"Multicenter, randomized, prospective trial comparing the Efficacy and Safety of Adalimumab to that of Tocilizumab in severe uveitis of Behçet's disease"
UVB: treatment of **UV**eitis in **B**ehçet's diseases with biologics

UVB Study

CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE

Version N° 5.0 of 02/04/2024
Project code number: APHP200007 / EUDRACT No.: 2022-001316-26
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PROTOCOL SIGNATURE PAGE for a research PROTOCOL

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

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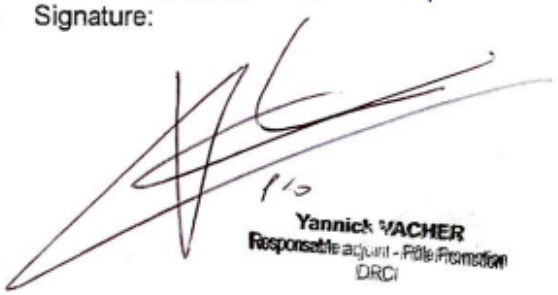

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1 SUMMARY

Full title	Multicenter, randomized, prospective trial comparing the Efficacy and Safety of Adalimumab to that of Tocilizumab in severe uveitis of Behçet's disease
Acronym	**UVB:** treatment of **UV**eitis in **B**ehçet's diseases with biologics
EU-CT number	**2024-513371-41-00**
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Sponsor	Assistance Publique-Hôpitaux de Paris
Scientific justification	UVB, is the first randomized prospective, head to head study, comparing Adalimumab to Tocilizumab in sight threatening uveitis of BD. Anti-TNFα has been used for BD uveitis for 15 years. The incidence of blindness in BD has been dramatically reduced in the recent years with the use of biologics. There is no firm evidence or randomized controlled trials directly addressing the best induction therapy in severe BD uveitis. BD uveitis is considered as the most devastating inflammatory ocular disease. Risk of visual loss reaches 25% at 5 years and 80% of patients have a bilateral involvement. Contrasting with immunosuppressors or interferon-alpha, biotherapies act rapidly and are highly effective in steroid's sparing thus preventing occurrence of cataract and/or glaucoma. However, anti-TNFα failed to demonstrate sustainable complete remission over 50 % of severe sight threatening uveitis. There is little published information on use of biologics other than anti-TNFα for severe BD uveitis. Tocilizumab has been used with success in severe and/or resistant cases and is one of the most promising biologics in BD. IL-6 expression correlates with BD activity and other immunological data provide a strong rationale for targeting BD with tocilizumab. Despite a strong rationale, these compounds are not yet approved in BD, which guarantees the innovative nature of this study that aims selecting or dropping any arm when evidence of efficacy already exists.
Main objective and primary endpoint	• To assess the benefit of tocilizumab comparatively to that of adalimumab in sight-threatening Behçet's disease uveitis at week 16 • Primary Endpoint: Efficacy will be defined by a complete remission of ocular involvement (complete resolution of retinal vasculitis and/or macular edema) with prednisone (or prednisolone, only if prednisone is out of stock in the market) lower or equal to 5 mg/day at week 16 after randomization.
Secondary objectives and endpoints	1. To estimate and compare the change in best corrected visual acuity (BCVA) 2. Time to complete remission at week 4, 8, 12, 24, 36 and 48

	3. To evaluate and compare the safety of Adalimumab and tocilizumab 4. To evaluate and compare the change in macular edema 5. To evaluate and compare the change in other signs of ocular inflammation 6. To evaluate and compare the effect on retinal vessel leakage 7. To evaluate and compare the effect of Adalimumab and tocilizumab on steroid sparing 8. To evaluate and compare the change in ocular inflammation in the anterior chamber 9. To evaluate and compare the number and time to relapse of uveitis and the characteristics of uveitis at worsening. 10. To evaluate and compare the time to treatment failure (Patients will be considered to have treatment failure if any of the following criteria is met in at least 1 eye: new active, inflammatory retinal vascular lesions and/or macular edema; worsening best corrected visual acuity (BCVA) by ≥3 lines; 2-step increase in anterior chamber (AC) cell grade; 2-step increase in vitreous haze (VH) grade relative to Baseline. 11. To estimate and compare the effect on extra ophthalmologic manifestations of Behçet's Disease. 12. To estimate and compare the mean change in SF-36 quality of life and Behçet's Disease Quality of Life Measure (BD-QoL) 13. To estimate and compare the changes in Behcet's Disease Current Activity Form (BDCA) and Behcet's Syndrome Activity Score (BSAS) Secondary endpoints : 1. Measures of corticosteroid sparing (e.g., percent meeting targets [lower than 0.1 mg/day/kg of prednisone (or prednisolone, only if prednisone is out of stock in the market)], mean dose at week 16, and cumulative dose). 2. Time to response onset, 3. Measures of acute-phase reactants (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], at week 4, 8, 12, 16, 24, 36 and 48 4. Rate and Time to occurrence of relapse or worsening while on study. (Relapse will be defined as the reappearance of clinical and/or paraclinical features of active disease or by the occurrence of new lesions or progression of preexisting lesions). 5. Changes in Behcet's Disease Current Activity Form (BDCA) at week 8, 16 and 24 6. Changes in Behcet's Syndrome Activity Score (BSAS) at week 16 7. Changes in other organs involved by BD at week 4, 8, 12, 16, 24, 36 and 48 8. Changes in quality of life (QOL) (SF36v2 TM Health Survey) and Behcet's Disease Quality of Life Measure (BD-QoL) at week 16 and 24 9. Safety and tolerability of treatments in BD patients as assessed by frequency and severity of adverse clinical events at week 4, 8, 12, 16, 24, 36 and 48 10. Time to treatment failure (time to occurence) 11. Changes in Tyndall, flare and Vitreous Haze at week 8, 16, 24, 36 and 48 12. Changes in Best corrected visual acuity (SNELLEN score) at week 8, 16, 24, 36 and 48 13. Changes in central retinal thickness measured with Optical Coherence Tomography (OCT) at week 8, 16, 24, 36 and 48. 14. Percentage of patients with central retinal thickness <300 microns at week 8, 16, 24, 36 and 48.

	15. Percentage of patients without retinal vessel leakage on retinal angiography at week 16, and at week 24, 36 and 48, in case of retinal vasculitis
Design of the study	Bayesian design for phase II randomized clinical trial that aims at comparing a new treatment to a reference based on a binary end point, which offers greater flexibility and simplicity of inference for the monitoring of patient safety and evidence of efficacy in small randomized trials
Category	Cat 2: phase 2
Population of study participants	Adult patients with sight-threatening Behçet's disease associated uveitis.
Inclusion criteria	1. Age ≥ 18 at Inclusion 2. Provide written, informed consent prior to the performance of any study-specific procedures 3. Diagnosis of Behçet's disease according to the International Criteria for Behçet's Disease (ICBD) (see appendix 18.2) or history of aphtosis. 4. 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 5. Sight threatening uveitis defined according to the validated international definition as 2 lines of drop in visual acuity on a 10/10 scale, and/or retinal inflammation (macular oedema and/or retinal vasculitis). 6. Chest X-ray (postero-anterior and lateral) or CT-scanner results within 12 weeks prior to Inclusion with no evidence of active Tuberculosis, active infection, or malignancy 7. For female subjects of childbearing potential (premenopausal female capable of becoming pregnant), a negative serum pregnancy test (plasmatic or urinary) 8. For subjects with reproductive potential, a willingness to use contraceptive measures adequate to prevent the subject or the subject's partner from becoming pregnant during the study and 3 and 5 months after stopping therapy for tocilizumab 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: **For female subjects :**

	- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: ▪ oral ▪ intravaginal ▪ transdermal - progestogen-only hormonal contraception associated with inhibition of ovulation: ▪ 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). **<u>For male subjects :</u>** - use of a condom - vasectomy (with documentation of azoospermia) - sexual abstinence 9. Negative TB test obtained within 12 weeks prior to inclusion. A potential subject with a positive interferon-gamma release assay (IGRA) (e.g., QuantiFERON®-TB Gold or T-spot TB® Test) is eligible if her/his chest X-ray does not show evidence suggestive of active TB disease and there are no clinical signs and symptoms of pulmonary and/or extra-pulmonary TB disease. These subjects with a latent TB infection who have not already received a prophylactic TB treatment must agree in advance to complete such a treatment course. The treatment should be started at the latest at inclusion. 10. Affiliation to a social security system. Patients affiliated to universal medical coverage (CMU) are eligible for the study
Non inclusion criteria	1. Infectious uveitis, masquerade syndromes, or uveitis due to causes other than BD uveitis 2. Active tuberculosis or history of untreated tuberculosis and/or severe infection 3. Positive HIV antibody and/or positive hepatitis B surface antigen and/or positive hepatitis C RNA, results obtained within 1 month prior to inclusion 4. 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. 5. History of severe allergic or anaphylactic reactions to monoclonal antibodies 6. History of multiple sclerosis and/or demyelinating disorder 7. Hypersensitivity to the active substance or an excipient of the IMP or the auxiliary medicine 8. Active or suspected ocular infection 9. Active or suspected systemic infection 10. History of intestinal ulceration or diverticulitis 11. **Known** porphyria

	12. Laboratory values assessed during Inclusion: a. Neutrophil < 1.0 × 10^3/mm^3 b. Platelet count < 80× 10^3/mm^3 c. ASAT or ALAT > 5 ULN 13. Treatment with anti-TNF and/or Tocilizumab therapy within 1 month prior to inclusion 14. Patient on azathioprine, mycophenolate mofetil, or methotrexate at the time of inclusion (these drugs must be withdrawn prior to receiving the tocilizumab or adalimumab dose on Day 0) 15. Stage III and IV New York Heart Association (NYHA) cardiac insufficiency 16. Severe renal (Glomerular filtration rates (GFR) <30ml/min) or liver insufficiency (prothrombin <50% without other causes) 17. Any live (attenuated) vaccine within 30 days prior to inclusion 18. Breastfeeding or pregnant women
Investigational medicinal product(s)	After the collection of their free and informed consent, eligible patients with sight threatening Behçet's disease uveitis will be randomized into one of 2 groups at the randomization visit (D0): • **Arm A** Adalimumab 80 mg at D0 then 40 mg subcutaneous at week 1, 3, 5, 7, 9, 11, 13 and 15 • **Arm B** Tocilizumab 162 mg subcutaneous each week for 15 weeks
Comparator treatment	Not applicable
Interventions added for the study	- Visit with internist at week 4 and 12 - Visit with ophthalmologist at week 4 and 12 - ßHCG (urinary) at each visit and monthly until 3 and 5 months after stopping therapy for tocilizumab and adalimumab, respectively. - Optical Coherence Tomography (OCT) at W 8 - Retinal angiography at W24 in case of retinal vasculitis - QOL questionnaires at D0, 16 and 24 weeks
Expected benefits for the participants and for society	BD uveitis is considered as the most devastating inflammatory ocular disease. Anti-TNF is a rapidly acting agent when compared to methylprednisolone or interferon alpha in suppressing ocular inflammation. However, they failed to demonstrate sustainable complete remission over 50 % of patients. Also, TNFa antagonists seems to have suspensive effect on ocular inflammation in BD. Tocilizumab has been used with success in severe and/or resistant cases and is one of the most promising biologics in BD. Rapid onset of action and steroid-sparing effect characterize the efficacy of tocilizumab. Nowadays, the management of severe BD still remains largely empirical. This is the first randomized, head to head, study for therapeutic management of severe uveitis in BD with biologics. This study may assess the benefit of tocilizumab comparatively to that of adalimumab in sight-threatening Behçet's disease in terms of safety, efficacy and steroid sparing. It could thus improve the care of patients with BD and with uveitis in general. The expected benefit is both individual, in reducing morbidity and rate of blindness for young patients with BD, and collective, in reducing costs of hospitalization, and of dependence.
Risks and burdens added by the study	Risks associated with the toxicities of the investigational drugs Risks associated with use of contrast medium for retinal angiography The risk level of the study : Risk C
Practical implementation	After the collection of their free and informed consent, eligible patients with active sight threatening Behçet's disease uveitis will be randomized into one of 2 groups at the randomization visit (D0): • Arm A (Adalimumab) 80mg at D0 then 40 mg subcutaneously at week 1, 3, 5, 7, 9, 11, 13 and 15

