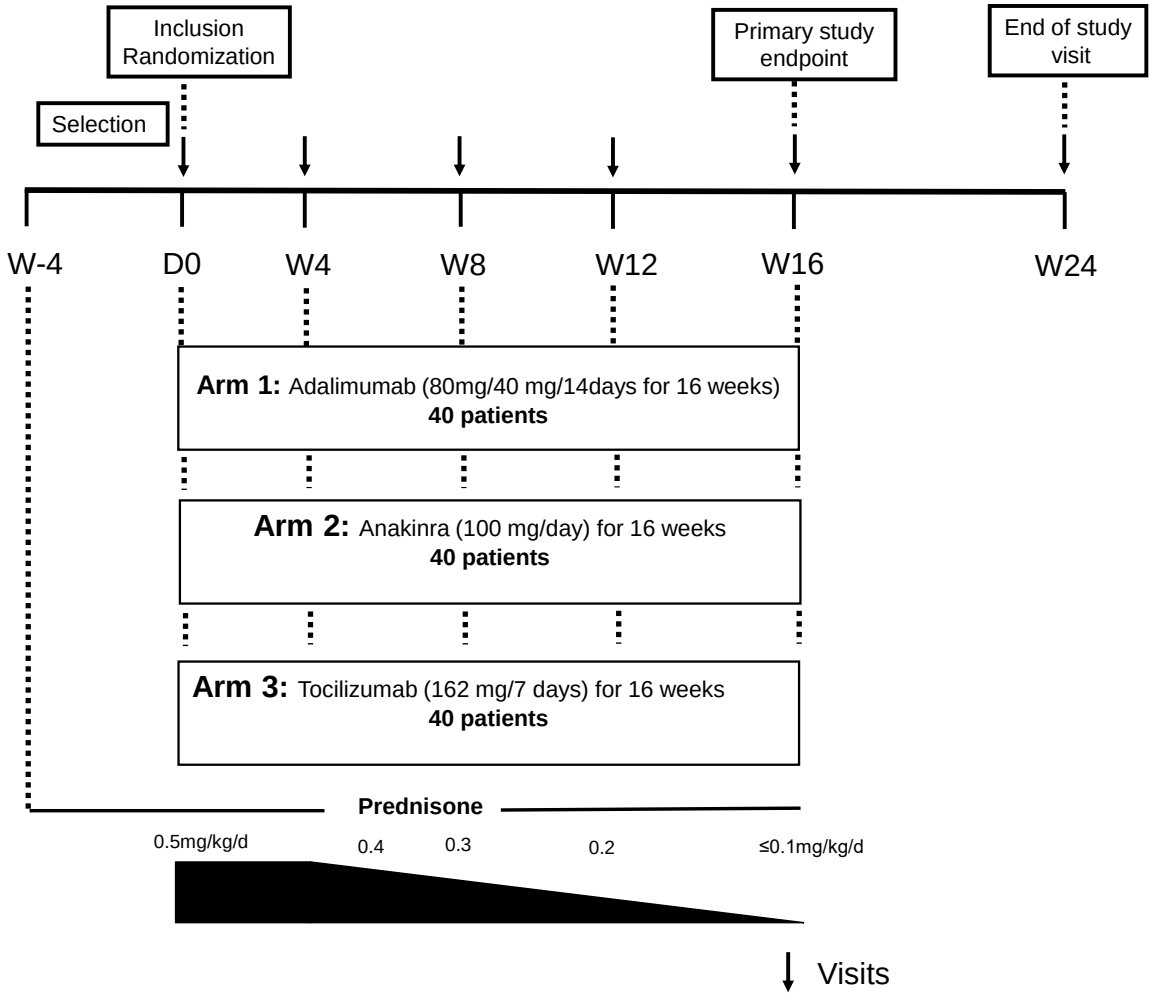
The purpose of additional follow-up beyond week 16 (from week 16 to week 24) is to gather safety and efficacy data with prolonged treatment with Adalimumab, anakinra and tocilizumab, as well as additional efficacy and safety data on patients who discontinue their treatment with Adalimumab, anakinra and tocilizumab at or before week 24. 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 16.

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

Figure 1 : Scheme of the study



1.6 **Rationale for Dose Level**

All systemic immunosuppressants must have been discontinued 30 days prior to the first study drug administration on Day 0.

In patients with bilateral uveitis, the eye with the highest disease activity will be chosen as the study eye.

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

- **Arm 1: Adalimumab (80mg then 40 mg/14 days subcutaneously) (n=40) for 16 weeks**
- **Arm 2: Anakinra (100 mg/day subcutaneously) (n=40) for 16 weeks**
- **Arm 3: Tocilizumab (162 mg/7 days subcutaneously) (n=40) for 16 weeks.**

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

At randomization (Day 0), patients receive treatment allocated by randomization. The following schedule of reduction of prednisone will apply to both groups as long as the disease is inactive:

- 0.5 mg/kg/day of prednisone until week 4.
- 0.4 mg/ kg/day of prednisone from week 4 to week 6
- 0.3 mg/ kg/day of prednisone from week 6 to week 8.
- 0.2 mg/ kg/day of prednisone from week 8 to week 12
  ≤0.1 mg/ kg/day of prednisone from week 12 to week 16.

All patients will be followed every 4 weeks from inclusion until week 16 and at week 24. 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.

Due to the CSI recommendation of the 18/06/2019, inclusion in the Anakinra arm has been stopped and the investigational medicinal product Anakinra has been discontinued in patients undergoing follow-up. Thus we modified the planned analyses and the randomisation accordingly. After the inclusion and randomisation of 54 patients, the next patients will be randomized 1:1 either in the 2 remaining arms:

- Arm 1: Adalimumab (80mg then 40mg/14 days subcutaneously) (n=40) for 16 weeks
- Arm 3: Tocilizumab (162 mg/7 days subcutaneously) (n=40) for 16 weeks.

In practice, it means that the remaining 66 planned patients will be randomized (33 in arm 1 and 33 in arm 3).

2. OBJECTIVES

The objective of this study is to compare the effectiveness and safety of Adalimumab, anakinra and tocilizumab in subjects with refractory non-infectious intermediate, posterior, or pan-uveitis.

2.1 **Primary Objective**

• To evaluate the efficacy of Adalimumab (80mg then 40mg/14 days) compared to anakinra (100mg/day) and tocilizumab (162mg/7 days) in subjects with refractory non-infectious intermediate, posterior, or pan- uveitis (NIU) and with a prednisone dose $\leq$ 0.1 mg/day of prednisone (or equivalent oral corticosteroid) at Week 16.

2.2 **Secondary Objectives**

• To evaluate the change in best corrected visual acuity (BCVA) at week 4, 8, 12, 16, and 24.
• To evaluate the safety of Adalimumab, anakinra and tocilizumab in patients with NIU at week 4, 8, 12, 16 and 24.
• To evaluate the change in macular edema at week 4, 8, 12, 16 and 24.
• To evaluate the change in other signs of ocular inflammation at week 4, 8, 12, 16 and 24.
• To evaluate the effect on retinal vessel leakage at week 16.
• To evaluate the effect of Adalimumab, anakinra and tocilizumab on steroid sparing at at week 4, 8, 12, 16 and 24.
• To evaluate the change in ocular inflammation in the anterior chamber at week 4, 8, 12, 16 and 24.
• To evaluate the effect on underlying systemic disease when appropriate at week 4, 8, 12, 16 and 24.
• To evaluate the effect on ocular disease at week 4, 8, 12, 16 and 24.
• To evaluate the number and time to relapse of uveitis and the characteristics of uveitis at worsening.
• To evaluate the time to treatment failure (Patients were considered to have treatment failure if they had new active, inflammatory lesions relative to baseline, a two-step increase in anterior chamber cell or vitreous haze grade, or a worsening of best corrected visual acuity by 15 or more letters, relative to the best state previously achieved, in at least one eye).

3. PLAN FOR THE RESEARCH

3.1 Concise description of the primary and secondary assessment criteria

3.1.1 Primary assessment criteria

Percentage of patients with at least 2-step reduction in Vitreous Haze (according to Miami 9-step Scale) and with a dose ≤ 0.1 mg/Kg/day of prednisone (or equivalent oral corticosteroid) at W16.

3.1.2 Secondary assessment criteria

• Mean change from baseline in Vitreous Haze at week 4, 8, 12, 16 and 24.

• 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) at week 4, 8, 12, 16 and 24.

• Mean change from baseline in BCVA (ETDRS letters score) at week 4, 8, 12, 16 and 24.

• Mean change from baseline in central retinal thickness measured with Optical Coherence Tomography (OCT) at week 4, 8, 12, 16 and 24.

• Percentage of patients with CRT <300 microns at week 4, 8, 12, 16 and 24.

• Percentage of patients without retinal vessel leakage on fluorescein angiography at week 16

• Measures of corticosteroid sparing:

- percent meeting targets [≤ 0.1 mg/day prednisone at week 16,
- mean change at week 4, 8, 12, 16 and 24.,
- mean dose at week 16,
- cumulative dose.

• Time to response onset,

• Underlying systemic disease when appropriate at week 4, 8, 12, 16 and 24.

• Ocular disease at week 4, 8, 12, 16 and 24.

• Number and time to relapse of uveitis and the characteristics of uveitis at worsening.

• Time to treatment failure (Patients were considered to have treatment failure if they had new active, inflammatory lesions relative to baseline, a two-step increase in anterior chamber cell or vitreous haze grade, or a worsening of best corrected visual acuity by 15 or more letters, relative to the best state previously achieved, in at least one eye).

• Adverse events including serious adverse events (SAE) at week 4, 8, 12, 16 and 24.

3.2 **Description of research methodology**

3.2.1 Experimental plan

This is a multicenter, Bayesian, multi-arm multi-stage, randomized (1:1:1), clinical trial, comparing the efficacy and safety of Adalimumab, anakinra and tocilizumab in subjects with active and refractory non-infectious intermediate, posterior, or pan-uveitis.

For the purposes of this study, active and refractory uveitic disease is defined as follow:

1. **Active disease:** either the presence of VH ≥4 on the Miami 9-step scale, and/or macular edema (CRT ≥300 microns), and/or other signs of intraocular inflammation (eg, perivascular sheathing of retinal vessels or leakage of retinal vessel on FA).

2. **Recently active disease:** evidence of activity within the 3 months prior to inclusion visit as per VH ≥4 on the Miami 9-step scale (or VH >1+ according to SUN classification), and/or macular edema (CRT ≥300 microns), and/or other signs of intraocular inflammation (e.g., perivascular sheathing of retinal vessels or leakage of retinal vessels on FA).

The activity status (active disease or recently active disease) has to be confirmed for all patients before the randomization by VH, OCT and FA assessments.

3. **Refractory disease:** At inclusion, subjects must be receiving oral corticosteroids (≥10 mg/day prednisone equivalent and <80mg/day) and at least one other immunosuppressive (azathioprine, methotrexate, mycophenolate mofetyl, cyclosporine, leflunomide, cyclophosphamide); or interferon (IFN)-α ; or being intolerant to such immunosuppressive therapies.

All systemic immunosuppressants must have been discontinued 30 days prior to the first study drug administration on Day 0. Patients will have access to oral corticosteroids if needed before Day 0.The study will be stratified by inclusion retinal vasculitis, macular oedema and underlying disease. At randomization, the patient will be under treatment with prednisone at initial dose of 0.5 mg/d (maximum of 40 mg/d).

One study eye will be selected. If both eyes are eligible for the study (as per inclusion/exclusion criteria) the following rules will be respected:

• The eye with active disease will be selected versus the eye with recently active disease, as defined by the protocol.

• If both eyes present active disease documented by the same unique parameter, the eye with the worse score will be selected.