	• Arm B (Tocilizumab) 162mg subcutaneously every week for 15 weeks All treatment groups will receive the same corticosteroid regimen. All patients will receive oral prednisone (or prednisolone, only if prednisone is out of stock in the market) at 1 mg/kg/day (up to 80 mg/day) at randomization. The following schedule of reduction of prednisone (or prednisolone, only if prednisone is out of stock in the market) will apply to both groups as long as the disease is inactive: • 1 mg/kg/day (maximum 80 mg/d) week D0-W4, • 40 mg/day W4-W6 • 30 mg/day W6-W8, • 20 mg/day W8-W10, • 15 mg/day W10-W12, • 10 mg/day W12-W14, • 5 mg/day W14-W16, Dose of corticosteroids will be left at the investigator discretion after W16
Number of participants included	60 patients (30 patients in each arm)
Number of sites	Multicenter national study including 26 centers
Duration of the study	Inclusion period: 36 months Participation period (treatment+follow-up): 12 months Total duration: 48 months
Number of enrolments expected per site and per month	0,07
Statistical analysis	The experimental design is an open multicenter randomized clinical trial stratified on the characteristics of the initial uveitis in Behçet's disease : retinal inflammation (retinal vascularitis and/or macular edema) and according to the diagnosis (newly diagnosed or relapsing disease), with evaluation of the primary assessment criteria at 16 weeks. The primary assessment criteria will be reviewed by a scientific committee blinded of the randomization. The RCT will use a Bayesian design for phase II randomized national multicenter clinical trial that aims at comparing a new treatment to a reference based on a binary endpoint (i.e. complete remission at week 16), which offers greater flexibility and simplicity of inference to the monitoring for patient safety and evidence of efficacy of small randomized trials. It will use a Beta-Binomial model with a non-informative prior (Berry 2006). The posterior probability that the remission rate is at least 0.65 will be estimated in both arms, and the probability that the rate of remission in Arm B is above that in Arm A will be computed, with B indicating the tocilizumab group and A the adalimumab group. We will use a Bayesian inference framework, where $\pi_A = P(Y = 1\|A)$ denotes the probability of remission in the arm A. After inclusion of n_A patient in Arm A and y_A complete remission observed. Using a beta Be(a_A, b_A) prior for π_A, the posterior probability of π_A is still a beta distribution given by Be(a_A+y_A, b_A+$n_A - y_A$) due to the natural conjugate property of the beta family for binomial sampling. In our setting, the efficacy of the drug in arm A will be first assessed by comparison to some historical minimal value of interest, sometimes called the "minimum required treatment remission rate". It has been set at 0.65 in this trial. Thus, we will compute $$P(\pi_A > 0.65\|y_A, n_A)$$ Similar analyses will be performed in arm B.

	However, in randomized phase II settings, the selection of a new drug is mostly based on evaluating the potential benefits of experimental treatments. Thus, one may consider dropping a new drug from further studies only if there is a rather low posterior probability that this drug is beneficial over the other by some targeted minimal level. This will be done by computing the posterior probability of the difference in remission rates between the two experimental arms (Kawasaki in 2012) being greater than zero, with B being the tocilizumab group and A the adalimumab group: $$P(\pi_B - \pi_A > 0 | y_A, y_B, n_A, n_B)$$ As we consider a Bayesian design an interim analysis will be performed without any "alpha spending" after inclusion of 30 patients. If $P(\pi_A > 0.65 | y_A, n_A)$ >0.80, $P(\pi_B > 0.65 | y_B, n_B)$ >0.80 and if $P(\pi_B - \pi_A > 0 | y_A, y_B, n_A, n_B)$ >0.80. The trial will be stopped. If $P(\pi_A > 0.65 | y_A, n_A)$ <0.10 or $P(\pi_B > 0.65 | y_B, n_B)$ <0.10 the corresponding arm will be stopped and the following patients will be included in the other arm. If $P(\pi_A > 0.65 | y_A, n_A)$ <0.10 and $P(\pi_B > 0.65 | y_B, n_B)$ <0.10, the trial will be stopped.
Sources of funding for the trial	PHRC National 2019 - Ministère des solidarités et de la Santé
Trial will have a Data Monitoring Committee	Yes

2 SCIENTIFIC JUSTIFICATION FOR THE STUDY

2.1 Hypothesis for the study

Behçet's disease (BD) is a systemic vasculitis of arterial and venous vessels of any size, involving young patients (from 15 to 45 years). BD significantly increases morbidity and mortality (1). Ocular disease in Behçet's disease is frequent (60-90%) and may be associated with a poor functional prognosis. BD can involve anterior and/or posterior segment. It develops within the first few years of the disease onset and runs its most severe course during these years. Bilateral involvement is observed in 70–80% of patients at the beginning and becomes 90% when followed long-term (2). Male gender, posterior involvement, frequent attacks, strong vitreous opacity, and exudates alongside retinal vascular arcade are identified as poor prognostic factors. Sight-seeing BD include posterior uveitis and retinal vasculitis. The risk of visual loss reaches 25% at 5 years (3). TNFα antagonists (anti-TNF) has been used for BD uveitis for 15 years (4). The incidence of blindness in BD has been dramatically reduced in the recent years with the use of biologics. There is no firm evidence or randomized controlled trials directly addressing the best induction therapy in severe BD uveitis. The European League Against Rheumatism (EULAR) recommendation for the management of BD advocated TNFα antagonists and steroids for all patients with sight threatening uveitis (5). Adalimumab and infliximab seems to be as effective for treatment of refractory non-infectious uveitis (6,7). According to the 'Expert panel recommendations for the use of anti-TNF-a drugs in patients with ocular inflammatory disorders', published in 2014, infliximab (IFX) or adalimumab (ADA) may be used as first- or second-line corticosteroid-sparing therapy in patients with ophthalmic manifestations of BD (8). In 2016, the Food and Drug Administration (FDA) and European Medicines Agency (EMA) (http://www.fda.gov) (http://www.ema.europa.eu) approved ADA for use in non-infectious intermediate, posterior and panuveitis, including those due to BD, based on two randomized double-blinded studies (9,10). Interferon-alpha can be used as an alternative but has a delayed action and induces many side effects (11). Contrasting with immunosuppressors or interferon-alpha, biotherapies act rapidly and are highly effective in steroid's sparing thus preventing occurrence of cataract and/or glaucoma. The only controlled study with a biologic was a non-randomized observational study that compared TNFα antagonists with cyclosporine-A (3-5 mg/kg). The number of ocular attacks was significantly lower (MD -0.80, 95% CI -1.50 to -0.91 perattacks/ 6 months) and the number of patients achieving complete remission was significantly higher in the TNFα antagonists arm (RR 1.83, 95% CI 1.071 to 3.12)(12). However, anti-TNFα failed to demonstrate sustainable complete remission over 50 % of severe sight threatening uveitis (7).

There is little published information on use of biologics other than anti-TNFα for severe BD uveitis. There were no controlled studies comparing biotherapies in BD uveitis. Tocilizumab (TCZ), an anti-interleukin 6 (IL6) receptor, has been used with success in severe and/or resistant cases and is one of the most promising biologics in BD (13–18). It seems to be rapidly effective in BD uveitis. TCZ may be effective in highly refractory BD-related uveitis (13–18). TCZ yielded a rapid reduction of ocular inflammation and led to long-term remission in these patients. According to several studies, IL6 level seems to be correlated to disease activity. IL6 is a pro-inflammatory cytokine primarily secreted by mononuclear phagocytes, activated astrocytes and T cells. Increase IL6 level in CSF of neuro-BD patients has been reported to be correlated to long-term outcome and disease activity and proposed as disease activity marker. Chang et al. have found an increase susceptibility to BD in subjects carrying the IL6vntr*C allele and the IL6prom*G/IL6vntr*C haplotype (19). Increased IL-6 concentrations have been demonstrated in the vitreous fluid of chronic or acute
uveitis patients (20). Moreover, TCZ has demonstrated efficacy in patients with
refractory ocular inflammatory diseases (21–24). Interestingly, in the experimental model of autoimmune uveitis in mice, treatment with an anti-IL-6 receptor antibody also yielded dramatic reduction of uveal inflammation (20).

UVB, is the first randomized prospective, head to head study, comparing Adalimumab to Tocilizumab in sight threatening uveitis of BD. Despite a strong rationale, these compounds

are not yet approved in BD, which guarantees the innovative nature of this study that aims selecting or dropping any arm when evidence of efficacy already exists.

2.2 Description of knowledge relating to the condition in question

2.2.1 Description of Behçet's disease

Behçet's disease (BD) is a rare form of vasculitis of unknown origin. Its main characteristics include recurrent oral aphthous ulcers, along with genital ulcerations, skin lesions and uveitis. Patients may also present with arthralgia, venous, arterial and cardiac lesions, or neurological involvement with varying frequency depending on the studies and ethnicity. This disease mainly affects young men and has a peculiar geographical distribution in the "silk road" countries, the ancient route between the Mediterranean, the Middle East and the Far East (25). Diagnosis is only based on clinical criteria as in BD there is no relevant biological test for diagnosis. Carrying the human leukocyte antigen (HLA)-B51 increases the risk of developing BD by 1.5 to 16 times. Except for the severity of ocular disease, HLA-B51 does not seem to be correlated with the prognosis of the disease. The exact cause of the disease remains unknown, but it is believed that both genetic and environmental factors contribute to the development of the disease.