• If both eyes present active disease defined by several parameters, the eye with the worse score ranked as follows will be selected: 1 Vitreous Haze; 2 cystoid macular edema (CME); 3 retinal vascular leakage and 4 best corrected visual acuity (BCVA).

If both eyes have an equivalent score, the right eye will be selected. All patients will receive a ocular coherence tomography (OCT) at selection, month 1, 2, 3, 4 and 6, and fluorescein and indocyanine green angiogram (FA/ICG) at selection, month 2 and 4 or at all visits in case of vasculitis or worsening.

All patients will be followed every 4 weeks from inclusion to week 16. 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 24. The purpose of additional follow-up beyond week 16 (at week 24) is to gather safety and efficacy data with prolonged treatment with adalimumab, anakinra and tocilizumab, as well as additional efficacy and safety data on patients who discontinue their treatment with Adalimumab, anakinra and tocilizumab at or before week 24.

3.2.2 Number of centres participating

This national multicenters study, involving 37 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 a investigator 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.

3.2.3 Identification of the subjects

For this research, each patient is identified by a Subject Number (Subject No) that is assigned when the patient has signed the Study Informed Consent Form and is retained as the unique reference for the patient throughout his/her entire participation in the trial.

The Subject No consists of the:

Centre Number (3 numerical positions) - the patient inclusion number (4 numerical positions) - and patient's initials (surname initial - first name initial)

The allocation of the Subject No will be allocated using the eCRF web site.

3.2.4 Inclusion and Randomization

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 regestrited by connecting the 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 three groups will be made in a 1:1:1 ratio.

Due to the CSI recommendation of the 18/06/2019, inclusion in the Anakinra arm has been stopped and the investigational medicinal product Anakinra has been discontinued in patients undergoing follow-up. Thus we modified the planned analyses and the randomisation accordingly. After the inclusion and randomisation of 54 patients, the next patients will be randomized 1:1 either in the 2 remaining arms (adalimumab arm and tocilizumab arm).

The randomization list will be designed by the Sponsor/designee, and stratified by retinal vasculitis, macular oedema and underlying disease; between three 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 randomization.

4. PROCEDURE FOR THE RESEARCH

4.1 Selection visit

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

Subjects whose consent is sought	**Who informs the subject and collects their consent**	**When is the subject informed**	**When is the subject's consent collected**
Patient	*Ophtalmologist or Internists or rheumatologist,*	*Selection visit*	*Inclusion visit*

The treatment will be started at randomization 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 wich include fundoscopy, Vitreous Haze, (Tyndall and flare, BCVA (ETDRS letters 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, total bilirubin, albumin), ESR, CRP, fibrinogen, haptoglobin, orosomucoid, urea, creatinine, glucose, ,quantiferon test, HIV, HBV, HCV serologies and TPHA-VDRL and chest xray or thoracic CT scan, ECG, and Triglyceride and cholesterol (at day 0, and W8).

If HIV, HBV, HCV serologies and TPHA-VDRL have been realized within 1 month prior to inclusion visit, repeated test is unnecessary.

If quantiferon test, within 6 month prior to screening visit, repeated test is unnecessary.

- inform the patient about the protocol, and give them the information and consent form.

4.2 **Inclusion and randomization visit**

- The inclusion/randomization visit takes place at Day 0.

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, total bilirubin, albumin), ESR, CRP, fibrinogen, haptoglobin, orosomucoid, urea, creatinine, glucose, 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 age.
- When the patient is considered eligible, investigator will insure the inclusion and randomization on eCRF web site (CleanWeb).
- Assure the prescription of study treatment by using eCRF
- Assess Quality of life
- Provide the first treatment and patient card to patient

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

- **Arm 1 (n=40 patients) Adalimumab** 80mg then 40mg/14 days subcutaneously for 16 weeks
- **Arm 2 (n=40 patients)** Anakinra (100 mg/day subcutaneously) for 16 weeks
- **Arm 3 (n=40 patients)** Tocilizumab (162 mg/kg/7 days subcutaneously) for 16 weeks

The first administration of the treatment will be done in the service by a nurse who will train the patient to the modalities of injection to enable him to carry out the following.

Due to the CSI recommendation of the 18/06/2019, inclusion in the Anakinra arm has been stopped and the investigational medicinal product Anakinra has been discontinued in patients undergoing follow-up. Thus, we modified the planned analyses and the randomisation accordingly. After the inclusion and randomisation of 54 patients, the next patients will be randomized 1:1 either in the 2 remaining arms:

- Arm 1: Adalimumab (80mg then 40mg/14 days subcutaneously) (n=40) for 16 weeks
- Arm 3: Tocilizumab (162 mg/7 days subcutaneously) (n=40) for 16 weeks.

In practice, it means that the remaining 66 planned patients will be randomized (33 in arm 1 and 33 in arm 3).

4.3 **Follow-up Visits**

Monitoring should continue for all patients until the end of the Study according to the schedule, even if they discontinue treatment. Consultations at these visits will be with the patient's usual Study investigator. Patients will be reviewed at 4, 8, 12, 16 and 24 weeks and will have:

- Ophtalmic examination by ophthalmologist to follow the efficacy, will take place before the internist visit, (including fundoscopy, Vitreous Haze, (Tyndall and flare), change from baseline in BCVA (ETDRS letters score), Optical Coherence Tomography (OCT) will be performed at 4, 8, 12, 16 and 24 weeks and fluorescein and indocyanine green angiogram (FA/ICG) at selection and week 16 or in case of vasculitis occurrence during follow-up or worsening).
- A physical examination will be performed by the patient's Study internist at each visit to dispensiate the treatment and follow tolerance (neurological exam to detect demyelinating disorders, infections, skin cancer, lymphoma, and autoimmune disorder)
- At each visit blood count, platelets, serum electrolytes, creatinine, ESR, CRP, fibrinogen, haptoglobin, orosomucoid, CBC, liver function tests (AST, ALT, GGT, total bilirubin, albumin), and glucose will be measured.
- For childbearing women, urine pregnancy test will be performed at 4, 8, 12, and 16 weeks.

- Quality of life Assessment at 16 and 24 weeks.

- **Arm 1 (n=40 patients)** Adalimumab 80mg then 40mg/14 days subcutaneously
- **Arm 2 (n=40 patients)** Anakinra (100 mg/day subcutaneously)
- **Arm 3 (n=40 patients)** Tocilizumab (162 mg/kg/7 days subcutaneously)

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 16. All patients will be followed every 4 weeks from inclusion to week 16. 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 24. The purpose of additional follow-up beyond week 16 (at week 24) is to gather safety and efficacy data with prolonged treatment with Adalimumab, anakinra and tocilizumab, as well as additional efficacy and safety data on patients who discontinue their treatment with Adalimumab, anakinra and tocilizumab at or before week 24. Treatment between week 16 and 24 will be left at the discretion of the physician in charge of the patient. Physicians who decide to prescribe off protocol treatment with Adalimumab, anakinra or tocilizumab, beyond week 16 should monitor blood count and platelets at week 20.

4.4 **End of research visit**

After Month 6, all subjects will be followed after the study according to their usual routine hospital care every 3 months until one year.

4.5 **Expected length of participation and description of the chronology and duration of the research**

The total duration of the Study will be 63 months (5.25 years). The duration of the inclusion phase will be 56 months. The duration of participation of each patient will be of 7 months maximum. The duration of experimental treatment of each patient will be 16 weeks.

4.6 **Table summarising the chronology of the research**

	W-4 to D0	D0	W4	W8	W12	**W16§**	W20***	W24
Selection visit Oral and written Information about the protocol	R							
Verification of inclusion and non inclusion criteria	R	R						
Inclusion/randomization visit signature of informed consent		R						
Clinical examination	C	C	C	C	C	C	C	C
Ophtalmologic examination*	C		C	R	C	**R**		C
Biological tests **	C		C	C	C	C	**C**	C
Inflammatory proteins	C		C	C	C	C		C
Quantiferon, HIV, HBV, HCV serologies and TPHA-VDRL***	C							
Pregnancy test		R (βHCG or urine)	R (urine)	R (urine)	R (urine)	R (urine)		
ECG	C							
Chest X Ray or thoracic CT scan	C							
QOL questionnaires		R				**R**		R
Dispensation of treatments		R	R	R	R			
Compliance		R	R	R	R	**R**		
Adverse events		R	R	R	R	**R**		R

C= care / R = 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 (ETDRS letters score), Optical Coherence Tomography (OCT) and fluorescein angiography at selection and week 16 or in case of vasculitis occurrence during follow-up or worsening.

** complete blood count with platelets, serum electrolytes, liver function tests (AST, ALT, GGT, total bilirubin, albumin), fibrinogen, haptoglobin, orosomucoid, urea, creatinine, glucose. Triglyceride and cholesterol (at day 0, and W8).
***Physicians who decide to prescribe off protocol treatment with Adalimumab, anakinra or tocilizumab, beyond week 16 should monitor blood count and platelets at week 20.
*** If HIV, HBV, HCV serologies and TPHA-VDRL have been realized within 1 month prior to inclusion, repeated test is unnecessary.
*** If quantiferon test, within 6 month prior to screening, repeated test is unnecessary.

4.7 **Measures to Minimize Bias**

The following measures have been taken in order to minimize bias:

- Centralized balanced randomization, with stratification by retinal vasculitis, macular oedema and underlying disease.
- Treatment group allocation through CleanWeb e CRF; the randomization list will be designed by the Sponsor or designee
- Predefined standardized corticosteroid tapering procedure beginning at week 4

- To the extent possible, the same evaluator will be used throughout the study for a given subject and ophthalmologic assessment

4.8 **Distinction between care and research**

Procedures and treatments carried out as part of the research	**Procedures and treatments associated with <u>care</u>**	**Procedures and treatments added because of <u>the research</u>**
Treatments	- oral prednisone - Reduction of corticosteroid regimen - supportive treatment to reduce the adverse effects associated with the use of steroids - systemic immunosuppressant	- Adalimumab 80mg then 40mg/14 days subcutaneously - Anakinra 100 mg/day subcutaneously (+histamine-H1 blocker) - Tocilizumab 162 mg/kg/7 days subcutaneously Due to the CSI recommendation of the 18/06/2019, inclusion in the Anakinra arm has been stopped and the investigational medicinal product Anakinra has been discontinued in patients undergoing follow-up.
Consultations	- one visit per month	- Visit with ophtalmologist at 8 and 16 weeks
Blood samples	- blood sampling every 4 weeks	- bHCG plasmatic or urine pregnancy test at inclusion and urine pregnancy test at 4, 8, 12 and 16 weeks
Imaging	- ECG: before starting treatment - Chest X Ray before starting treatment - Fundoscopy, Optical Coherence Tomography (OCT) and fluorescein angiography before starting treatment and every 2 months	- Fundoscopy, Optical Coherence Tomography (OCT) at 8 and 16 weeks and fluorescein angiography at 16 weeks
Others		- QOL questionnaires at D0, 16 and 24 weeks

4.9 **Terminations rules**

4.9.1 Criteria and methods for prematurely terminating the research treatment

4.9.1.1 *Different situations*

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

The investigator must:

- Document the reason(s)
- Collect the assessment criteria when participation in the researchends, if the subject agrees
- Normal management of the subject's illness must be required anyway specially if SAE.

4.9.1.2 *Criteria and methods for the premature termination of the research*

Any subject can withdraw from participating in the research at any time and for any reason.
The investigator can temporarily or permanently end a subject's participation in the research for any reason that affects the subject's safety or which would be in the subject's best interests.

The subject must be permanently discontinued from treatment in the event of any of the following:

- Pregnancy
- During the study: Active TB, or positive results from the IGRA indicating latent TB and the subject’s refusal to complete a prophylactic TB treatment course
- Serious allergic study drug reaction including anaphylactic reaction
- Flare of the disease, or worsening ocular inflammation requiring another immunosuppressant and/or immunomodulator
- Treatment protocol interruption >15 days
- Serious infections
- Confirmed absolute neutropenia (< 1.0 x 10^9/L)
- Malignancy other than carcinoma in situ of the cervix, or adequately treated, non-metastatic squamous or basal cell carcinoma of the skin
- Multiple sclerosis or any other demyelinating or neurodegenerative disorder
- Auto-immune disorder
- HIV/AIDS, viral hepatitis (B or C) known during the study

- Consent withdrawal
- Any condition, which in the opinion of the investigator, would place the subject at undue risk by continuing the study treatment
- In case of lost to follow up: All reasonable efforts must be made to locate subjects to determine and report their ongoing status

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

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

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

In a case of premature termination of treatment, the reason(s) for a subject's discontinuation treatment must be clearly documented in the subject's medical records and on the appropriate page of the eCRF and follow up visits will be done according to protocol calendar until week 24 except in case of consent withdrawal.

The subject will receive the most appropriate care in the opinion of the investigator (possibly including rescue therapy for an occurrence of uveitic disease). The subject will receive appropriate treatment(s) by her or his physician.
Ending a subject's participation does not affect the normal management of the subject's illness in any way.
The adverse event reporting period for safety surveillance begins when the subject is included into the trial (date of first signature of informed consent) and continues through the trial's post treatment follow-up period, defined as week 24 (±3) days after last trial drug administration.

If there are serious adverse events, the investigator must notify the sponsor and monitor the subject for 1 month following the premature termination of treatment. If treatment is stopped prematurely due to a serious adverse event, a serious adverse event notification form will be sent by e-mail (**eig-vigilance.drc@aphp.fr**) to the sponsor. The serious adverse event will be monitored until it is resolved.

4.9.3 Methods for replacing subjects, if applicable

If a patient consent is withdrawn then this patient will be excluded from the analysis except if the patient allows investigators to use the already collected data. If the study is still in the inclusion period, a new patient will be included, otherwise all patients included will be analyzed and not replaced (Intention to treat Analysis).

4.9.4 Terminating part or all of the research

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

- first of all, if suspected unexpected serious adverse reactions (SUSARs) are seen in an arm being treated or if there is a discrepancy in the serious adverse reactions between the 3 arms being treated, and which require a reassessment of the benefit-risk ratio for the research. In the particular sitation in which only one arm is stopped, the trial would continue with the two remaining arms.
- Every 10 patients in each arm an interim analysis will be performed: one arm could be stopped according to the the Data and Safety Monitoring Board and the trial would continue with the two remaining arms.

Due to the CSI recommendation of the 18/06/2019, inclusion in the Anakinra arm has been stopped and the investigational medicinal product Anakinra has been discontinued in patients undergoing follow-up. Thus we modified the planned analyses and the randomisation accordingly. After the inclusion and randomisation of 54 patients, the next patients will be randomized 1:1 either in the 2 remaining arms (adalimumab arm and tocilizumab arm).

- Unexpected facts, new information about the product, in light of which the objectives of the research or of the clinical programme are unlikely to be achieved, can lead AP-HP as sponsor or the Competent Authority (ANSM) to prematurely halt the research**.**
- AP-HP as sponsor reserves the right to permanently suspend inclusions at any time if it appears that the inclusion objectives are not met.

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

5. ELIGIBILITY CRITERIA

5.1 Inclusion criteria

The eligibility criteria will be checked at the selection visit (which takes place within four weeks 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. 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
3. Currently uncontrolled uveitic disease. Uncontrolled uveitic disease is defined as fulfilling 1 of the two following criteria within 4 weeks prior to inclusion:
    a. Active inflammatory chorioretinal and/or inflammatory retinal vascular lesions and/or macular edema (CRT ≥300 microns), OR
    b. Vitreous haze grade ≥4 on the Miami 9-step scale (or VH >1+ according to SUN/NEI classification)
4. a. Patient who are receiving prednisone ≥10 mg/day and <80mg/day (or equivalent dose of another corticosteroid) at stable dose 30 days prior to the first study drug administration on Day 0 and who received at least 1 other systemic immunosuppressant (*All systemic immunosuppressants must have been discontinued 30 days prior to the first study drug administration on Day 0)*, or,
    b. Patient who received IFNα (*All systemic immunosuppressants must have been discontinued 30 days prior to the first study drug administration on Day 0),* or,
    c. To be intolerant to immunosuppressant
5. Best corrected visual acuity (BCVA) by ETDRS ≥ to 20/400 in either eye
6. Stable dose for two weeks prior to inclusion of topical corticosteroids and/or NSAIDs
7. Male or female, age ≥ 18 at Inclusion
8. Weight 40 – 120 kg (88.2 – 264 lbs) at Inclusion
9. Chest X-ray or thoracic CT scan results (postero-anterior and lateral) within 12 weeks prior to Inclusion with no evidence of active Tuberculosis, active infection, or malignancy
10. For female subjects of child-bearing age, a negative serum or urine pregnancy test
11. 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 and 5 months after stopping therapy for roactemra and adalimumab, respectively. Birth control 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:

- combined (estrogen and progestogen containing) hormonal contraception

associated with inhibition of ovulation 1:

  - oral
  - intravaginal
  - transdermal

- progestogen-only hormonal contraception associated with inhibition of ovulation 1:
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- 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).

12. A QuantiFERON®-Tuberculosis (TB) test within 6 months prior to Screening

5.2 **Non-inclusion criteria**

Subjects will be not 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. Presence of cataract or posterior capsular opacification so severe that an assessment of the posterior segment of either eye is inadequate or impossible
4. Contraindication to mydriasis in either eye or presence of posterior synechiae in the study eye such that mydriasis is inadequate for posterior segment examination
5. Intraocular pressure ≥ 25mmHg by Goldmann tonometry or advanced glaucoma in either eye
6. Monocular patient
7. Active tuberculosis

8. Known positive syphilis serology, HIV antibody, hepatitis B surface antigen and/or anti-nucleocapsid antibody of hepatitis B virus and/or Hepatitis C virus within 1 month prior to inclusion.
9. 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.
10. History of severe allergic or anaphylactic reactions to monoclonal antibodies
11. Infectious disease:
    a. Fever or infection requiring treatment with antibiotics within 3 weeks prior to Inclusion
    b. History of recurrent infection or predisposition to infection
12. Known immunodeficiency
13. History of multiple sclerosis and/or demyelinating disorder
14. Laboratory values assessed during Inclusion:
    a. Hemoglobin < 8 g/dL
    b. WBC < 2.0 × 103/mm3
    c. Platelet count < 80× 10^3/mm^3
    d. Glomerular filtration rates (GFR) <30ml/min.
    e. Transaminases > 3 times upper normal value
15. Use of the following systemic treatments during the specified periods:
    a. Any previous systemic biologic therapy
    b. Treatment with any systemic alkylating agents within 12 months prior to Inclusion (e.g., cyclophosphamide, chlorambucil) or dose modification of immunosuppressant 30 days before inclusion
    c. Any live (attenuated) vaccine within 3 months prior to Inclusion
16. Use of the following ocular treatments during the specified periods:
    a. Previous anti-VEGF intravitreal therapy (applies to both eyes) within 3 months prior to Inclusion, or anticipated use during the study period
    b. Treatment with dexamethasone intravitreal implant [Ozurdex®] within 6 months prior to Inclusion
    c. Intravitreal corticosteroids within 3 months prior to Inclusion. Previous Subtenon's corticosteroid injections are permitted if administered at least 2 months prior to Inclusion
17. Stage III and IV New York Heart Association (NYHA) cardiac insufficiency

5.3 **Recruitment methods**

The dynamism of the French national reference center for inflammatory ocular diseases and uveitis network, habit of investigating centers to participate in studies concerning the treatment of uveitis, and the level of recruitment in the investigation centers ensures the feasibility of this study. The French uveitis network recently conducted a study on efficacy of anti-TNF in NIU and recruited 250 patients in 1 year.

	Number of subjects
Total number of subjects to be included	*120*
Number of centres	*37*
Inclusion period (months)	*56*
Number of subjects/centre	*8*
Number of subjects/centre/month	***0.33***

6. TREATMENT ADMINISTERED TO RESEARCH PARTICIPANTS

6.1 Description of the experimental medications

Eligible patients (n=120) with active and refractory non-infectious posterior, or pan- uveitis will be randomized at 1:1:1 into three groups during the inclusion/randomization visit (D0):

- **Arm 1 (n=40): patients will receive prednisone (at the dose shown below) + Adalimumab (80mg then 40 mg/14 days starting at D0 subcutaneously) for 16 weeks.**
- **Arm 2 (n=40): patients will receive prednisone (at the dose shown below) + anakinra (100 mg/day subcutaneously) for 16 weeks**
- **Arm 3 (n=40): patients will receive prednisone (at the dose shown below) + tocilizumab (162 mg/7 days subcutaneously) for 16 weeks.**

Due to the CSI recommendation of the 18/06/2019, inclusion in the Anakinra arm has been stopped and the investigational medicinal product Anakinra has been discontinued in patients undergoing follow-up. Thus, we modified the planned analyses and the randomisation accordingly. After the inclusion and randomisation of 54 patients, the next patients will be randomized 1:1 either in the 2 remaining arms:

- Arm 1: Adalimumab (80mg then 40mg/14 days subcutaneously) (n=40) for 16 weeks
- Arm 3: Tocilizumab (162 mg/7 days subcutaneously) (n=40) for 16 weeks.

In practice, it means that the remaining 66 planned patients will be randomized (33 in arm 1 and 33 in arm 3).

6.1.1 Experimental medication 1

Adalimumab (Humira®) 40 mg solution for injection in pre-filled pen.

Each 0.8 ml single dose pre-filled pen contains 40 mg of adalimumab

Patient will be treated with 80mg loading dose then 40mg every 14 days starting at D0, subcutaneously for 16 weeks (9 injections per patient).

Pre-filled pens should be stored in a refrigerator (2°C – 8°C), should not be frozen and kept in the outer carton in order to protect from light.

A single pen may be stored at temperatures up to a maximum of 25°C for a period of up to 14 days. The pen must be protected from light, and discarded if not used within the 14-day period.

Humira® will be packaged in its standard french commercial packaging (one box with 2 pens), completed with an additional label in accordance with regulatory requirements for investigational medicinal product.

For adverse events related to the experimental medication refer to the summary of Product Characteristics (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).

6.1.2 Experimental medication 2

Anakinra (Kineret®) 100 mg solution for injection in pre-filled syringe.
Each pre-filled syringe contains 100 mg of anakinra* per 0.67 ml (150 mg/ml).
Patients will be treated with 100mg per day subcutaneously for 16 weeks (112 injections per patients). Associated medications will include histamine H1 blocker for the first month.
Pre-filled syringe should be store in a refrigerator (2 °C – 8 °C), should not be frozen and should be store in the original container in order to protect from light.
Kineret may be removed from the refrigerator for 12 hours at temperature not above 25 °C, without exceeding the expiry date. At the end of this period, the product must not be put back in the refrigerator and must be disposed of.
Kineret® will be packaged in its standard french commercial packaging (one box with 7 syringes), completed with an additional label in accordance with regulatory requirements for investigational medicinal product.
For adverse events related to the experimental medication refer to the summary of Product Characteristics (SmPC) for Kineret (see EMEA website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000363/human_med_000874.jsp&mid=WC0b01ac058001d124).