2.2.2 Morbidity and mortality

BD significantly increases morbidity and mortality. The leading cause of morbidity in BD is eye involvement with the potential threat of visual loss. Panuveitis is the most common ocular BD manifestation, which can jeopardize the visual prognosis and involves intense vitritis, arterial and venous occlusive vasculitis and chorioretinitis. The prognosis of eye disease has been reported to be very poor in the past. Despite new biotherapies, BD uveitis still remains a blinding disease: blindness occurs in 16 to 25 % of all patients after 5 years and 10 years respectively. Total blindness was often considered as the eventual outcome in an average of 3 years after the onset of ocular symptoms. Approximately 12% of acquired visual loss in adulthood in Japan was reported to be caused by BD and more than half of the Japanese BD patients were reported to have lost their useful vision within 5 years of disease onset (26). In a study from Israel, 75% of treated patients were found to have lost useful vision in 6–10 years after the onset of uveitis (27). In a 20 year survey, 17% (25/146) of males and 10.5% (4/38) of females with eye involvement had bilateral useful vision loss at their initial presentation (28). After two decades, additional 27% (39/146) of males and 10.5% (4/38) of the females with initially useful vision had lost their eye sight. This added up to a total of 44% (64/146) and 21% (8/38), loss of vision for males and females, respectively. The majority of the bilateral loss of vision among males had already developed at the initial years of follow-up (40%) and during the first 4 years following inception (42%) decreasing substantially thereafter.
The overall mortality of Behçet patients reaches 5% at 10 years. Among 2,031 patients from Japan, 31.7% were clinically deteriorated, and 0,9% died during the course of a single year's follow-up. In Turkey, 42 patients out of 428 died mainly due to major vessel disease and neurologic involvement. Most of the death occurred 5 years after the diagnosis of BD. Male gender, arterial involvement and a high number of flares are independently associated with mortality in BD. The main causes of death included major vessel disease, and central nervous system involvement. In large studies specifically addressing neurologic disease of BD the mortality rate range between 5.5 and 20% (29,30). The vasculitis of BD is distinctive because of involvement of both arteries and veins of all sizes.

2.2.3 Disease Prevalence

With more than 30 published prevalence estimates for Behçet's disease (BD), covering many different regions worldwide, the prevalence of BD is quite well described. Even though the interpretation of these data is complicated by between-study differences in methodology, which may substantially influence the results, these data suggest large geographic variations in

frequency of BD, with prevalence rates of 20–420/100,000 inhabitants for Turkey, 2.1–19.5 for other Asian countries, 1.5–15.9 for southern Europe and 0.3–4.9 for northern Europe. The prevalence in France is 7/100,000. Additional epidemiological studies or cases series from North and South America, the Caribbean Islands, and individuals of sub-Saharan ancestry further suggest that the geographic distribution of BD is much wider than the boundaries of the ancient Silk road. The few available incidence rates prevent from making strong inferences as to whether the frequency of BD has changed over time. Recent population-based studies of immigrants or migrant populations consistently indicate that migrants from areas of high BD prevalence remain at high risk for BD, which may even be close to the prevalence observed in their countries of origin.

2.2.4 Pathophysiology of Behçet's disease

The pathogenesis of BD remains unclear. The relative risk of having BD in the siblings of affected individuals has been estimated to be between 11 and 53, implying a genetic influence on disease development. Although an autosomal recessive inheritance pattern has been suggested among paediatric patients, Mendelian inheritance patterns seem not to be operative. Genetic anticipation in the form of earlier disease onset in the second generation compared to their affected parents has also been reported. HLA-B51 has been the most consistently reported HLA association, has been showed in many ethnic groups although with differing risk ratios and has lately been confirmed in a whole genome analysis in 2430 cases and 2660 controls along with IL-10 and IL23R-IL12RB2 loci. Imputation analyses of genome wide association studies revealed new associations such as ERAP-1, CCR1-CCR3, KLRC4 and STAT4. The absence of concordance in monozygotic twins, however, suggests that other factors are also involved in pathogenesis. BS does not exhibit the properties of a true autoimmune disease: it lacks consistent autoantibodies, and the prevalence of autoimmunity is not increased. Nor is it a typical autoinflammatory disease. However, a targeted re-sequencing study among patients with BS found variants of IL-23R, IL1R1 and TLR and NOD2 among the Japanese and IL-23R, TLR4, MEVF (M694V) and NOD2 among the Turks suggesting that certain autoinflammatory aspects may be operative.
Both the innate and adaptive immune systems are activated in BD. Tumor Necrosis Factor alpha (TNFα) is an important proinflammatory cytokine which has been implicated in the pathogenesis of a number of inflammatory disorders including BD. Interestingly, TNF is encoded in the class III region of the HLA complex, adjacent to HLA-B. Several studies highlighted the higher frequency of TNFα promoter polymorphism in BD patients. IL6 is a pro-inflammatory cytokine primarily secreted by mononuclear phagocytes, activated astrocytes and T cells. Increase in IL6 in CSF of neuro-BD patients has been reported to be correlated to long-term outcome and disease activity and proposed as disease activity marker (31,32).
What drives the immune system and sustains the inflammation is not clear, but an infectious trigger linked to an innate immune abnormality (eg, a genetic mutation affecting an adhesion molecule, a pro-inflammatory cytokine or an intra-cellular signalling abnormality of a transcription factor) is an attractive hypothesis. The diminished m-RNA expression and low protein production of the disease associated IL-10 variant (the rs158111 A allele) in the whole genome study mentioned above support this hypothesis since IL-10 production usually has an inhibitory role in inflammation. The inhibitory properties of IL-10 in eye disease have also been shown. There is evidence that the clinical picture is not homogeneous and that there are various clusters of disease expression.

2.2.5 Criteria of disease activity

The complete clinical response will be defined by the remission of uveitis and the absence of clinical relapse. Remission of ocular inflammation will be defined as the percentage of patients with a decrease > 2 steps in vitreous haze or resolution of haze (for patients with 1+ haze at baseline) based on SUN standardized international grading associated with a complete resolution of retinal vasculitis and/or macular edema (33). In patients with bilateral uveitis, the eye with the highest disease activity will be chosen as the study eye.
Other manifestations of Behçet's disease will be also evaluated as secondary endpoints:

- Cardiac remission is evaluated clinically (improvement of chest pains and other cardiac events), echocardiography (normalization of left ventricular function and/or disapearance of cardiac thrombosis), and cardiac magnetic resonance imaging (diseappearance of gadolinium enhancement and normalization of left ventricular function), and biologically (normalization of troponin and of inflammatory syndrome) (34).
- Vascular remission is defined as the resolution of clinical and laboratory features of active disease (normalization of inflammatory syndrome) and the absence of new vascular lesions (in previously unaffected vascular territories) or the progression of preexisting vascular lesions detected on serial imaging studies (i.e. doppler sonography, and angio-CT scan)(35).
- Remission of neurological involvement is defined as a complete clinical, and imaging (as evaluated by MRI) remission, biologically (normalization of inflammatory syndrome) (29).
- The skin and articular remissions are evaluated clinically (disappearance of skin lesions and/or ulcers, disappearance of arthralgia and/or arthritis).
- Digestive remission is evaluated clinically (improvement of abdominal pain and other gastrointestinal symptoms), by endoscopy (improvement of potential gastrointestinal lesions seen at baseline) and/or by Xray (improvement of any abnormalities found on baseline imaging).

2.3 Summary of relevant pre-clinical experiments and clinical trials

Behçet's disease (BD) is a systemic large-vessel vasculitis characterized by a wide clinical spectrum including recurrent oral and genital ulcerations, uveitis, vascular, neurological, articular, and gastrointestinal manifestations. Therapeutic management of BD depends of the clinical presentation and organ involved. Although colchicine, nonsteroidal antiinflammatory agents and topical treatments with corticosteroids are often sufficient for mucocutaneous and joint involvement, a more aggressive approach with immunosuppressive agents is warranted for severe manifestations such as posterior uveitis, retinal vasculitis, vascular, neurological and gastrointestinal involvement. However, some patients still have refractory disease, relapses, sight threatening eye disease, or irreversible organ damage.
The European League Against Rheumatism (EULAR) recommendation for the management of BD advocated TNFα antagonists (adalimumab or infliximab) and steroids for all patients with sight threatening uveitis (5). Interferon-alpha can be used as an alternative but has a delayed action and induces many side effects (11). However, there is no firm evidence or randomized controlled trials directly addressing the best induction therapy in severe uveitis in BD.

- Anti-TNFα

The immunosuppressive agents used in BD treatments are usually non-specific. Tumor necrosis factor alpha (TNFα) has been identified as a potential target in BD. Indeed, TNFα production is altered in BD patients: both spontaneous and LPS-induced production of TNFα by monocytes are increased in active BD patients compared to healthy control. Other groups have found an increase in TNFα levels in vitreous and sera of BD patients with active untreated uveitis compared to patient with BD treated by infliximab (IFX) and to healthy control.
Anti-TNF agents are increasingly used for ocular manifestations of patients with BD, especially IFX and adalimumab (ADA). A prospective observational study showed that anti-TNF is a rapidly acting agent when compared to methylprednisolone in suppressing ocular inflammation. The effect of anti-TNF started within the first 24 hours for suppressing ocular inflammation, as well as in decreasing anterior chamber cells, clearing retinal vasculitis and

resolution of retinitis and cystoid macular edema (36). In contrast, studies indicated that retinal infiltrates resolved within 2 weeks and infiltration of anterior chamber, vasculitis, and macular edema resolved within 4 weeks with interferon-alpha treatment (37). Anti-TNF agents has been used in more than 1000 reported cases, mainly for refractory ocular BD, and were associated with clinical improvement in up to 90% of patients who were resistant to conventional therapies. The relapse rate of uveitis and daily corticosteroid doses were significantly lower during anti-TNF agents treatment in patients with BD in whom uveitis was resistant to combination therapy with corticosteroids, azathioprine, and/or cyclosporine. Rapid onset of action and steroid-sparing effect characterize the efficacy of TNFα-antagonists, mainly reported in patients resistant to conventional therapies. The monoclonal antibodies, infliximab and adalimumab, seem more effective than the soluble antibodies, etanercept notably for uveitis (5). Adalimumab seems as effective as Infliximab in BD uveitis. In a multicenter observational study of 160 patients, the cumulative incidences of complete response, serious side effects and event-free survival were not significantly different between ADA and IFX (6).
However, repeated long term infusions are warranted to sustain remission as TNFα-antagonists are likely suspensive. According to the 'Expert panel recommendations for the use of anti-TNF-a drugs in patients with ocular inflammatory disorders', published in 2014, infliximab (IFX) or adalimumab (ADA) may be used as first- or second-line corticosteroid-sparing therapy in patients with ophthalmic manifestations of BD (8). In 2016, the Food and Drug Administration (FDA) and European Medicines Agency (EMA) (http://www.fda.gov) (http://www.ema.europa.eu) approved ADA for use in non-infectious intermediate, posterior and panuveitis, including those due to BD, based on two randomized double-blinded studies (9,10).

- Tocilizumab

In the experimental model of autoimmune uveitis in mice, treatment with an anti-IL-6 receptor antibody also yielded dramatic reduction of uveal inflammation (20). TCZ has demonstrated efficacy in patients with refractory ocular inflammatory diseases (21–24). Biologic agents different from TNFα-antagonists, have been rarely reported in BD uveitis treatment. However, TCZ is one of the most promising treatment of BD. Targeting IL6 in BD is based on several reports involving IL6 in pathogenesis of BD. Active BD patients showed increased serum levels of IL-6 cytokines. Active BD is characterized by a higher increase of IL-6 compared to remission BD (38). IL-6 CSF levels are higher in patients with acute neurological attacks than in patients with chronic progressive neurologic involvement, while patients with progressive neuro-BD show a marked increase of CSF IL-6 activity, suggesting that IL-6 is a possible marker of disease activity and longterm outcome in such patients.
An increasing number of case reports and case series have been published about TCZ use in BD uveitis. TCZ may be effective in highly refractory BD-related uveitis (9–14). TCZ yielded a rapid reduction of ocular inflammation and led to long-term remission in these patients. In a multicenter retrospective study about 11 patients, TCZ led to rapid and maintained improvement in all ocular parameters of the patients, with complete remission in eight of them (13). All patients experienced an improvement in best visual acuity. Moreover, all patients who had retinal vasculitis, choroiditis and retinitis, reached complete remission at the end of the follow-up. In another study, five patients with BD uveitis who failed after interferon alfa and IFX therapy were treated with TCZ. Clinical remission was obtained after one infusion in all patients except one who achieved complete remission after five perfusions. Remission was maintained in all patients with no ocular inflammation flare (14).

In the current international expert recommendation on the management of uveitis the use of biotherapies (i.e. adalimumab or infliximab) is mandatory for two distincts situations. Firstly, as second line therapy, in cases of non infectious uveitis refractory to steroids and/or DMARDs. RUBI study (PHRCN-15-0026) tackles this population by comparing efficacy and safety of adalimumab to that of anakinra and tocilizumab in refractory (i.e. steroid dependence ≥ 10mg/d and refractory to at least 1 immunosuppressant) non infectious uveitis. Secondly, as first line therapy, for sight threatening uveitis. However, no randomized studies have directly evaluated

the best induction therapy in this context. In addition, Behçet's disease is considered as the most severe cause of noninflammatory uveitis. UVB study, will address the best biologic (adalimumab vs tocilizumab) as induction therapy for sight threatening uveitis. Therefore, the positioning of RUBI (PHRCN-15-0026) and UVB are clearly different and answer different and complementary questions about the management of non infectious uveitis.

2.4 Description of the population to be studied and justification for this choice of participants

Eligible patients with active sight threatening Behçet's disease uveitis [sight threatening uveitis will be defined according to the validated international definition as 2 lines of drop in visual acuity on a 10/10 scale, and/or retinal inflammation (macular oedema and/or retinal vasculitis)] will be randomized into one of 2 groups at the randomization visit (D0).

2.5 Identification and description of the investigational medication or medications

After the collection of their free and informed consent, eligible patients with sight threatening Behçet's disease uveitis will be randomized into one of 2 groups at the randomization visit (D0):

- **Arm A** Adalimumab 80 mg at D0 then 40 mg subcutaneous at week 1, 3, 5, 7, 9, 11, 13 and 15
- **Arm B** Tocilizumab 162 mg subcutaneous each week for 15 weeks

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

- **Arm A** Adalimumab 80 mg at D0 then 40 mg subcutaneous at week 1, 3, 5, 7, 9, 11, 13 and15
- **Arm B** Tocilizumab 162 mg subcutaneous each week for 15 weeks

2.7 Summary of the known and foreseeable benefits and risks for the Clinical trial participants

Current treatment of BD is guided by organ involvement and the severity of the disease. BD uveitis is considered as the most devastating inflammatory ocular disease with up to 25% of blindness and high risk of bilateral involvement. TNFa-antagonists have been used for sight-threatening BD uveitis for 15 years. Anti-TNF is a rapidly acting agent when compared to methylprednisolone or interferon alpha in suppressing ocular inflammation. The effect of anti-TNF started within the first 24 hours for suppressing ocular inflammation, as well as in decreasing anterior chamber cells, clearing retinal vasculitis and resolution of retinitis and cystoid macular edema. However, they failed to demonstrate sustainable complete remission over 50 % of patients. Also, TNFa antagonists seems to have suspensive effect on ocular inflammation in BD. Tocilizumab has been used with success in severe and/or resistant cases and is one of the most promising biologics in BD. Other biologic agents such as IL-1 and IL-17 blockers have also been tried. The IL-1 blocker gevokizumab and IL-17 blocker secukinumab failed to meet their primary endpoints in RCTs (39,40). Rapid onset of action and steroid-sparing effect characterize the efficacy of tocilizumab. Although the results of several studies have suggested that tocilizumab could be effective and rescue refractory case to anti-TNF therapy in severe BD, therapeutic controlled trial comparing biologics has not yet been thoroughly conducted. Nowadays, the management of severe BD still remains largely empirical. This is the first randomized, head to head, study for therapeutic management of severe uveitis in BD with biologics. This study may assess the benefit of tocilizumab comparatively to that of adalimumab in sight-threatening Behçet's disease in terms of safety, efficacy and steroid sparing. It could thus improve the care of patients with BD and with uveitis

in general. The expected benefit is both individual, in reducing morbidity and rate of blindness for young patients with BD, and collective, in reducing costs of hospitalization, and of dependence.

The main rare side effects associated with taking biotherapies are : potentially serious bacterial or viral infections, allergic reactions, skin rash or local reaction at the injection site. Exceptionally, renal failure, arterial hypertension, decrease in white blood cells and platelets and liver abnormalities have been described.

Adalimumab:

The most common side effects with Humira (which may affect more than 1 in 10 people) are infections (including in the nose, throat and sinuses), injection site reactions (redness, itching, bleeding, pain or swelling), headache and muscle and bone pain.

Humira and other medicines of its class may also affect the ability of the immune system to fight off infections and cancer, and there have been some cases of serious infections and blood cancers in patients using Humira.

Other rare serious side effects (which may affect up to 1 in 1,000 people) include failure of bone marrow to produce blood cells, nerve damage caused by breakdown of the covering around the nerve fibres, lupus and lupus-like conditions (causing inflammation and organ damage), and Stevens-Johnson syndrome (a life-threatening reaction with flu-like symptoms and painful rash affecting the skin, mouth, eyes and genitals)..

Fabiani and *al.* evaluated the efficacy of adalimumab (ADA) in a large series of Behçet's disease (BD)-related uveitis. They reported 40 patients. At 3-month follow-up, ADA was withdrawn in five cases due to lack of efficacy (ocular inefficacy, n = 2; intestinal relapses, n = 2) and a severe adverse event (pneumonia, n = 1). One patient was lost at follow-up between month 3 and month 12. Regarding safety, no other adverse events or severe adverse events were recorded in addition to the mentioned pneumonia. (41)

Atienza-Mateo and *al.* compared the efficacy of infliximab (IFX) versus adalimumab (ADA) as a first- line biologic drug over 1 year of treatment in a large series of patients with refractory uveitis due to Behçet's disease (BD), in 177 patients (316 affected eyes), of whom 103 received IFX and 74 received ADA. Minor adverse effects, such as mild infusion reaction to IFX and local reactions at the site of the injection of ADA, were the most commonly observed side effects. Severe complications leading to discontinuation of the biologic therapy were observed in 8 cases in the IFX group and 4 in the ADA group. The treatment was discontinued due to inefficacy in 18 cases in the IFX group and 11 in the ADA group(17.5% and 14.9%, respectively). Further randomized, controlled trials comparing IFX and ADA head-to-head are needed, but they observed favorable results of both ADA and IFX therapy for BD- related refractory uveitis after 1 year of treatment, with significantly greater improvement in visual acuity and higher drug retention rate in the ADA group than the IFX group (42)

Tocilizumab:

The common side effects of Tocilizumab include upper respiratory tract infection, increased transaminases level, dyslipidemia, neutropenia, thrombocytopenia, gastrointestinal perforation, headache, rash (including exfoliative rash), muscle and bone pain, hypersensitivity reaction and reaction at the site of injection (including erythema).

Rare but severe side effects include serious hepatic toxicity.

In patients with rheumatoid arthritis, systemic juvenile idiopathic arthritis, juvenile idiopathic polyarthritis, giant cell arteritis or cytokine release syndrome, the most common side effects (which may affect up to 1 patient in 10) with Tocilizumab are upper respiratory tract infections (nose and throat infection), nasopharyngitis (inflammation of the nose and throat), headache, hypertension and abnormal liver function tests. The most serious side effects are serious infections, complications of diverticulitis (a disease affecting the gut) and hypersensitivity (allergic) reactions.

In patients with COVID-19 treated with Tocilizumab, the most common reported side effects (which may affect up to 1 patient in 10) were high levels of transaminases, constipation, and urinary tract infections.

Atienza-Mateo and *al.* assessed the efficacy of TCZ in the different clinical phenotypes of BD, in 16 patients (10 men/6 women); mean age 36.5±18.2 years. The main indications for TCZ prescription were refractory uveitis (n=14) and refractory neurobehçet (n=2). TCZ is effective in BD with major clinical involvement. However, it does not seem to be effective in oral/genital ulcers or skin lesions.TCZ was overall well tolerated with no new safety alarms detected. (43)

Akiyama and *al.* investigated the Effectiveness of tocilizumab in Behcet's disease, by performing a systematic literature review from the inception dates until April 10, 2020 for articles reporting tocilizumab administration for the treatment of Behcet's disease. A total of 47 patients with Behcet's disease treated with tocilizumab retrieved from 20 articles were analyzed in this study. Tocilizumab was effective and can serve as an alternative treatment for refractory ocular-, neuro-, and vasculo-Behcet's disease, as well as secondary amyloidosis, but was not recommended for patients with mucocutaneous and articular involvement.
Tocilizumab was well tolerated as a treatment of Behcet's disease. Among 47 patients, 5 patients had adverse events; 2 had dyslipidemia, 1 had scrotal abscess, 1 had recurrent labial herpes, and 1 had infusion reaction. However, no new safety signal was reported. (44)

Atienza-Mateo and *al.* assessed the efficacy of tocilizumab (TCZ) in refractory uveitis of Behcet’s disease (BD) in a multicentre retrospective study, of 11 patients (7 men) (20 affected eyes); median age 35 years. The only severe adverse effect found was an infusion reaction (13). The patterns of ocular involvement were panuveitis (n=8, with retinal vasculitis in 4), anterior uveitis (n=2) and posterior uveitis (n=1). Cystoid macular oedema was present in seven patients. The clinical course was recurrent (n=7) or chronic (n=4). At TCZ onset the following extraocular manifestations were present: oral and/or genital ulcers (n=7), arthritis (n=4), folliculitis/pseudofolliculitis (n=4), erythema nodosum (n=2), livedo reticularis (n=1) and neurological involvement (n=2). TCZ yielded rapid and maintained improvement in all ocular parameters of the patients, with complete remission in eight of them. However, this was not the case for the extraocular manifestations, since TCZ was only effective in three of them. After a mean (S.D.) follow-up of 9.5 (8.05) months, TCZ was withdrawn in two cases, due to a severe infusion reaction and arthritis impairment, respectively.

3 OBJECTIVES

3.1 Primary objective

To assess the benefit of tocilizumab comparatively to that of adalimumab in sight-threatening Behçet's disease uveitis at week 16.