6.1.3 Experimental medication 3

Tocilizumab (RoActemra®) 162 mg solution for injection in pre-filled syringe.
Each pre-filled syringe contains 162 mg of tocilizumab in 0.9 ml.
Patient will be treated with 162mg per week, subcutaneously, for 16 weeks (17 injections per patients).
Pre-filled syringes should be stored in a refrigerator (2°C–8°C), should not be frozen and should be kept in the outer carton in order to protect from light and moisture.
Once removed from the refrigerator, RoActemra must be administered within 8 hours and should not be kept above 30°C.
RoActemra® will be packaged in its standard french commercial packaging (one box with 4 syringes), completed with an additional label in accordance with regulatory requirements for investigational medicinal product.

For adverse events related to the experimental medication refer to the summary of Product Characteristics (SmPC) for RoActemra (see EMEA website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000955/human_med_001042.jsp&mid=WC0b01ac058001d124).

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

6.2.1 Systemic Corticosteroid Therapy Corticosteroids

All patients will receive the same corticosteroid regimen at inclusion.

The three treatment groups will receive the same corticosteroid regimen. All patients with NIU will receive oral prednisone 0.5 mg/kg/day with a maximum of 40 mg/day of prednisone or equivalence at inclusion visit. A progressive reduction of corticosteroids will then be made in stages for both groups as follows:

-- 0.5 mg/kg/day of prednisone until week 4.
-- 0.4 mg/ kg/day of prednisone from week 4 to week 6
-- 0.3 mg/ kg/day of prednisone from week 6 to week 8.
-- 0.2 mg/ kg/day of prednisone from week 8 to week 12
-- ≤0.1 mg/ kg/day of prednisone from week 12 to week 16.

This above schedule of prednisone is recommended as guideline

Side effects of corticosteroids

These are related to the cumulative dose administered, ie the amount taken from the onset of the disease. See the Adult adverse event severity rating scale. They are numerous, but there are ways to reduce their intensity:

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

- Steroids can induce the onset of diabetes

6.2.2 Fluorescein and indocyanin green

All patients will receive a fluorescein and indocyanine green angiogram (FA/ICG) at selection, and week 16 or in case of occurrence of vasculitis or worsening.
Examination at month 4 (S16) is added by the research.
Products will be used according to their respective marketing authorization and angiogram made following local usual procedure.

6.2.3 Antihistaminic (Kineret arm)

Patient in the Kineret arm will receive concomitant histamine-H1 blocker during the first month of treatment.

6.2.4 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 or Tocilizumab with a positive interferon-gamma release assay (IGRA) (e.g.,QuantiFERON®-TB Gold or T-spot TB® Test) at inclusion.

6.3 Description of the traceability elements that accompany the experimental medication or medications

The experimental product will be supplied by AP-HP. DEC- AGEPS insures the labeling and the distribution to the study sites
In each site, the pharmacist will ensure that medicinal products are stored under recommendation storage conditions and in accordance with applicable regulatory requirements.
To ensure adequate records, medicinal product will be accounted in the drug accountability inventory forms as instructed by AP-HP in the pharmacy annex.
At the end of the clinical trial all drug supplies unused will be destroyed by each study site after AP-HP authorization.
For more details see the pharmacy annex.

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

6.4.1 Authorised 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 treatment will be administered routinely starting on day 0:

- a potassium supplement (DIFFU K, 1 capsule 3 times/day)
- a calcium/vitamin D supplement (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.
- a diet low in fat, salt and rapidly-absorbed sugars.

Topical treatment for cycloplegia is permitted.

6.4.2 Prohibited treatments

All systemic immunosuppressants must have been discontinued 30 days prior to the first study drug administration on Day 0. Immunosuppressive drugs should not be prescribed in the month previous to inclusion.

6.5 **Methods for monitoring compliance with the treatment**

Subjects will receive subject diaries before starting the experimental treatment and the diaries will be the only ones allowed to document self-administration. Subjects should be instructed to bring with them to each visit all treatment packages, including empty packages and unused treatment, in order to allow the assessment of compliance with trial treatment. The investigator will review the subject diary at each visit of the subject at the hospital. At that time a new one 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.

7. ASSESSMENT OF EFFICACY

7.1 Description of parameters for assessing efficacy

The primary endpoint will be percentage of patients with at least 2-step reduction in Vitreous Haze (according to Miami 9-step Scale) and with a dose ≤ 0.1 mg/Kg/day of prednisone (or equivalent oral corticosteroid) at W16.

For the secondary endpoints, the different aspects of clinical response will be evaluated monthly from day 0 to week 16 and at the end of study (week 24). For details see § 3 Plan for the research.

7.2 Anticipated methods and timetable for measuring, collecting and analysing the parameters for assessing efficacy

A physical examination will be performed by the patient's Study physician at each visit.
Ophtalmic examination will be performed at 4, 8, 12, 16 and 24 weeks and will include:

- Mean change from baseline in Vitreous Haze
- 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 in BCVA (ETDRS letters score)
- Mean change from baseline in central retinal thickness measured with Optical Coherence Tomography (OCT)
- Percentage of patients with CRT <300 microns
- Percentage of patients without retinal vessel leakage on fluorescein angiography (performed only at 16 week)

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 by the following outcome measures for the timing of the assessments.

- Adverse events
- Clinically significant abnormal 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 values (hematology, chemistry, and urinalysis) compared to baseline for listing of the assessments and for the timing of the assessments).
- Standard 12-lead ECGs will be performed after 10 minutes rest with subject in the supine position, relaxed and not talking. These will be interpreted either by the investigator, if she/he considers herself/himself to have the expertise, or by a cardiologist or other physician capable of interpreting an ECG. The results will be recorded in the appropriate section of the eCRF. ECG abnormalities will be reported as adverse events only if they are considered clinically significant by the investigator and they are not already entered as pre-existing conditions, or if they constitute evidence of a deterioration of a pre-existing condition.
- Chest X-rays (frontal and lateral) or thoracic CT scan will be performed at selection (unless performed within 12 week prior to 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 only if they are considered clinically significant by the investigator and they are not already entered as pre-existing conditions, or if they constitute evidence of a deterioration of a pre-existing condition.
- Clinically significant abnormalities observed on optical coherence tomography
- Intraocular pressure

8. SPECIFIC RESEARCH COMMITTEES

8.1 Steering committee

Members of the committee:

Investigator Coordonator Pr David SAADOUN	Internist	Hospital Pitie Salpetriere	Tel.0142178088 Email: david.saadoun@aphp.fr
Co-coordinator Pr Bahram BODAGHI	Ophtalmologist	Hospital Pitie Salpetriere	Tel. 0142163728 Email: bahram.bodaghi@aphp.fr
Pr Pascal SEVE	Internist	Hospital Croix rousse	
Methodologist Mathieu RESCHE-RIGON	Methodologist	APHP, Hôpital Saint-Louis	Tel 01 42 49 97 47 Email: matthieu.resche-rigon@univ-paris-diderot.fr
Others Elodie SOLER	Project Manger	DRCI-Siège	Tel 01 44 84 17 35 Email: elodie.soler@aphp.fr
Nabil RAKED	Clinical Research Coordinator	DRCI-URC du GH saint Louis Lariboisière, site Saint Louis Hôpital Saint	01 42 49 97 49 Email: nabil.raked@univ-paris-diderot.fr

		Louis	

Missions: Organization of the research, coordination of informations relative to protocol.

Operating methods: - will meet every 3 months or more if necessary.

9. SAFETY ASSESSMENT - RISKS AND RESTRICTIONS ADDED BY THE RESEARCH

9.1 Description of parameters for assessing safety

The safety assessment shall be done by collecting all adverse events that occur during the research. All events shall be graded according to the CTCAE (Common Terminology Criteria for Adverse Events) document, version 4 (*http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf*).
Serious Adverse events shall be assessed, collected and reported to the Vigilance department of the sponsor (DRCI)
For any question concerning the reporting of an adverse event, the Vigilance Department of the DRCI can be contacted by e-mail at: vigilance.drc@aphp.fr

9.2 Procedures in place for recording and reporting adverse events

9.2.1 Definitions

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

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

Adverse drug reaction : Any response to a medicinal product which is noxious and unintended.

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

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

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

New safety issue

Any new information regarding safety:

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

Examples:

a) any clinically significant increase in the frequency of an expected serious adverse reaction occurring
b) suspected unexpected serious adverse reactions (SUSAR) occurring in patients who have finished the trial and about whom the sponsor is notified by the investigator, who also provides any follow-up reports
c) any new fact relating to the conduct of the clinical trial or the development of the experimental medication, if the new fact is likely to affect participant safety
   Examples:
   a. a serious adverse event likely to be related to the investigations and to the trial's diagnostic procedures and which could modify the conduct of this trial
   b. a significant risk for the trial participants such as ineffectiveness of the experimental medication used in the trial in treating a life-threatening illness
   c. significant safety results from a recently completed research carried out on animals (such as a carcinogenicity research)
d) the premature termination, or temporary interruption, of a trial conducted with the same experimental medication in another country, for safety reasons
e) an unexpected serious adverse reaction associated with a non-experimental medication required for carrying out the trial, (e.g., challenge agents, rescue treatment)
   a. recommendations from the data safety monitoring board (DSMB), if applicable, if they are relevant to the safety of the participants
   b. any unexpected serious adverse reaction reported to the sponsor by another sponsor of a trial carried out in a different country but relating to the same medication

9.2.2 The investigator's roles:

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

The investigator must notify the sponsor, **immediately on the day when the investigator becomes aware**, of all the serious adverse events, except those that are listed in the protocol (see. section 9.2.3.1)

These serious adverse events are recorded in the "adverse event" section of the case report form and the investigator must immediately notify the sponsor's Vigilance division (see 9.3).

9.2.2.2 ***The investigator's other roles***

The investigator must document the serious adverse event as thoroughly as possible and provide the medical diagnosis, if possible.

The investigator assesses the severity of the adverse events:

- either by using an adverse events: rating scale, attached to the protocol: *Common Terminology Criteria for Averse Events (v4.0) [National Cancer Institute]*
- *or by using more general terms:*
    - *Mild: tolerated by the patient, does not interfere with daily activities*
    - *Moderate: sufficiently uncomfortable to affect daily activities*
    - *Serious: preventing daily activities*

The investigator assesses the causal relationship between the serious adverse events and the experimental medication and the procedures added by the research**.**

9.2.3 Specific features of the protocol

All serious and non-serious adverse events must be reported in the CRF.

9.2.3.1 ***Serious adverse events that do not require the investigator to immediately notify the sponsor***

These serious adverse events are only recorded in the "adverse event" section of the case report form.

Normal and natural evolution of the pathology:

- *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
- worsening of the disease under study (progression)

Special circumstances

In some circumstances, the investigator can delayed event's report. For examples: hospitalization for a preexisting condition, hospitalization for medical or surgical treatment before the planned research, transition to emergency lower than 12 hours, hospitalization for a social or an administrative reason.

Adverse events likely to be associated with the treatments prescribed as part of the patient's care during the monitoring of the research

9.2.3.2 ***Serious adverse events that require the investigator to immediately notify the sponsor***

The investigator must report immediately all adverse events that meet one of the seriousness criteria below, except for events listed in section 9.2.3.1. as not requiring immediate notification to the sponsor:

1- Death

2- Life threatening situation

3- Requiring hospitalisation or prolonging hospitalisation

4- Persistent or significant disability or incapacity

5- Congenital abnormality or birth defect

6- Or any other adverse event considered "medically significant"

Serious adverse events related to the experimental medication and which are expected are described in **summaries of Product Characteristics** (SmPC) available on EMEA website (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124) for the following drugs:

- Adalimumab (Humira®) 40mg
- Anakinra (Kineret®) 100mg
- Tocilizumab (Roactemra®) 162mg

Adverse events related to the research procedures:

- Corticosteroid regimen: refer to SmPC of the specialty administered.
- Reduction of corticosteroid regimen
- Prophylactic tuberculosis treatment for patients treated with Adalimumab: refer to SmPC of Rifinah® (isionazide+rifampicine), Rifadine® (rifampicine) or Rimifon® (isoniazide).
- Administration of anti-histaminics for patients treated with Anakinra: refer to SmPC of Xyzal® (levocetirizine dihydrochloride), Aerius® (Desloratadine)
- Use of fluorescein and indocyanine green for angiogram: refer to SmPC of Fluoresceine Sodique Faure® (Fluoresceine) and Infracyanine® (Vert d'Indocyanine).

Events of Special Interest (Serious or Non-serious)

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

- Serious infections leading to death, hospitalization and/or IV antibiotics.
- Neutropenia (defined as absolute neutrophil count [ANC] < 1.0 x 109/L)
- Autoimmune and demyelinating disorders regardless of the seriousness of the events
- Malignancy other than carcinoma in situ of the cervix, or adequately treated, non-metastatic squamous or basal cell carcinoma of the skin
- HIV/AIDS, viral hepatitis (B or C) known during the study
- Tuberculosis occurrence
- skin cancer
- Stevens Johnson syndrome
- Increase of ALAT > 3N
- Gastro-Intestinal perforation and diverticulitis complications

9.2.3.3 ***Other events that require the investigator to immediately notify the sponsor:***

<u>Overdose</u>

A case of excessive intake of the study drug(s) (i.e., intake at a dose greater than the maximal dose recommended in the protocol for a given subject), such overdose must be reported immediately if:

- There are serious signs or symptoms
- There are no signs or symptoms or if there are non-serious signs or symptoms, in the following cases:
    - The intake of treatment is intentional (including suicide attempt)

A case of study drug(s) intake by a person other than the subject must be reported immediately to the sponsor if:

- There are serious signs or symptoms
- There are no signs or symptoms but intake of treatment is thought to pose a potential health risk in the opinion of the investigator

<u>In utero exposure</u>

As reminder, a pregnancy test for all childbearing women is performed at the inclusion visit. However the sponsor must be notified immediately about any pregnancy during which the foetus (from the pre-embryonic stage up to birth) could have been exposed at a given time to an experimental medication, even if the pregnancy is not associated with an adverse event.

Exposure while breastfeeding

Exposure while breastfeeding occurs if an infant or child could have been exposed to a medication *via* the breast milk of a mother being treated with an experimental medication.
Even if such exposure is not associated with an adverse event, the investigator must always notify the sponsor about exposure while breastfeeding as soon as the investigator becomes aware.

9.2.4 Procedures and deadlines for notifying the sponsor:

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

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

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

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

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

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

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

In utero exposure:

The investigator completes the "form for monitoring a pregnancy that developed during a biomedical research", found in and sends it by e-mail to the Vigilance Division at **eig-vigilance.drc@aphp.fr**.

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

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

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

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

9.2.5 Period for notifying the sponsor

The investigator must report all SAE that occur in research subjects:

- From the date on which treatment with the experimental medication began
- throughout the period during which the participant is treated and monitored, as determined by the research
- with no time limit, if the SAE is likely to be due to the experimental medication or to the research procedures (for example, serious reactions that could appear long after exposure to the medication, such as cancers or congenital abnormalities)

9.2.6 The sponsor's roles

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

9.2.6.1 *Analysis and declaration of serious adverse events*

The sponsor assesses:

- the seriousness of all adverse events reported
- the causal relationship of these events with each experimental medication and/or specific medical procedures/exams added by the research and with other possible treatments

- the expected or unexpected nature of these adverse reactions

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

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

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

Any suspected unexpected serious adverse reaction must also be declared electronically in the Eudravigilance European database for adverse events due to medications, established by the European Medicines Agency (EMA).
The sponsor must notify all relevant investigators about any data that could adversely affect the safety of the research subjects.

Specific cases of serious adverse events of special interest:
At the request of ANSM, the sponsor may be asked to declare serious adverse events of special interest, in accordance with the same procedures and deadlines as SUSARs.

9.2.6.2 ***Analysis and declaration of other safety data:***

This relates to any emerging safety issue that may lead to a reassessment of the risk/benefit ratio of the trial or the investigational medicinal product, modifications in the investigational medicinal product use, the conduct of the clinical trial, or the clinical trial documents, or a suspension, interruption or modification of the protocol of the clinical trial or other similar trials.
The sponsor will report to the competent authority and the Ethics Committee without delay upon knowledge any emerging safety issues and, if applicable, describe what urgent safety measures have been taken by the sponsor.

Following the initial declaration of any emerging safety issue, the sponsor will report to ANSM and the Ethics committee any additional relevant information about the emerging

safety issue in the form of a follow-up report, which must be sent no later than 8 days upon knowledge of the sponsor.

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

9.2.6.3 ***Annual safety report***

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

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

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

9.2.7 Data Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) will be established by the sponsor. Its primary mission is to serve as a committee for monitoring safety data. It can have other missions, such as monitoring efficacy data (especially if the protocol includes interim analyses).
The DSMB is mentioned in Article L. 1123-7 of the French Public Health Code.

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

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

<u>General information about the DSMB</u>

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

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

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

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

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

<u>Definition of the DSMB's missions</u>:

- Validation of the research methodology:
  The proposed methodology for the clinical trial will be validated by the DSMB so that it does not jeopardise the safety of subjects, in particular relating to the inclusion and randomisation methods.
- Validation of tolerance monitoring methods:
    - nature of the evaluated parameters
    - frequency of the evaluations, consultation schedule
- Validation of termination criteria:
    - criteria for terminating a subject's participation for tolerance reasons
    - criteria for the temporary or permanent termination of the research (leading to the establishment of certain recommendations ("stopping rules"))
- Modification of the protocol and recommendations:

- In light of the interim analyses of the primary enpont if one arm seems to be clearly in defavour of patients
- In light of the analysis of tolerance data for the research, the DSMB can, when applicable: propose substantial modifications in order to modify certain data, in particular relating to the protocol (inclusion and non-inclusion criteria, monitoring, additional exams, etc.). Likewise the DSMB can issue any recommendations it deems useful in order to best ensure the safety of the research subjects and to maintain a favourable benefit-risk balance throughout the research.

Definition of the DSMB's operating methods:
Meetings modalities (open session, then closed sessions) and frequency will be detailed in the DSMB charter at the latest before inclusion of the first patient,
Modalities and format expected for the transmission of SAE from the sponsor to the DSMB will be detailed in the DSMB charter at the latest before inclusion of the first patient,
The sponsor retains decision-making authority. When applicable, the sponsor delivers its decision, with justification, and DSMB reports to the Competent Authority (ANSM) and the CPP.

10. DATA MANAGEMENT

10.1 Data collection methods

The investigator will permit the sponsor's representatives to monitor the study at the frequency defined in the contract, depending on enrolment at each center.
Case Report Forms (CRFs) and related source documents will be reviewed in detail during monitoring visit (completeness, adherence to the guidelines, accuracy compared to source documents). The sponsor's representative will also review regulatory documents, drug storage and accountability.
The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by sponsor's monitors or representatives of other regulatory agencies.

10.2 Right to access source data and documents

10.2.1 Access to data

In accordance with GCPs:
- the sponsor is responsible for obtaining the permission of all parties involved in the research to guarantee direct access to all locations where the research will be carried out, to

the source data, to the source documents and the reports, with the goal of quality control and audit by the sponsor

- the investigators will make available to those in charge of monitoring, quality control and audit relating to the biomedical research the documents and personal data strictly necessary for these controls, in accordance with the legislative and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

10.2.2 Source documents

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

10.2.3 Data confidentiality

Those responsible for biomedical research quality control (Article L.1121-3 of the French Public Health Code) will take all necessary precautions to ensure the confidentiality of information about the experimental medications, the research, the research subjects and in particular the identity of the subjects and the results obtained.

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

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

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

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

10.3 **Data processing and storage of documents and data**

Data processing will be performed by Pr. Sylvie Chevret in the « Service de Biostatistique et Information Médicale (SBIM), hôpital Saint-Louis, Paris ».

10.3.1 Data entry

Data will be entered in the electronic case report form (eCRF) by staff dedicated to this task.

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

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

10.3.3 Archival

Specific documents for biomedical research relating to a medication for human use will be archived by the investigator and the sponsor for a period of 15 years after the end of the research.
This indexed archival includes, in particular:

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

10.4 Ownership of the data

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

11. STATISTICAL ASPECTS

Due to the CSI recommendation of the 18/06/2019, inclusion in the Anakinra arm has been stopped. Thus we modified the planned analyses and the randomisation accordingly. After the inclusion and randomisation of 54 patients, the next patients will be randomized 1:1 either in the 2 remaining arms:

- Arm 1: Adalimumab (80mg then 40mg/14 days subcutaneously) (n=40) for 16 weeks
- Arm 3: Tocilizumab (162 mg/7 days subcutaneously) (n=40) for 16 weeks.

In practice, it means that the remaining 66 planned patients will be randomized (33 in arm 1 and 33 in arm 3).

11.1 Determination of Sample Size

The study will use a Bayesian multi-arm multi-stage design, where patients will be randomly allocated to three treatment arms. This design has been derived from that proposed by Xie et al. in 2012 for dose-finding trials (Xie 2012). The authors reported throughout a simulation study that the design has good operating characteristics on the basis of a sample of 40 patients in each arm. Thus, a total of 120 patients will be randomized.

11.2 Analysis Populations

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 study drug.

11.3 Interim Analyses

Interim analyses will be done every once 10 patients had been enrolled in each arm. They will be done at W16 after inclusion, based on Bayes inference (see below). This will avoid any inflation of type I error rate due to multiple testing. If an interim analyse lead to stop one of the 3 arms, all following patients will be randomized in the two remaining arms. One interim analysis will be added based on the first 15 randomized in each arm as requested by the DSMB of the study on January 2019. This analysis will be performed following the rules of the others planned interim analyses.

11.4 **Statistical Methods**

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 categoriel characteristics)

Analyses by treatment group will be presented according to the treatment to which subjects were randomized

Disposition of the Study Subjects

The disposition of subjects will be described with summaries by treatment group of the number of subjects enrolled, the number of subjects treated, and the number of subjects for whom study drug was permanently discontinued (including the reasons for discontinuation).

Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group.

Exposure to Study Treatment and Compliance

Frequency distributions of the number of received doses will be presented by treatment group. Treatment duration and treatment compliance for all randomized subjects will be described by treatment group.

Analysis of Primary Efficacy Endpoint

The 24-month progression free-survival will be estimated using Kaplan Meier estimator on the total sample and per arm. Estimation with their 95% Confidence Intervals will be given. Test between survival curves will be performed using Logrank test. Hazard Ratio will be estimated using Cox model.
Sensitivity analyses will be performed with various priors to assess the robustness of the results.