3.2 Secondary objectives

1. To estimate and compare the change in best corrected visual acuity (BCVA)
2. Time to complete remission at week 4, 8, 12, 24, 36 and 48
3. To evaluate and compare the safety of Adalimumab and tocilizumab
4. To evaluate and compare the change in macular edema
5. To evaluate and compare the change in other signs of ocular inflammation
6. To evaluate and compare the effect on retinal vessel leakage
7. To evaluate and compare the effect of Adalimumab and tocilizumab on steroid sparing
8. To evaluate and compare the change in ocular inflammation in the anterior chamber
9. To evaluate and compare the number and time to relapse of uveitis and the characteristics of uveitis at worsening.
10. To evaluate and compare the time to treatment failure (Patients will be considered to have treatment failure if any of the following criteria is met in at least 1 eye: new active, inflammatory retinal vascular lesions and/or macular edema; worsening best corrected visual acuity (BCVA) by ≥3 lines; 2-step increase in anterior chamber (AC) cell grade; 2-step increase in vitreous haze (VH) grade relative to Baseline.
11. To estimate and compare the effect on extra ophthalmologic manifestations of Behçet's Disease.
12. To estimate and compare the mean change in SF-36 quality of life and Behçet's Disease Quality of Life Measure
13. To estimate and compare the changes in Behcet's Disease Current Activity Form and Behcet's Syndrome Activity Score

4 STUDY DESIGN

4.1 Study endpoints

4.1.1 Primary endpoint

Efficacy will be defined by a complete remission of ocular involvement with prednisone (or prednisolone, only if prednisone is out of stock in the market) lower or equal to 5 mg/day at week 16 after randomization.
Complete remission of ocular inflammation will be defined as a complete resolution of retinal vasculitis and/or macular edema with prednisone (or prednisolone, only if prednisone is out of stock in the market) lower or equal to 5 mg/day at week 16 (33). In patients with bilateral uveitis, the eye with the highest disease activity will be chosen as the study eye.

4.1.2 Secondary endpoints

1. Measures of corticosteroid sparing (e.g., percent meeting targets [lower than 0.1 mg/day/kg of prednisone (or prednisolone, only if prednisone is out of stock in the market)], mean dose at week 16, and cumulative dose).
2. Time to response onset,
3. Measures of acute-phase reactants (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], at week 4, 8, 12, 16, 24, 36 and 48
4. Rate and Time to occurrence of relapse or worsening while on study. (Relapse will be defined as the reappearance of clinical and/or paraclinical features of active disease or by the occurrence of new lesions or progression of preexisting lesions).

5. Changes in Behcet's Disease Current Activity Form (BDCA) at week 8, 16 and 24
6. Changes in Behcet's Syndrome Activity Score (BSAS) at week 16
7. Changes in other organs involved by BD at week 4, 8, 12, 16, 24, 36 and 48
8. Changes in quality of life (QOL) (SF36v2 TM Health Survey) and Behcet's Disease Quality of Life Measure (BD-QoL) at week 16 and 24
9. Safety and tolerability of treatments in BD patients as assessed by frequency and severity of adverse clinical events at week 4, 8, 12, 16, 24, 36 and 48
10. Time to treatment failure (time to occurence)
11. Changes in Tyndall, flare and Vitreous Haze at week 8, 16, 24, 36 and 48
12. Changes in Best corrected visual acuity (SNELLEN score) at week 8, 16, 24, 36 and 48
13. Changes in central retinal thickness measured with Optical Coherence Tomography (OCT) at week 8, 16, 24, 36 and 48.
14. Percentage of patients with central retinal thickness <300 microns at week 8, 16, 24, 36 and 48.
15. Percentage of patients without retinal vessel leakage on retinal angiography at week 16, and at week 24, 36 and 48, in case of retinal vasculitis.

4.2 Description of research methodology

4.2.1 Design of the trial

The experimental design is an open multicenter randomized clinical trial stratified by the main involvement at baseline (retinal vasculatis, and/or macular oedema), and according to newly diagnosed or relapsing disease with evaluation of the primary assessment criteria at week 16.

We choose a Bayesian Phase II randomized clinical trial that aims at comparing the response rate at week 16 of an experimental treatment (Tocilizumab) to the reference (Adalimumab). Randomized phase II trials are still poorly used, with still large use of single-arm phase II trial results that are interpreted relative to historical control subjects, introducing selection bias and confounding that may limit the validity of the conclusions. Thus, planning a phase II randomized trial appears a worthy investment considering finite patient and financial resources (Sharma 2011).
Moreover, we choose to design the trial as a Bayesian clinical trial, for three main reasons. First, this allows incorporating information outside the trial that results in a decrease in required sample size due to such "fictive" observations. Secondly, Bayes designs are particularly well-suited for adaptive designs, given inference is based on accumulated data along the trial, allowing interim and sequential analyses without any inflation of type I error or biased estimation (Wang 2016). Third, this design is adapted to binary outcomes observed at the end of a fixed follow-up period and analyzed using an absolute difference in proportions that has been shown to greatly reduce sample size requirements. Thus, an interim analysis that will use Bayesian inference will be performed after one year of enrolment.
Given the uncertainty in the tocilizumab benefit over adalimumab in severe Behçet's disease uveitis at this early stage of evaluation, and the fact that the severe population focused in this trial is not very large in size, the selection approach to planning sample size was worthy of consideration. We thus used the approach for phase II randomized trials proposed by Simon R, Wittes RE, and Ellenberg SS (1985) that aims at controlling the probability of detecting a given difference in response rates.
We will use a Beta-Binomial model, with a non-informative prior (sensitivity analyses will be run with informative prior). The posterior probability that the treatment response rate is above 0.65, and the posterior probability that the Arm A is below the Arm B will be computed. A total of 60 patients will be enrolled (30 patients in Arm A and 30 patients in Arm B), previously shown as allowing conclusive results.
An interim analyse will be performed after the inclusion of 30 patients.

4.2.2 Study scheme:

• Day 0 : Eligibility for enrollment is determined. Patients who satisfy all entry criteria including informed consent will be included in the trial.
Inclusion and Randomization in a 1:1 ratio :

- Arm A (Adalimumab) 80mg at D0 then 40mg subcutaneously at week 1, 3, 5, 7, 9, 11, 13 and15
- Arm B (Tocilizumab) 162mg subcutaneously every week for 15 weeks

All treatment groups will receive the same corticosteroid regimen. All patients will receive oral prednisone (or prednisolone, only if prednisone is out of stock in the market) at 1 mg/kg/day (up to 80 mg/day) at randomization. The following schedule of reduction of prednisone (or prednisolone, only if prednisone is out of stock in the market) will apply to both groups as long as the disease is inactive:

- 1 mg/kg/day (maximum 80 mg/d) week D0-W4,
- 40 mg/day W4-W6
- 30 mg/day W6-W8,
- 20 mg/day W8-W10,
- 15 mg/day W10-W12,
- 10 mg/day W12-W14,
- 5 mg/day W14-W16.

Dose of corticosteroids will be left at the investigator discretion after W16.

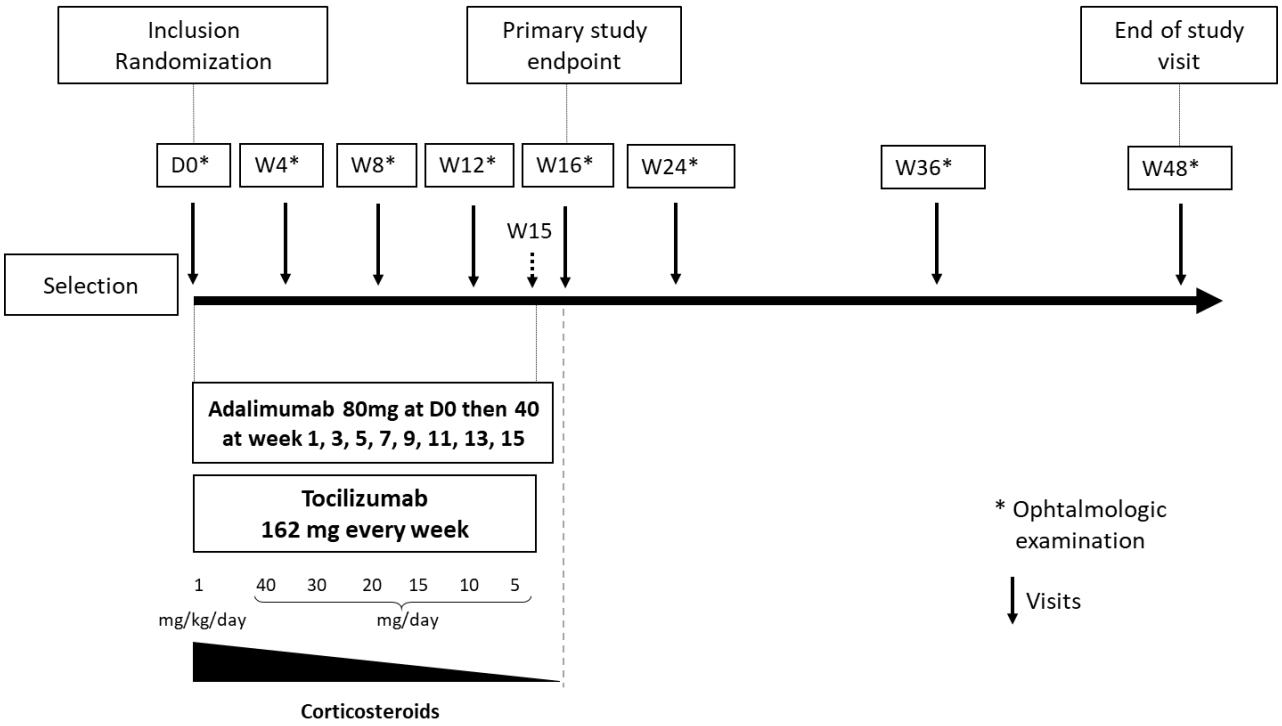
At each step, the prednisone (or prednisolone, only if prednisone is out of stock in the market) dose will be reduced only in the absence of signs of uveitis activity. Other immunosuppressants agents (methotrexate, azathioprine, mycophenolate mofetil…) will be proscribed during the study follow-up as long as the disease is inactive.

• Monitoring: All patients will be reviewed at the follow-up visits at 4, 8, 12, 16, 24, 36 and 48 weeks. Monitoring will include systemic physical examination, ophthalmologic examination, laboratory testing and imaging (Optical Coherence Tomography and retinal angiography).
Additional visits will take place in case of any clinical or laboratory findings suggestive of a flare-up of the disease.

Assessment criteria will be evaluated as follows:

- Week 8 and 12: Evaluation of secondary assessment criteria
- Week 16: Evaluation of primary and secondary assessment criteria
- Week 24: Evaluation of secondary assessment criteria
- Week 36: Evaluation of secondary assessment criteria
- Week 48: Evaluation of secondary assessment criteria

Figure 1. Scheme of the study



4.2.3 Number of participating sites

This national multicenters study, involving 26 clinical centers. Participating centers will be Internal medicine (or rheumatology) and Opthalmology departments of public hospitals located in France.

The Selection of patient will be conducted by investigator of internal medicine (or rheumatology) and ophthalmology centers.

- **Recruitment centres**

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

- **Non-recruitment centres**

Visits of Follow-up will be conducted by investigator of ophthalmology centers where a specific intervention to the research will be carried out (e.g. Optical Coherence Tomography (OCT), Retinal angiography).

4.2.4 Identification of participants

For this Clinical Trial, 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:
Site 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.

4.2.5 Inclusion and Randomization

When selected, the patient eligibility will be evaluated from inclusion and non-inclusion criteria. Once the consent will be signed by the patient and investigator, the patient will be included and randomised 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 two groups will be made in a 1:1 ratio.
The randomization list will be designed by the Sponsor/designee, and stratified by the main involvement at baseline : retinal inflammation (retinal vasculatis, and/or macular oedema) and according to the diagnosis (newly diagnosed or relapsing disease), between the two arms.
Each list will be based on permutation blocks, the size of which will be unknown to practitioners involved in patient accrual.

5 IMPLEMENTATION OF THE STUDY

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

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

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

5.1 Inclusion and randomization visit

The Inclusion and randomization visit takes place *at day 0*.

Whose consent must be obtained	**Who informs the individuals and collects their consent**	**At what point the individuals are informed**	**At what point the consent is obtained**
Adult patients with sight-threatening Behçet's disease associated uveitis.	the investigator of internal medicine or Rheumatologist informs and collect consent	During Inclusion/randomization visit	After time reflexion during Inclusion/randomization visit

The Inclusion and randomization visit will be carried out by the physician who is responsible for the patient during the Study. During this visit, the investigator will:

- verify the eligibility criteria,
- interview the patient and record: medical, surgical and therapeutic histories, history of undercurrent disease and current treatments,
- perform a physical examination including a search for active lesions of Behçet's disease, Behçet's Syndrome Activity Score (BSAS), Behcet's disease Current Activity Form (BDCA)
- perform complete blood count with platelets, serum electrolytes, liver function tests (AST, ALT, GGT, PAL, total bilirubin, albumin), LDH, CRP, ESR, urea, glucose, creatinine, triglyceride and cholesterol,
- for women with reproductive potential ßHCG (urinary or plasmatic),

- quantiferon test obtained within 6 months prior to inclusion
- HIV serologies, HBV surface antigen and HCV RNA, obtained within 1 month prior to inclusion
- ECG
- Assess the results of the ophthalmology exams obtained within 1 month prior inclusion: ocular examination which included fundoscopy, Slit-lamp examination (Vitreous Haze, flare and cells in anterior chamber), intraocular pressure (IOP), BCVA (SNELLEN score), Optical Coherence Tomography (OCT) and retinal angiography.
- Assess the results of chest X-ray or CT-scanner of less than 12 weeks.
- Assess other exams according to others active BD manifestations have to be obtained within 3 months prior inclusion.
- If all eligibility criteria are met the investigator will inform the patient about the protocol, and give him/her the information and consent form.
- collect the free and informed written consent of the patient complete the Study Inclusion Form listing the eligibility criteria and assure the randomization on CleanWeb, an online randomization system
- Quality of life assessment (SF-36, BD-QoL),
- Provide the first treatment and patient card to patient

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

- **Arm A (n=30 patients)** Adalimumab 80mg at D0 then 40mg subcutaneously at week 1, 3, 5, 7, 9, 11, 13 and15
- **Arm B (n=30 patients)** Tocilizumab (162 mg/7 days subcutaneously) for 15 weeks

The first treatment will be administered under medical supervision who will train the patient to the modalities of injection to enable him to carry out the following.

5.2 Follow up visits

Monitoring should continue for all patients until the end of the Study according to the schedule, **even if they discontinue treatment**. Consultations at these visits will be with the patient's usual Study investigator. Patients will be reviewed at 4, 8, 12, 16, 24, 36 and 48 weeks and will have:

- Ophthalmic examination by ophthalmologist to follow the efficacy, will take place at 4, 8, 12, 16, 24, 36 and 48 weeks including fundoscopy, Slit-lamp examination (Vitreous Haze, Tyndall and flare in anterior chamber), intraocular pressure (IOP), change from baseline in BCVA (SNELLEN score) ; Optical Coherence Tomography (OCT) will be performed at 8, 16, 24, 36 and 48 weeks; retinal angiography will be performed at 16 weeks. In case of retinal vasculitis, retinal angiography will be performed at 24, 36 and 48 weeks.
- A physical examination will be performed by the patient's study physician at each visit to dispensate the treatment and follow tolerance (neurological exam to detect demyelinating disorders, infections, skin cancer, lymphoma, and autoimmune disorder) and Behçet's Syndrome Activity Score (BSAS) assessement at 16 weeks, and Behcet’s disease Current Activity Form (BDCA) at, 8, 16 and 24 weeks.
- Other exams according to others active BD manifestations will be performed at the discretion of the patient’s study physician, as part of standard of care.
- At each visit complete blood count with platelets, serum electrolytes, liver function tests (AST, ALT, GGT, PAL, total bilirubin, albumin), LDH, CRP, ESR, urea, glucose, creatinine, triglyceride and cholesterol,

- Toxicities: evaluated by CTCAE scale, adverse events
- Quality of life QOL) (SF36v2 TM Health Survey) and Behcet's Disease Quality of Life Measure (BD-QoL)at 16 and 24 weeks.
- For women with reproductive potential urinary ßHCG at each visit during treatment and monthly until 3 and 5 months after stopping therapy for tocilizumab and adalimumab, respectively..

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 48. The purpose of additional follow-up beyond week 16 (at week 48) is to gather safety and efficacy data with prolonged treatment with Adalimumab and tocilizumab, as well as additional efficacy and safety data on patients who discontinue their treatment with Adalimumab and tocilizumab at or before week 16.
Treatment between week 16 and 48 will be left at the discretion of the physician in charge of the patient.

5.3 End of study visit

After Month 12, all subjects will be followed after the study according to their usual routine hospital care.

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

The total duration of the Study will be 48 months (4 years). The duration of the inclusion phase will be 36 months. The duration of participation of each patient will be of 12 months. The duration of experimental treatment of each patient will be 16 weeks.

Length of Inclusion period	36 months
Duration of participation for each subject, of which:	48 weeks
• Treatment period:	15 Weeks
• Post treatment follow-up period:	33 Weeks
Total study duration:	48 months

5.5 Table or diagram summarising the chronology of the study

	D0	W4 ± 3 days	W8 ± 3 days	W12 ± 3 days	**W16** ± 3 days **§**	W24 ± 3 days	W36 ± 3 days	W48 ± 3 days
Verification of inclusion and non inclusion criteria	R							
Inclusion/randomization visit (Oral and written Information about the protocol and Signature of informed consent)	R							
Clinical examination#	C	R	C	R	**C**	C	C	C
Ophthalmologic examination*	C	R	C	R	**C**	C	C	C
Optical Coherence Tomography (OCT)	C		R		**C**	C	C	C
Retinal angiography	C				**C**	R**	C**	C**
Biological tests †	C	C	C	C	**C**	C	C	C
Quantiferon, HIV serology, HBV surface antigen, HCV RNA	C							
bhCG***	C	R	R	R	**R**	R	R	
ECG	C							
Chest X Ray or chest CT-scan (within 12 weeks)	C							
QOL questionnaires (SF-36 and BD-Qol)	R				**R**	R		
Behçet's Syndrome Activity Score (BSAS)	R				**R**			
Dispensation of treatments	R	R	R	R				
Compliance	R	R	R	R	R			
Adverse events	R	R	R	R	R	R	R	R

C= care / R = research

§ Primary study endpoint

Clinical examination will include exams according to others active BD manifestations and BDCA at baseline, W8, 16 and 24. All these exams will be performed as part of standard of care

* Ophtalmic examination will include fundoscopy, Slit-lamp examination (Vitreous Haze, Tyndall and flare), IOP measure, change from baseline in BCVA. The baseline ophthalmologic exams have to be obtained within 1 month prior inclusion.

†complete blood count with platelets, serum electrolytes, liver function tests (AST, ALT, GGT, PAL, total bilirubin, albumin), LDH, CRP, ESR urea, creatinine, glucose, triglyceride and cholesterol.

** in case of retinal vasculitis

***For women with reproductive potential urinary ßHCG at each visit and monthly until 3 and 5 months after stopping therapy for tocilizumab and adalimumab, respectively.

5.6 Distinction between standard care and study

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

Interventions, procedures and treatments carried out for research purposes	**Interventions, procedures and treatments associated with <u>standard care</u>**	**Interventions, procedures and treatments added for <u>research purposes</u>**
Treatments	- oral prednisone (or prednisolone, only if prednisone is out of stock in the market) - Reduction of corticosteroid regimen - supportive treatment to reduce the adverse effects associated with the use of steroids	- Adalimumab 80mg at D0 then 40mg at week 1, 3, 5, 7, 9, 11, 13 and 15 subcutaneously - Tocilizumab 162 mg/7 days subcutaneously for 15 weeks
Consultations	- one visit with physician (internist or rheumatologist) every 2 months - Visit with ophthalmologist every 2 months	- Visit with internist at week 4 and 12 - Visit with ophthalmologist at week 4 and 12
Blood samples	- blood sampling at baseline and every 4 weeks - BHCG (plasmatic or urinary) at baseline	- ßHCG (urinary) at each visit and monthly until 3 and 5 months after stopping therapy for tocilizumab and adalimumab, respectively.
Imaging	- ECG: before starting treatment - Chest X Ray / Chest CT-Scan before starting treatment - Optical Coherence Tomography (OCT) (before starting treatment and at week 16, 24, 36 and 48) - Retinal angiography before starting treatment and at week 16 (and at week 36 and 48 in case of retinal vasculitis)	- Optical Coherence Tomography (OCT) at W 8 - Retinal angiography at W24 in case of retinal vasculitis
Others		- QOL questionnaires at D0, 16 and 24 weeks - Behçet's Syndrome Activity Score (BSAS) assessement at D0, and weeks 16

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

The eligibility criteria will be checked at the inclusion/randomization visit. Adult patients meeting the following criteria may be included in the study:

1. Age ≥ 18 at Inclusion
2. Provide written, informed consent prior to the performance of any study-specific procedures
3. Diagnosis of Behçet's disease according to the International Criteria for Behçet's Disease (ICBD) (see appendix 18.2) or history of aphtosis.
4. 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
5. Sight threatening uveitis defined according to the validated international definition as 2 lines of drop in visual acuity on a 10/10 scale, and/or retinal inflammation (macular oedema and/or retinal vasculitis).
6. Chest X-ray (postero-anterior and lateral) or CT-scanner results within 12 weeks prior to Inclusion with no evidence of active Tuberculosis, active infection, or malignancy
7. For female subjects of child-bearing potential (premenopausal female capable of becoming pregnant), a negative serum pregnancy test (plasmatic or urinary)
8. For subjects with reproductive potential, a willingness to use contraceptive measures adequate to prevent the subject or the subject's partner from becoming pregnant during the study and 3 and 5 months after stopping therapy for tocilizumab 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:

   For female subjects :
   - 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 :
     - 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).

   For male subjects :
   - use of a condom
   - vasectomy (with documentation of azoospermia)
   - sexual abstinence
9. Negative TB test obtained within 12 weeks prior to inclusion. A potential subject with a positive interferon-gamma release assay (IGRA) (e.g., QuantiFERON® -TB Gold or T-spot TB® Test) is eligible if her/his chest X-ray does not show evidence suggestive of active TB disease and there are no clinical signs and symptoms of pulmonary and/or

extra-pulmonary TB disease. These subjects with a latent TB infection who have not already received a prophylactic TB treatment must agree in advance to complete such a treatment course. The treatment should be started at the latest at inclusion.