Analysis of Secondary Endpoints

- 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) at week 4, 8, 12, 16 and 24 will be estimated then compared using beta-binomial models, with non-informative uniform priors
- Mean change from baseline in BCVA and all other continuous endpoint at week 4, 8, 12, 16 and 24 for subjects randomized to each arm will be estimated then compared across arms using Normal Bayesian models with non informative priors.
- Mean change from baseline in central retinal thickness measured with Optical Coherence Tomography (OCT) at week 4, 8, 12, 16 and 24 for subjects randomized to each arm will be estimated then compared across arms using Normal Bayesian models with non informative priors.
- Mean change from baseline in Vitreous Haze at week 4, 8, 12, 16 and 24 for subjects randomized to each arm will be estimated then compared across arms using Poisson-Gamma models with non informative priors.
- Percentage of patients with CRT <300 microns at week 4, 8, 12, 16 and 24 will be estimated then compared using beta-binomial models, with non-informative uniform priors
- Percentage of patients without retinal vessel leakage on fluorescein angiography at week 16 will be estimated then compared using beta-binomial models, with non-informative uniform priors
- Measures of corticosteroid sparing (mean change at week 4, 8, 12, 16 and 24, mean dose at week 16, cumulative dose) arm will be estimated then compared across arms using Normal Bayesian models with non informative priors.
- Time to response onset will be estimated then compared across arms using Kaplan Meier estimator and Log-rank test respectively.
- Underlying systemic disease when appropriate at week 4, 8, 12, 16 and 24 will be estimated then compared using beta-binomial models, with non-informative uniform priors
- Ocular disease at week 4, 8, 12, 16 and 24 will be estimated then compared using beta-binomial models, with non-informative uniform priors
- Time to relapse of uveitis and the characteristics of uveitis at worsening will be estimated then compared across arms using Kaplan Meier estimator and Log-rank test respectively.
- Time to treatment failure will be estimated then compared across arms using Kaplan Meier estimator and Log-rank test respectively.

- Number of relapse will be estimated then compared across arms using Poisson-Gamma models with non informative priors.
- Presence of adverse events including serious adverse events (SAE) at week 4, 8, 12, 16 and 24 will be estimated then compared using beta-binomial models, with non-informative uniform priors

References statistics :

Jacob L, Boscher IB, Boulet S, Uvarova M, Chevret S. Evaluation of a Multi-arm Multi-stage Bayesian Design for Phase II Drug Selection Trials in Hemato-oncology (submitted)

Jung SH. Randomized phase II trials with a prospective control. Stat Med 2008; 27:568-586

Kawasaki Y, Miyaoka E. A Bayesian inference of Pfor two proportions. Journal of Biopharmaceutical Statistics 2012;22: 425-437

Analysis of Safety

Safety analyses will involve examination of the incidence, severity, and type of treatmentemergent adverse events reported, changes in vital signs and laboratory test results from baseline (Day 0 pre-dose) to specified time points throughout the study, and concomitant medications use.

Adverse Events

Adverse events reported during the study will be coded using a MedDRA dictionary. Incidence of treatment-emergent adverse events will be summarized by treatment group and the following:

- System organ class and preferred term
- System organ class, preferred term and severity

These summaries will be presented for the following subsets:

- Serious adverse events
- All adverse events
- Drug-related adverse events
- Adverse events resulting in discontinuation of study drug
- Outcome of adverse events

- Action taken

For tables reporting adverse events by severity, if a subject has multiple occurrences of an adverse event with the same organ class and preferred term, the most severe event will be presented.
A summary and by-subject listing will be provided for all subjects who experienced any adverse events, serious adverse events, or adverse events resulting in discontinuation of study drug.

Clinical Laboratory Evaluation

Laboratory parameters will be summarized by treatment group at each visit. Each summary will include the values of the laboratory parameters and their change from baseline. Percent change from baseline will also be presented for continuous laboratory parameters. Shift tables from baseline will be presented for laboratory values in the chemistry and hematology panels. Parameters will be classified according to the laboratory reference normal ranges. A listing will be provided for out of normal range as well as clinically significant abnormal lab values.

Vital Signs

Vital signs, including pulse, blood pressure, temperature, height, and body weight will be summarized by treatment group and time point. For each assessment of vital signs, change and percent change in vital signs from baseline (Day 0 pre-dose) will be summarized by treatment group.

11.5 **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.

11.6 **Significance level**

All tests will be two sided at the 0.05 level.

12. QUALITY CONTROL AND ASSURANCE

Each biomedical research project managed by AP-HP is ranked from A to D according to the projected risk incurred by research subjects using the classification of biomedical research sponsored by AP-HP. In this case, the research is ranked in C risk.

12.1 General organisation

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

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

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

12.1.1 Strategy for opening the centers

The strategy for opening the centers established for this research is determined using the appropriate monitoring plan.

12.1.2 Level of center monitoring

In the case of this research, which is consideredat "**risk C**", the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the research. Thus, the sponsor and the coordinating investigator have agreed on the logistic score and impact, resulting in a research monitoring level to be implemented according to internal procedures high level.

12.2 Quality control

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

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

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

12.3 **Case Report Form**

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

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

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

12.4 **Management of non-compliances**

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

charge of the research location in question being asked for information or could lead to compliance or audit visits.

12.5 **Audits/inspections**

The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. Medical secrecy cannot be invoked in opposition to these audits and inspections.
An audit can be carried out at any time by individuals appointed by the sponsor and who are not associated with the research directors. The objective of the audit is to ensure the quality of the research, the validity of the results and compliance with the legislation and regulations in force.
The individuals who lead and monitor the research agree to comply with the sponsor's requirements and with the competent authority regarding research audits or inspections.
The audit may be applicable to all stages of the research, from the development of the protocol to the publication of the results and the organisation of the data used or produced as part of the research.

12.6 **Primary investigator's commitment to assume responsibility**

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

12.7 **Pharmacist's commitment to assume responsibility**

The Clinical Trial Department of EP-HP, AGEPS, will be in charge of purchase, labeling and shipping of the drugs cocktail to the pharmacies of each center.

13. ETHICAL AND LEGAL CONSIDERATIONS

13.1 Methods for obtaining information and consent from research participants

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

The patient will be first informed during their usual follow-up of the study if they are selected (visit of selection) by the internists (or rheumatologist) or ophthalologist responsible for the follow-up. Then he or she will receive oral and written information (note of information) by the internists or rheumatologist or ophthalologist and another consultation will be planned within 4 weeks later.

The subject will be granted a reflection period between the time when the subject receives the information at selection visit and the time when he or she signs the consent form at inclusion visit. The treatment will be started at randomization visit few days or weeks later.
The free and informed consent, in writing, of the subject is obtained by the internists, (or rheumatologist), or by a doctor representing the investigator, at inclusion visit.

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

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

13.2 Subject prohibited from participating in another research or an exclusion period anticipated after the research

During the research, the subject may not participate in other biomedical research protocols relating to medications*.* But the subject may participate in non-interventional studies.
The exclusion period after the research is 3 months.

13.3 **Legal obligations**

13.3.1 The sponsor's role

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

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

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

13.5 **Request for authorisation to ANSM**

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

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

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

13.7 **Modifications to the research**

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

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

13.8 **Final research report**

The final biomedical research report referred to in Article R1123-60 of the French Public Health Code is drawn up and signed by the sponsor and the investigator. A summary of the

report written according to the competent authority's reference plan will need to be sent to the competent authority and ethical review board within one year after the end of the research, meaning the end of the participation of the last research subject.

14. FUNDING AND INSURANCE

14.1 Funding source

This project is funded by the Programme Hospitalier de Recherche Clinique – PHRC 2015 (Ministère de la Santé).

14.2 Insurance

For the duration of the research, the Sponsor will take out an insurance policy covering the sponsor's own civil liability as well as the civil liability of all the doctors involved in carrying out the research. The sponsor will also provide full compensation for all harmful consequences of the research for the research subjects and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any agent. The act of a third party or the voluntary withdrawal of the person who initially consented to participate in the research cannot be invoked against said compensation.
Assistance Publique- Hôpitaux de Paris (AP-HP) has taken out insurance from HDI-GERLING through BIOMEDIC-INSURE for the full research period, covering its own civil liability and that of any agent (doctor or research staff), in accordance with Article L.1121-10 of the French Public Health Code.

15. PUBLICATION RULES

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

- If an author has multiple affiliations, the order in which the institutions are cited (AP-HP, University, INSERM ...) does not matter
- However, if the research is funded through a supply of AP-HP, the first affiliation should be "AP-HP"
- Each of these affiliations must be identified by a separated by a semicolon (address;)
- AP-HP institution must appear under the symbol "AP-HP" in the first address followed precisely by AP-HP, hospital, service, city, code, France

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

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

15.3 **Mention of the financier in the acknowledgements of the text**

The research was funded by a grant from Programme Hospitalier de Recherche Clinique – PHRC2015 (Ministère de la Santé)

This research has been registered on the website http://clinicaltrials.gov/ .

16. BIBLIOGRAPHY

1 Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature (SUN) Working Group, Results of the First International Workshop. Am J Ophthalmol. 2005 Sep;140(3):509-16.

2 Deschenes J[1], Murray PI, Rao NA, Nussenblatt RB; International Uveitis Study Group (IUSG): clinical classification of uveitis. Ocul Immunol Inflamm. 2008 Jan-Feb;16(1):1-2..

3 Durrani OM, Meads CA and Murray PI. Uveitis: a potentially blinding disease. Ophthalmologica 2004;218(4):223-36.

4 Krumpaszky HG and Klauss V. [Cause of blindness in Bavaria. Evaluation of a representative sample from blindness compensation records of Upper Bavaria]. Klin Monbl Augenheilkd 1992;200(2):142-6.

5 Becker MD, Smith JR, Max R and Fiehn C. Management of sight-threatening uveitis: new therapeutic options. Drugs 2005;65(4):497-519.

6 Schiffman RM, Jacobsen G and Whitcup SM. Visual functioning and general health status in patients with uveitis. Arch Ophthalmol 2001;119(6):841-9

7 Mello PR, Roma Ade C and Moraes Junior HV. [Analysis of the life quality of infectious and non-infectious patients with uveitis using the NEI-VFQ-25 questionnaire]. Arq Bras Oftalmol 2008;71(6):847-54.

8 Roesel M, Tappeiner C, Heiligenhaus A and Heinz C. Oral voclosporin: novel calcineurin inhibitor for treatment of noninfectious uveitis. Clin Ophthalmol 2011;5:1309-13.

9 Gritz DC and Wong IG. Incidence and prevalence of uveitis in Northern California; the Northern California Epidemiology of Uveitis Study. Ophthalmology 2004;111(3):491-500.

10 Suhler EB, Lloyd MJ, Choi D, Rosenbaum JT and Austin DF. Incidence and prevalence of uveitis in Veterans Affairs Medical Centers of the Pacific Northwest. Am J Ophthalmol 2008;146(6):890-6 e8.

11 Shaw J. Infectious uveitis: rule out the prime suspects. EyeNet. San Francisco, CA, American Academy of Ophthalmology. 2005.

12 Kurup SK and Chan CC. Immunotherapeutic approaches in ocular inflammatory diseases. Arch Immunol Ther Exp (Warsz) 2005;53(6):484-96

13 Ohno S, Nakamura S, Hori S, et al. Efficacy, safety, and pharmacokinetics of multiple administration of Adalimumab in Behcet's disease with refractory uveoretinitis. J Rheumatol 2004;31(7):1362-8.

14 Okada AA. Immunomodulatory therapy for ocular inflammatory disease: a basic manual and review of the literature. Ocul Immunol Inflamm 2005;13(5):335-51.

15 Thurau SR and Wildner G. Immunomodulatory therapy in uveitis. In: Uveitis and Immunological Disorders (Essentials in Ophthalmology). Pleyer U and Mondino B, eds. Berlin, Germany, Springer-Verlag Heidelberg. 2005:255-68

16 Rosenbaum JT. Future for biological therapy for uveitis. Curr Opin Ophthalmol 2010;21(6):473-7.

17 Petropoulos IK1, Vaudaux JD, Guex-Crosier Y. Anti-TNF-alpha therapy in patients with chronic non-infectious uveitis: the experience of Jules Gonin Eye Hospital. Klin Monbl Augenheilkd. 2008 May;225(5):457-61.

18 Pascual-Camps I, Hernández-Martínez P, Monje-Fernández L, Dolz-Marco R, Gallego-Pinazo R, Wu L, Arévalo JF, Díaz-Llopis M. Update on intravitreal anti-tumor necrosis factor alpha therapies for ocular disorders. J Ophthalmic Inflamm Infect. 2014 Oct 15;4:26.