10. Affiliation to a social security system. Patients affiliated to universal medical coverage (CMU) are eligible for the study

6.2 Non inclusion criteria

Subjects will be not included in the study if they meet any of the following criteria:

1. Infectious uveitis, masquerade syndromes, or uveitis due to causes other than BD uveitis
2. Active tuberculosis or history of untreated tuberculosis and/or severe infection
3. Positive HIV antibody and/or positive hepatitis B surface antigen and/or positive hepatitis C RNA, results obtained within 1 month prior to inclusion
4. 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.
5. History of severe allergic or anaphylactic reactions to monoclonal antibodies
6. History of multiple sclerosis and/or demyelinating disorder
7. Hypersensitivity to the active substance or an excipient of the IMP or the auxiliary medicine
8. Active or suspected ocular infection
9. Active or suspected systemic infection
10. History of intestinal ulceration or diverticulitis
11. **Known** porphyria
12. Laboratory values assessed during Inclusion:
    a. Neutrophil < 1.0×10^3/mm3
    b. Platelet count < 80×10^3/mm^3
    c. ASAT or ALAT > 5 ULN
13. Treatment with anti-TNF and/or Tocilizumab therapy within 1 month prior to inclusion
14. Patient on azathioprine, mycophenolate mofetil, or methotrexate at the time of inclusion (these drugs must be withdrawn prior to receiving the tocilizumab or adalimumab dose on Day 0).
15. Stage III and IV New York Heart Association (NYHA) cardiac insufficiency
16. Severe renal (Glomerular filtration rates (GFR) <30ml/min) or liver insufficiency (prothrombin <50% without other causes)
17. Any live (attenuated) vaccine within 30 days prior to inclusion;
18. Breastfeeding and pregnant women

6.3 Recruitment procedure

The French national reference center for rare systemic autoimmune diseases and for autoinflammatory diseases located in the Pitie Salpetriere hospital, in Paris, is a leading center in the field of Behçet's disease with a cohort of more than 1500 patients. The ophthalmology department of Pitie Salpétriere hospital is national reference center for uveitis. With the French Behçet's network, we recently conducted a study on efficacy of anti-TNF in severe Behçet's disease and recruited 124 patients in 1 year (7). The French Behçet's research network is composed of multiple competence centers for Behçet's disease related to the French national reference center for rare systemic autoimmune diseases and for autoinflammatory diseases and for uveitis. We are working in close collaboration with French ophthalmologists and rheumatologists including those from Pitie Salpetriere hospital, in Paris.

	Number of *participants*
Total number of *participants* to be included	60
Number of centres	26
Enrolment period (months)	36
Number of *participants* /centre	2.3
Number of *participants* /centre/month	**0.07**

6.4 Termination rules

6.4.1 Criteria and procedures for prematurely terminating the study treatment

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

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

In the case of severe adverse events, the investigator must notify the sponsor and follow up the participant for 1 month following the premature discontinuation of treatment. Notification of a serious adverse event must be sent by email (eig-vigilance.drc@aphp.fr) to the sponsor. The serious adverse event will be monitored until it is resolved. If a Data Safety Monitoring Board has been created, the committee can specify and/or validate the follow-up methods.

6.4.2 Permanent termination of the study treatment

A subject must be permanently discontinued the treatment for any of the following reasons:
- 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 (≥ grade 3) study drug reaction including anaphylactic reaction
- Flare of the disease, or worsening ocular inflammation requiring another immunosuppressant and/or immunomodulator and/or increased doses of corticosteroids (as describe on section 8.1.2 Non responders and 8.1.3 Relapse)
- Lack of improvement at 1 month.

- Treatment protocol interruption >15 consecutive days
- Serious infections (> grade 3)
- Persistant neutropenia (< 1.0 x 10^9/L) >15 days
- Malignancy other than carcinoma in situ of the cervix,, 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

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

- Participants may exit the study at any time and for any reason.

- The investigator can temporarily or permanently withdraw a participant from the study for any safety reason or if it is in the participant's best interests.

- Participant lost to follow-up: the participant cannot be located. The investigator must make every effort to reconnect with the participant (and record his attempts in the source file), at least to determine whether the participant is alive or dead.

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

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

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

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

6.4.4 Follow-up of participants following premature termination of study treatment

In a case of premature termination of treatment, the reason(s) for a participant’s discontinuation treatment must be clearly documented in the participant’s medical records and on the appropriate page of the eCRF and follow up visits will be done according to protocol calendar until week 48 except in case of consent withdrawal and lost to follow-up.
The participant will receive the most appropriate care in the opinion of the investigator (possibly including rescue therapy for an occurrence of uveitic disease). The participant will receive appropriate treatment(s) by her or his physician.
Ending a participant's participation does not affect the normal management of the participant's illness in any way.

The adverse event reporting period for safety surveillance begins when the participant is included into the trial (date of first signature of informed consent) and continues until 4 weeks after the end of the participant's treatment with the investigational medicinal product If there are serious adverse events, see section 10.1.2.

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

If a participant discontinues the study, this will in no way affect their usual care for their condition.
In the event of serious adverse events following premature discontinuation of treatment and participation of the patient in the study; see section 10.1.2.

6.4.6 Procedures for replacing participants

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

6.4.7 Full or partial discontinuation of the study

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

- first, if suspected unexpected serious adverse reactions (SUSARs) are observed in one of the treatment arms or if there is a discrepancy in the serious adverse reactions between the two treatment arms, requiring a reassessment of the benefit-risk ratio for the trial.
- if an interim analysis confirms the efficacy of one of the treatment arms or, alternatively, the lack of efficacy.

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

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

In all cases in which a study is discontinued, the participants included in the study be monitored until the end of their participation, as set forth in the protocol.

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

7 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

7.1 Description of the investigational medicinal product(s)

Eligible patients (n=60) with sight threatening BD uveitis will be randomized at 1:1 into two groups during the inclusion/randomization visit (D0):

- **Arm A (n=30):** patients will receive Adalimumab (80mg for first administration at D0 then 40 mg subcutaneous at week 1, 3, 5, 7, 9, 11, 13 and15.
- **Arm B (n=30):** patients will receive + tocilizumab (162 mg/7 days subcutaneously) for 15 weeks.

All treatment groups will receive the same corticosteroid regimen (at the dose shown below).

7.1.1 Investigational medicinal product 1 : Arm A

Adalimumab (Humira®) 40 mg solution for injection in pre-filled pen.
Each 0.4 ml single dose pre-filled pen contains 40 mg of adalimumab
Patient will be treated with 80mg loading dose then 40mg every 14 days starting at week 1, subcutaneously for 15 weeks (10 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, by Clinical Trial Department of central pharmacy of AP-HP (Département des Essais Cliniques, Agence Générale des Equipements et des Produits de Santé, AP-HP)

For adverse events related to the experimental medication refer to the summary of Product Characteristics (SmPC) for Humira on the CTIS platform and Investigator's file (see EMA website: https://www.ema.europa.eu/en/documents/product-information/humira-epar-product-information_en.pdf

7.1.2 Investigational medicinal product 2 : Arm B

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 15 weeks (16 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, by Clinical Trial Department of central pharmacy of AP-HP (Département des Essais Cliniques, Agence Générale des Equipements et des Produits de Santé, AP-HP)

For adverse events related to the experimental medication refer to the summary of Product Characteristics (SmPC) for RoActemra and the CTIS platform and Investigator's file (see EMA

website: https://www.ema.europa.eu/en/documents/product-information/roactemra-epar-product-information_en.pdf).

7.2 Description of Auxiliary medicinal product(s) (treatments required to conduct the study)

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

7.2.1 Auxiliary medicinal product 1: Systemic Corticosteroid Therapy Corticosteroids

All treatment groups will receive the same corticosteroid regimen.
At randomization (Day0), patients receive treatment allocated by randomization. The following schedule of reduction of prednisone (or prednisolone, only if prednisone is out of stock in the market) will apply to both groups as long as the disease is inactive:

- 1 mg/kg/day (maximum 80 mg/d) week W0-W4,
- 40 mg/day W4-W6
- 30 mg/day W6-W8,
- 20 mg/day W8-W10,
- 15 mg/day W10-W12,
- 10 mg/day W12-W14,
- 5 mg/day W14-W16

Dose of corticosteroids will be left at the investigator discretion after W16
This above schedule of prednisone (or prednisolone, only if prednisone is out of stock in the market) is recommended as guideline.

Patient treated with corticosteroids and any one of the medications listed below should have the posology of their medications adapted by the physician at the start of corticosteroid therapy and during the treatment period

- Acetylsalicylic acid (at inflammatory dose >= 1g at once and/or >= 3g per day)
- Strong CYP3A Inhibitors
- Mifamurtide
- Oral anticoagulants
- Other hypokaliemiant
- Enzymatic induceurs
- Cobimetinib
- Digoxin
- Isoniazid

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

Side effects related to tapering-of corticosteroids: Relapse of disease activity

7.2.2 Auxiliary medicinal products 2 & 3: Fluorescein and indocyanin green for Retinal angiography

All patients will receive a fluorescein and indocyanine green angiogram (FA/ICG) at selection, W16, W36 and W48 and in case of vasculitis at W24).
Examination at W24 is added by the research.
Products will be used according to their respective marketing authorization and angiogram made following local usual procedure.

7.2.3 Auxiliary medicinal product 4: Prophylactic TB treatment

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

Patient treated with Rifampicin or Isoniazid and any one of the medication listed below should have the posology of their medications adapted by the physician at the start of prohylactic TB treatment and during the treatment period :
- Carbamazepin
- Disulfiram (advised against isoniazid)
- Acetylsalicylic acid (at inflammatory dose >= 1g at once and/or >= 3g per day)
- Strong CYP3A Inhibitors
- Mifamurtide
- Oral anticoagulants
- Other hypokaliemiant
- Enzymatic induceurs
- Cobimetinib
- Digoxin
- Isoniazid
- Other medicines presented in the section 4.3 to 4.5 of Rimactan®, Rimifon® and Rifinah® SmPCs

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

7.3.1 Origins and storage conditions :

- Adalimumab

Origin : supply and labelling by DEC-AGEPS
Storage : in a refrigerator (2 °C – 8 °C).

- Tocilizumab

Origin : supply and labelling by DEC-AGEPS
Storage : in a refrigerator (2 °C – 8 °C).

7.3.2 Dispensing

Pharmacies will dispense to care givers the experimental medication on the basis of a specific prescription and with respect to local procedures.

Dispensing should be recorded on a specific traceability document.

7.3.3 Administration and follow up

Each administration should be recorded on a specific traceability document.
The first injection of Adalimumab and Tocilizumab should be administered under the close supervision of an experienced healthcare professional.

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

7.4.1 Authorized treatments

All treatments taken by the patient during the trial but not prescribed in the Protocol will be considered "treatments other than Study treatments". Whether allowed or not, they will be reported on the dedicated page of the CRF. The risks and benefits of using such drugs must be carefully assessed for all included patients.

To reduce the adverse effects associated with the use of steroids, the following supportive treatment will be administered routinely starting on day 0:

- a potassium supplement (DIFFU K, 1 capsule up to 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.

7.4.2 Prohibited treatments

Immununosuppressive or immunomodulatory therapies (azathioprine, mycophenolate mofetil, methotrexate, plaquenil) are contraindicated for the duration of the study, as long as the disease is inactive.

7.5 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.

8 EFFICACY ASSESSMENT

8.1 Description of efficacy endpoints assessment parameters

8.1.1 Clinical response

- Complete clinical remission

Efficacy will be defined by a complete remission of ocular involvement with prednisone (or prednisolone, only if prednisone is out of stock in the market) lower or equal to 5 mg/day at week 16 after randomization.
Complete remission of ocular inflammation will be defined as a complete resolution of retinal vasculitis and/or macular edema. In patients with bilateral uveitis, the eye with the highest disease activity will be chosen as the study eye. The complete clinical response will be defined by the remission of uveitis and the absence of clinical relapse.