19 Suhler EB, Lowder CY, Goldstein DA, Giles T, Lauer AK, Kurz PA, Pasadhika S, Lee ST, de Saint Sardos A, Butler NJ, Tessler HH, Smith JR, Rosenbaum JT. Adalimumab therapy for refractory uveitis: results of a multicentre, open-label, prospective trial. Br J Ophthalmol. 2013 Apr;97(4):481-6.

20 Semeraro F, Arcidiacono B, Nascimbeni G, Angi M, Parolini B, Costagliola C. Anti-TNF therapy for juvenile idiopathic arthritis-related uveitis. Drug Des Devel Ther. 2014 Mar 24;8:341-8.

21 Artornsombudh P, Gevorgyan O, Payal A, Siddique SS, Foster CS. Adalimumab treatment of patients with birdshot retinochoroidopathy. Ophthalmology. 2013 Mar;120(3):588-92.

22 Toussirot E1, Pertuiset E. [TNFα blocking agents and sarcoidosis: an update]. Rev Med Interne. 2010 Dec;31(12):828-37.
23 Erckens RJ, Mostard RL, Wijnen PA, Schouten JS, Drent M. Adalimumab successful in sarcoidosis patients with refractory chronic non-infectious uveitis. Graefes Arch Clin Exp Ophthalmol. 2012 May;250(5):713-20.
24 Kiltz U, Sieper J, Braun J et al. [ASAS/EULAR recommendations for the management of ankylosing spondylitis : evaluation of the 2010 update in the German-speaking area]. Z Rheumatol. 2013 Feb;72(1):71-80.
25 Niccoli L, Nannini C, Benucci M, et al. Long-term efficacy of Adalimumab in refractory posterior uveitis of Behcet's disease: a 24-month follow-up study. Rheumatology (Oxford). 46(7), 1161–1164 (2007).
26 Onal S, Tugal-Tutkun I et al. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. Ophthalmology. 2014 Oct;121(10):e57-8.
27 Tognon S, Graziani G, Marcolongo R et al. Anti-TNF-alpha therapy in seven patients with Behcet's uveitis: advantages and controversial aspects. Ann N Y Acad Sci. 2007 Sep;1110:474-84.
28 Vallet H, Riviere S, Bodaghi B, Cacoub P, Saadoun D; French Behçet Network. Efficacy of anti-TNF alpha in severe and/or refractory Behçet's disease: Multicenter study of 124 patients. J Autoimmun. 2015 Aug;62:67-74.
29 Calvo-Río V , González-Gay MA and al. Anti-TNF-α therapy in patients with refractory uveitis due to Behçet's disease: a 1-year follow-up study of 124 patients. Rheumatology (Oxford). 2014 Dec;53(12):2223-31.
30 Artornsombudh P, Gevorgyan O, Payal A, Siddique SS, Foster CS. Adalimumab treatment of patients with birdshot retinochoroidopathy. Ophthalmology. 2013 Mar;120(3):588-92.
31 Giampietro C, Ridene M, Lequerre T, Costedoat Chalumeau N, Amoura Z, Sellam J, Sibilia J, Bourgeois P, Fautrel B. Anakinra in adult-onset Still's disease: long-term treatment in patients resistant to conventional therapy. Arthritis Care Res (Hoboken). 2013 May;65(5):822-6.
32 McPherson SW, Heuss ND, Pierson MJ, Gregerson DS. Retinal antigen-specific regulatory T cells protect against spontaneous and induced autoimmunity and require local dendritic cells. J Neuroinflammation. 2014 Dec 11;11:205.
33 Haruta H, Ohguro N, Fujimoto M, Hohki S, Terabe F, Serada S, Nomura S, Nishida K, Kishimoto T, Naka T. Blockade of interleukin-6 signaling suppresses not only th17 but also interphotoreceptor retinoid binding protein-specific Th1 by promoting regulatory T cells in experimental autoimmune uveoretinitis. Invest Ophthalmol Vis Sci. 2011 May 17;52(6):3264-71.
34 Papo M, Bielefeld P, Vallet H, Seve P, Wechsler B, Cacoub P, Le Hoang P, Papo T, Bodaghi B, Saadoun D. Tocilizumab in severe and refractory non-infectious uveitis. Clin Exp Rheumatol. 2014 Jul-Aug;32(4 Suppl 84):S75-9.
35 Arida A, Sfikakis PP. Anti-cytokine biologic treatment beyond anti-TNF in Behçet's disease. Clin Exp Rheumatol. 2014 Jul-Aug;32(4 Suppl 84):S149-55.
36 Tappeiner C, Heinz C, Ganser G, Heiligenhaus A. Is tocilizumab an effective option for treatment of refractory uveitis associated with juvenile idiopathic arthritis? J Rheumatol. 2012 Jun;39(6):1294-5.
37 Gül A, Tugal-Tutkun I, Dinarello CA, Reznikov L, Esen BA, Mirza A, Scannon P, Solinger A. Interleukin-1β-regulating antibody XOMA 052 (gevokizumab) in the treatment of acute exacerbations of resistant uveitis of Behcet's disease: an open-label pilot study. Ann Rheum Dis. 2012 Apr;71(4):563-6.

17. LIST OF ADDENDA

17.1 List of Investigators

Cf. addendum

17.2 **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.

17.2.1 Assessment of Best Corrected Visual Acuity (BCVA) by the ETDRS Method

Best corrected visual acuity (BCVA) will be assessed and graded using the ETDRS method. As stated in the ETDRS manual of operations, if the subject's visual acuity is so poor that he/she cannot read the largest chart letters when tested at one meter (i.e., the number of letters read correctly at one meter is zero), then the subject's ability to count fingers, detect hand motion, or have light perception should be evaluated.

17.2.2 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.

17.2.3 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.

17.2.4 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 (Jabs et al., 2005; Nussenblatt et al., 1985). 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).

17.2.5 Assessment of Macula Edema by Optical Coherence Tomography (OCT)

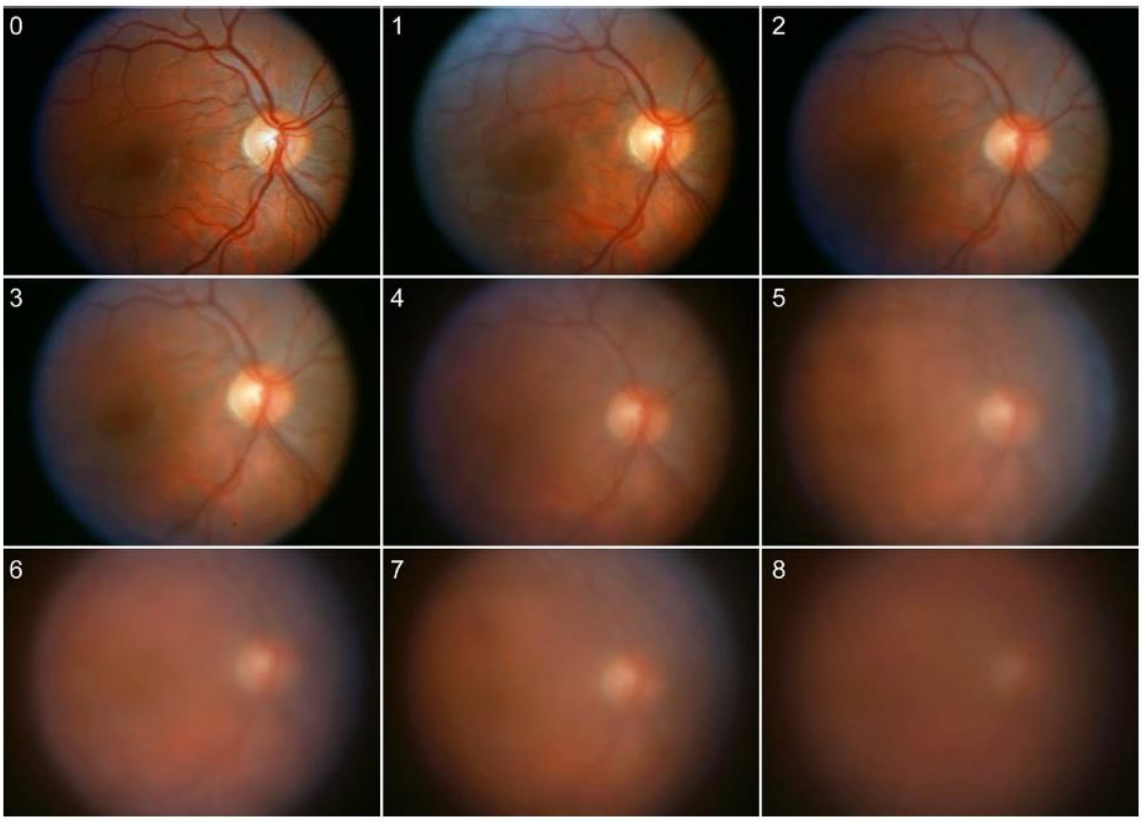
Spectral domain OCT will be performed through a dilated pupil to document macular thickness and presence of macular edema.

17.2.6 Fundus Photography

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

17.2.7 Appendix A Vitreous Haze: VH Miami scale

Nine fundus photographs are available: vitreous haze scale grades 0 through 8.



The 9 images are displayed in increasing order of opacity each equivalent to approximately 0.3 log units of degradation in visual acuity based on the Bangerter calibration. Grade 8 is equivalent to or slightly more opaque than grade 3+ in the Nussenblatt vitreous haze scale. Diffraction rings from combining the Bangerter filters prevented creating increasing levels of haze beyond grade 8. A 10th grade equivalent to haze more than standard 8, and an 11th grade in which no fundus details are visible are possible, but would not be linear.

17.3 **Specificities according to biotherapy**

1. Adalimumab:

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.

The following events are of special interest with respect to the evaluation of study drug safety and should be closely monitored: tuberculosis, autoimmune disease, and demyelinating disorder, skin cancer.

2. Tocilizumab:

The following events are of special interest with respect to the evaluation of study drug safety and should be closely monitored: arterial hypertension, lipid tests, neutropenia, and sigmoiditis.

3. Anakinra:

Patients in the Kineret arm will receive concomitant histamine-H1 blocker during the first month of treatment.

The following events are of special interest with respect to the evaluation of study drug safety and should be closely monitored: cellulitis and local reaction.

17.4 **Questionnaire SF36**

9 Echelles de qualité de vie

Evaluer la qualité de vie d'un individu permet de juger du degré de répercussion d'un traumatisme sur la santé (troubles de santé mentale) et sur le fonctionnement social ou au travail. Ceci permet d'évaluer également le besoin de soins des individus. Plusieurs outils standardisés existent à l'heure actuelle.

Le Medical Outcome Study Short Form (MOS-SF–36)

Auteur(s) : Ware et al.

Type : Echelle d'auto-évaluation

Objectifs : Evaluer la qualité de vie liée à la santé

Caractéristiques : Cette échelle est issue de la « Medical Outcome Study [5]» (Ware and Sherbourne 1992). L'outil original était constitué de 149 items ; l'échelle dérivée n'en contient plus que 36.

Le SF-36 doit sa notoriété à un projet international (International Quality of Life Assessment) qui a adapté et validé cet outil dans 15 pays différents, dont la France (Leplege, Ecosse et al. 1998). Il s'agit d'une échelle de qualité de vie générique qui explore la santé physique, émotionnelle et sociale. On n'y trouve ni le bien-être matériel, ni les valeurs, ni la satisfaction globale de la vie. Le SF-36 évalue 8 dimensions de la santé : l'activité physique, la vie et les relations avec les autres, les douleurs physiques, la santé perçue, la vitalité, les limitations dues à l'état psychique, les limitations dues à l'état physique et la santé psychique. Pour chaque échelle, on obtient un score variant de 0 à 100, les scores tendant vers 100 indiquant une meilleure qualité de vie. A partir de ces huit échelles, il est possible de calculer deux scores synthétiques qui ont été identifiés par analyse factorielle : un score agrégé de santé physique et un score agrégé de santé mentale.

Mode de passation, cotations, scores : Il s'agit d'un auto-questionnaire rempli par le sujet (en 8 à 15 minutes) en fonction de son ressenti par rapport à son état au cours des 4 dernières semaines. Les algorithmes de traitement des scores sont disponibles sur le site internet suivant : http://www.snof.org/melody/interface/qualite

Des données de référence ont été publiées pour la population française. Ces données peuvent servir de normes afin d'interpréter des résultats d'études de qualité de vie. Elles ont

[5] Medical Outcome Study : étude d'observation comprenant une enquête transversale (sur 20 000 patients) et une enquête longitudinale qui s'est déroulée sur 4 années consécutives

été recueillies par la société SOFRES Médicale auprès d'un échantillon de 3 617 individus (Leplege 2001).

Population cible : L'échelle a été utilisée dans différents types de population : patients souffrant de maladies chroniques graves (cancer, VIH) ou d'autres maladies chroniques (asthme, diabète, arthrite, polyarthrite rhumatoïde…). Le SF-36 se prête aux enquêtes en population générale car son spectre de mesure permet de mesurer aussi des différences entre des états de santé globalement bons. Le SF-36 peut être administré à des personnes de plus de 14 ans (Leplege 2001).

Qualités métrologiques : Le SF-36 présente des coefficients de Cronbach compris entre 0,80 et 0,92 pour les différentes sous-échelles selon les études. Tous les items ont une corrélation avec leur propre échelle supérieure à 0,4 et la plupart du temps, cette corrélation est significativement supérieure à celle observée avec les autres échelles.

Le taux de succès pour la validité discriminante est de 99,3 %, ce qui signifie que les dimensions physique et mentales présentent extrêmement peu de corrélation.

Langues : 15 langues dont l'anglais et le français. La traduction et l'adaptation culturelle en français ont été réalisées dans le cadre du projet IQOLA par Leplege et al. (1995). La procédure de traduction a suivi le schéma du projet.

Intérêts et limites : Selon certains auteurs, ce questionnaire est complexe car il comporte des instructions assez longues et spécifiques, qui peuvent causer des problèmes dans certaines populations (personnes ayant un faible niveau d'éducation par exemple). Si le SF-36 convient bien à des personnes vivant indépendamment, il n'est pas idéal pour un usage en milieu hospitalier.

Bibliographie :

Leplege A., Mesbah M., Marquis P. (1995). Preliminary analysis of the psychometric properties for the French version of an international questionnaire measuring the quality of life: the MOS SF 36 (version 1.1). RESP, 43: 371-9.

Leplege A., Rude N., Ecosse E., Ceinos R., Dohin E., Pouchot J. (1997). Measuring quality of life from the point of view of HIV-positive subjects: the HIV-QL31. Qual Life Res, 6(6): 585-94.

Leplege A., Ecosse E., Verdier A., Perneger TV. (1998). The French SF-36 Health Survey: translation, cultural adaptation and preliminary psychometric evaluation. J Clin Epidemiol, 51(11): 1013-23.

Leplege A., Ecosse E., Pouchot J., Coste J., Perneger TV. (2001). Le questionnaire SF-36. Manuel de l'utilisateur et guide d'interprétation des scores. Ed. Estem, Paris.

Perneger TV., Leplege A., Etter JF., Rougemont A. (1995). Validation of a French-language version of the MOS 36-Item Short Form Health Survey (SF-36) in young healthy adults. J Clin Epidemiol, 48(8): 1051-60.

Ware JE., Gandek B., Kosinski M., Aaronson NK., Apolone G., Brazier J. et al. (1998). The equivalence of SF-36 summary health scores estimated using standard and country-specific algorithms in 10 countries: results from the IQOLA Project. International Quality of Life Assessment. J Clin Epidemiol, 51(11): 1167-70.

Ware JE., Kosinski M., Bayliss MS., McHorney CA., Rogers WH., Raczek A. (1995). Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. Med Care, 33: AS264-79.

Nom de l'outil	SF-36
Type d'outil	Echelle d'auto-évaluation
Objectifs	Evaluation de la qualité de vie
Population cible	Population générale, patients
Administration	Autoévaluation
Période de temps sur laquelle porte les échelles	Dernier mois
Langues / traduction	15 langues dont anglais et français / Leplege et al.

Questionnaire : SF-36

Consigne : *Les questions qui suivent portent sur votre santé, telle que vous la ressentez. Ces informations nous permettront de mieux savoir comment vous vous sentez dans votre vie de tous les jours.*

Veuillez répondre à toutes les questions en entourant le chiffre correspondant à la réponse choisie, comme il est indiqué. Si vous ne savez pas très bien comment répondre, choisissez la réponse la plus proche de votre situation.

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

Excellente

Très bonne

Bonne

Médiocre

Mauvaise

2. Par rapport à l'année dernière à la même époque, comment trouvez-vous votre état de santé en ce moment ?

Bien meilleur que l'an dernier

Plutôt meilleur

A peu près pareil

Plutôt moins bon

Beaucoup moins bon

SF36

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

Cochez la case qui correspond à votre choix

- Excellente ❑
- Très bonne ❑
- Bonne ❑
- Médiocre ❑
- Mauvaise ❑

2. Par rapport à l'année dernière à la même époque, comment trouvez-vous votre état de santé **en ce moment** ?

Cochez la case qui correspond à votre choix

- Bien meilleur que l'an dernier ❑
- Plutôt meilleur ❑
- A peu près pareil ❑
- Plutôt moins bon ❑
- Beaucoup moins bon ❑

3. Voici une liste d'activités que vous pouvez avoir à faire dans votre vie de tous les jours. Pour chacune d'entre elles indiquez si **vous êtes limité(e) en raison de votre état de santé actuel**

Cochez la case qui correspond à votre choix, une par ligne

Liste d'activités	**oui, beaucoup limité(e)**	**oui, un peu limité(e)**	**non, pas du tout limité(e)**
a. **Efforts physiques importants** tels que courir, soulever un objet lourd, faire du sport	❑	❑	❑
b. **Efforts physiques modérés** tels que déplacer une table, passer l'aspirateur, jouer aux boules	❑	❑	❑
c. Soulever et porter les courses	❑	❑	❑
d. Monter **plusieurs étages** par l'escalier	❑	❑	❑
e. Monter **un étage** par l'escalier	❑	❑	❑
f. Se pencher en avant, se mettre à genoux, s'accroupir	❑	❑	❑
g. Marcher **plus d'1 km** à pied	❑	❑	❑
h. Marcher **plusieurs centaines de mètres**	❑	❑	❑
I. Marcher **une centaine de mètres**	❑	❑	❑
J. Prendre un bain, une douche ou s'habiller	❑	❑	❑

4. Au cours de ces **4 dernières semaines**, et en raison de votre **état physique**

Cochez la case qui correspond à votre choix, une par ligne

	OUI	NON
a. Avez-vous réduit **le temps passé** à votre travail ou à vos activités habituelles	❑	❑
b. Avez-vous **accompli moins** de choses que vous auriez souhaité	❑	❑
c. Avez-vous dû arrêter de faire **certaines choses**	❑	❑
d. Avez-vous eu des **difficultés** à faire votre travail ou toute autre activité (par exemple, cela vous a demandé un effort supplémentaire)	❑	❑

5. Au cours de ces **4 dernières semaines**, et en raison de votre **état émotionnel** (comme vous sentir triste, nerveux(se) ou déprimé(e))

Cochez la case qui correspond à votre choix, une par ligne

	OUI	NON
a. Avez-vous réduit **le temps passé** à votre travail ou à vos activités habituelles	❑	❑
b. Avez-vous **accompli moins** de choses que vous auriez souhaité	❑	❑
c. Avez-vous eu des **difficultés** à faire ce que vous aviez à faire **avec autant de soin et d'attention** que d'habitude	❑	❑

6. Au cours de ces **4 dernières semaines** dans quelle mesure votre état de santé, physique ou émotionnel, vous a t-il gêné(e) dans votre vie sociale et vos relations avec les autres, votre famille, vos amis, vos connaissances ?

Cochez la case qui correspond à votre choix

- Pas du tout ❑
- Un petit peu ❑
- Moyennement ❑
- Beaucoup ❑
- Enormément ❑

7. Au cours de ces **4 dernières semaines**, quelle a été l'intensité de vos **douleurs physiques** ?

Cochez la case qui correspond à votre choix

- Nulle ❑
- Très faible ❑
- Faible ❑
- Moyenne ❑
- Grande ❑
- Très grande ❑

8. Au cours de ces **4 dernières semaines**, dans quelle mesure vos douleurs physiques vous ont-elles limité(e) dans votre travail ou vos activités domestiques ?

Cochez la case qui correspond à votre choix

- Pas du tout ❑
- Un petit peu ❑
- Moyennement ❑
- Beaucoup ❑
- Enormément ❑

9. Les questions qui suivent portent sur comment vous vous êtes senti(e) **au cours de ces 4 dernières semaines**. Pour chaque question, veuillez indiquer la réponse qui vous semble la plus appropriée. **Au cours de ces 4 dernières semaines**, y a-t-il eu des moments où :

Cochez la case qui correspond à votre choix, une par ligne

	en permanence	très souvent	souvent	quelquefois	rarement	jamais
a. Vous vous êtes senti(e) dynamique ?	❑	❑	❑	❑	❑	❑
b. Vous vous êtes senti(e) très nerveux (se) ?	❑	❑	❑	❑	❑	❑
c. Vous vous êtes senti(e) si découragé(e) que rien ne pouvait vous remonter le moral ?	❑	❑	❑	❑	❑	❑
d. Vous vous êtes senti(e) calme et détendu(e) ?	❑	❑	❑	❑	❑	❑
e. Vous vous êtes senti(e) débordant(e) d'énergie ?	❑	❑	❑	❑	❑	❑
f. Vous vous êtes senti(e) triste et abattu(e) ?	❑	❑	❑	❑	❑	❑

(Suite de la question 9)

	en permanence	très souvent	souvent	quelquefois	rarement	jamais
g. Vous vous êtes senti(e) épuisé(e) ?	❑	❑	❑	❑	❑	❑
h. Vous vous êtes senti(e) heureux (se) ?	❑	❑	❑	❑	❑	❑
i. Vous vous êtes senti(e) fatigué(e) ?	❑	❑	❑	❑	❑	❑

10. Au cours de ces **4 dernières semaines** y a t-il eu des moments où votre **état de santé, physique ou émotionnel**, vous a gêné(e) dans votre vie sociale et vos relations avec les autres, votre famille, vos amis, vos connaissances ?

Cochez la case qui correspond à votre choix

- En permanence ❑
- Une bonne partie du temps ❑
- De temps en temps ❑
- Rarement ❑
- Jamais ❑

11. Indiquez, pour **chacune** des phrases suivantes, dans quelle mesure elles sont vraies ou fausses dans votre cas :

Cochez la case qui correspond à votre choix, une par ligne

	totalement vraie	plutôt vraie	Je ne sais pas	plutôt fausse	totalement fausse
a. Je tombe malade plus facilement que les autres	❑	❑	❑	❑	❑
b. Je me porte aussi bien que n'importe qui	❑	❑	❑	❑	❑
c. Je m'attends à ce que ma santé se dégrade	❑	❑	❑	❑	❑
d. Je suis en excellente santé	❑	❑	❑	❑	❑