- Partial clinical remission

Partial remission of ocular inflammation will be defined as the percentage of patients with an improvement in vitreous haze (< 2 steps) and/or an improvement but with an incomplete resolution of retinal vasculitis and/or macular edema; with prednisone (or prednisolone, only if prednisone is out of stock in the market) lower or equal to 5 mg/day at week 16 after randomization.

- Non-response (see 8.1.2)

Patients with uncontrolled, worsening and/or flare of uveitis at any time of the study will be considered as no responders and will be treated at the discretion of their physician according to the best standard of care.

8.1.2 Non responders

Changes in therapy may be required in case of non-response which will be defined by the presence of at least one of the followings:

- Death related to persistent disease activity and/or side effects of treatments
- Lack of improvement at 1 month. Such a patient will be considered a primary non response (treatment resistant) and included in the intention to treat analysis. They will receive ongoing clinical care according to good medical practice.
- Treatment failure: Patients will be considered to have treatment failure if any of the following criteria is met in at least 1 eye: new active, inflammatory retinal vascular lesions and/or macular edema; worsening best corrected visual acuity (BCVA) by ≥3 lines; 2-step increase in anterior chamber (AC) cell grade; 2-step increase in vitreous haze (VH) grade relative to Baseline
- Inability to tolerate decreasing doses of corticosteroids because of persistent or recurrent disease and/or the requirement of requires (additional) immunosuppressive therapy.
- Relapse of uveitis activity is defined by the reappearance of ocular inflammation of Behçet's disease with an inability to follow the corticosteroid regimen as defined by the protocol and/or which requires local corticosteroids.

All patients who will be considered non responders will be included in the intention to treat analysis. They will receive ongoing clinical care according to good medical practice.

8.1.3 Relapse

- Relapse of uveitis activity is defined by the reappearance of ocular inflammation of Behçet's disease with an inability to follow the corticosteroid regimen as defined by the protocol and/or which requires local corticosteroids.
- A severe disease flare is defined by the reappearance of ocular inflammation of Behçet's disease which requires (additional) immunosuppressive therapy and/or increased doses of systemic corticosteroids.

8.1.4 Other manifestations of Behçet's disease will be also evaluated.

- The skin and articular remissions are evaluated clinically (disappearance of skin lesions and/or ulcers, disappearance of arthralgia and/or arthritis).
- Digestive remission is evaluated clinically (improvement of abdominal pain and other gastrointestinal symptoms), by endoscopy (improvement of potential gastrointestinal lesions seen at baseline) and/or by Xray (improvement of any abnormalities found on baseline imaging).
- Cardiac remission is evaluated clinically (improvement of chest pains and other cardiac events), echocardiography (normalization of left ventricular function and/or disapearance of cardiac thrombosis), and cardiac magnetic resonance imaging (diseappearance of gadolinium enhancement and normalization of left ventricular function), and biologically (normalization of troponin and of inflammatory syndrome).
- Vascular remission is defined as the resolution of clinical and laboratory features of active disease (normalization of inflammatory syndrome) and the absence of new vascular lesions (in previously unaffected vascular territories) or the progression of preexisting vascular lesions detected on serial imaging studies (i.e. doppler sonography, and angio-CT scan).
- Remission of neurological involvement is defined as a complete clinical, and imaging (as evaluated by MRI) remission, biologically (normalization of inflammatory syndrome)

9 SPECIFIC STUDY COMMITTEES

9.1 Steering Committee

Members: Coordinating Investigator, one of more other investigators, biostatistician, the sponsor's appointed representatives for the trial.
• Members of the committee: Pr B Bodaghi, Pr D Saadoun, Dr L BRIARD, N Raked, M Camus.
• Missions: Define the overall structure of the study, coordinate information, determine the initial methodology and oversee the trial.
• Operating procedures: Propose procedures to be followed every 6 months during the study, acknowledging any recommendations from the Data Monitoring Committee. The sponsor retains the decision-making authority.

9.2 Scientific Committee

This committee will consist of the Coordinating Investigator (Pr Bodaghi CHU Pitié-Salpétrière), the scientific director (Pr Saadoun CHU Pitié-Salpétrière), a representative of the associated centers (Pr Gilles Kaplanski, CHU La Conception, Marseille), and a representative of the sponsor (Dr Lucie BRIARD, Hôpital Saint Louis, Clinical Research Unit). The management committee will meet regularly to determine the objective, write the protocol, recommend changes to the protocol during the trial, assess Study recruitment, to provide scientific answers to questions from investigators, and to consider operational aspects of the trial and the recommendations of the committee for the evaluation of adverse events.

10 SAFETY ASSESSMENT - RISKS AND BURDEN ADDED BY THE STUDY

10.1 Recording and reporting adverse events

10.1.1 Definitions

According to Article 2 of the Regulation (EU) N° 536/2014::

- **Adverse event (AE)**

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

- **Serious adverse event (SAE)**

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

- **Unexpected serious adverse reaction (SUSAR)**

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

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

- **Unexpected event**

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

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

- **Urgent safety measure**

Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects. The sponsor shall notify the Member States concerned, through the EU portal, of the event and the measures taken.
That notification shall be made without undue delay but no later than seven days from the date the measures have been taken.

10.1.2 The role of the investigator

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

*For all serious adverse events, the investigator **must also notify the SAE to the safety department** as soon as possible, except SAE not requiring a notification without delay described in section 11.3.2.2.2. "Serious adverse events that do not require the investigator to notify the sponsor without delay"*

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

The investigator must **assess the intensity** of the adverse events:
- either by using a rating scale with general terms:
    - *Mild: tolerated by the patient, does not interfere with daily activities*
    - *Moderate: sufficiently uncomfortable to affect daily activities*
    - *Serious: preventing daily activities*
- Or by using *Common Terminology Criteria for Adverse Events [National Cancer Institute]*.

The investigator must **assess the causal relationship** between the serious adverse events and the investigational medicinal product(s) or or interventions/procedures added by the study. Three situations are possible for auxiliary medicinal products:
1 - In case of a suspected interaction between authorized auxiliary medicinal product and the investigational medicinal product(s), the reporting rules for the IMP apply: SAE must be notify to the sponsor's safety department as soon as possible.
2 - In case of adverse reactions related to non-authorized auxiliary medicinal products, the reporting rules for the IMP apply: SAE must be notify to the sponsor's safety department as soon as possible.

3 - In case of adverse reactions only related to authorized auxiliary medicinal products (without interaction with IMP): SAE must be notify to the relevant regional pharmacovigilance center (Centre Régional de Pharmacovigilance (CRPV)).

The investigator used a binary method:

- Reasonable possibility
- No reasonable possibility

10.1.2.1 Serious adverse events that require the investigator to notify the sponsor without delay

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

A serious adverse event is any untoward medical occurrence that:

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

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

Moreover, special circumstances require the investigator to notify the sponsor without delay are:
-medication errors,
-in utero exposure / pregnancy / breastfeeding
- uses outside what is foreseen in the protocol, including misuse and abuse of the product.

All pregnancies must be reported to the safety department by the investigators within 24 hours on the day the investigator becomes aware of it.

Special circumstances associated to an SAE must be reported to the safety department by the investigators.

Special circumstances not associated to an SAE must be reported to the CRF by the investigators and notify as a deviation to the protocol by the clinical trial unit.

10.1.2.2 Specific features of the protocol

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

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

- The adverse events of grade 3-4 CTCAE except those listed in section 10.1.2.2.2.
- Blindness

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

- **Overdose**

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 case:
    - The intake of treatment is intentional (including suicide attempt)

- **In utero exposure**

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

If the investigational medicinal product is genotoxic, every case of maternal or paternal exposure must be notified.

- Exposure **while breastfeeding**

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

Even if it is not associated with an adverse event, the investigator must notify the sponsor without delay on the day the investigator becomes aware of exposure while breastfeeding.

10.1.2.2.2 Serious adverse events that do not require the investigator to notify the sponsor without delay

These serious adverse events are only recorded in the case report form. A CRF extraction of these serious adverse events will be realized every 6 months.

- *Normal and natural course of the condition*:

- Scheduled hospitalization to monitor the disease being studied
- hospitalization for routine treatment or monitoring of the disease being studied
- worsening of the disease under study (progression) except those leading to death occurrence of major organ involvement such as :
    - vascular involvement : venous thrombosis or arterial thrombosis, aneurysm or stenosis
    - neurological involvement
    - cardiac involvement

- *Special circumstances*

In some circumstances, the investigator can delay 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 exclusively related to authorized auxiliary medicinal products (medicinal products used within the framework of its marketing authorization) and to treatments prescribed as part of the care provided during the study follow-up*

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

10.1.2.3 Period during which SAEs must be notified without delay by the investigator to the sponsor

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

- starting from the date on which the subject signs the consent form
- throughout the whole follow-up period intended by the trial
- or until 4 weeks after the end of the participant's treatment with the investigational medicinal product for premature termination of treatment
- indefinitely, if the SAE is likely to be due to the investigational medicinal product or to the study interventions (e.g. serious reactions that could appear at long term after exposure to the medication, such as cancers or congenital abnormalities)*

*NB: In this last case, the investigator **does not have to collect indefinitely in the case report form (CRF or eCRF)** all **SAEs possibly related** to the clinical trial, **but must notify them**, to the sponsor, **as soon as he/she becomes aware of them, by the SAE notification form or by email or by fax (as described below)**.

10.1.2.4 Procedures and deadlines for notifying the sponsor

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

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

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

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

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

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

When sending the email, please:
- Adopt a standardized nomming of the email subject in the following form:
<< Objet : YYYYYY_XXXXXX_jjmmaaaa (avec YYYYYY : code de la recherche, XXXXXX : acronyme de la recherche et jjmmaaaa : date de transmission). >>

- Send a SAE initial notification form and/or a follow-up report concerning a single participant for a given SAE, attachment may contain one (or more) document(s) (follow-up and hospitalization reports, for example).
The total size of the email must be less than 8 MB, otherwise please send several e-mails.

- Ensure that all documents transmitted (e.g. hospital reports) are anonymized and identified with the participant's identification number.

<u>For studies which use e-CRF</u>

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

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

For cases of *in utero* exposure, the investigator will complete the initial notification and follow-up report forms for pregnancy exposure during participation in a study.
The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy is terminated, and must notify the sponsor of the outcome of the pregnancy using this form.
If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, pregnancy termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAEs.
The initial pregnancy notification, the SAE follow-up reports, and any other documents will be sent to the sponsor according to the same procedures specified herein.
If the investigational medicinal product is genotoxic and if it was the father who was exposed, the investigator must obtain the pregnant woman's permission before collecting information about the pregnancy.

10.1.3 Role of the sponsor

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

10.1.3.1 Analysis and declaration of serious adverse events

The sponsor assesses:

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

- For serious adverse events likely to be related to the investigational medicinal product(s):
  - refer to section 4.8 “Undesirable effects” of the the SmPC for Humira® and Roactemra® enclosed in CTIS platform and in the investigator study file.
- For serious adverse events likely to be related to auxiliary medicinal products (treatments required for the trial):
  - refer to the SmPC for the specialties of oral corticosteroids (prednisone or prednisolone), isoniazid, rifampicin, Fluorescein and indocyanin green
  - enclosed in CTIS platform,

- Where the auxiliary medicinal product is authorised in the Member State concerned, no additional information apart from a valid SmPC is required.
- In principle, only authorised medicinal products should be used as auxiliary medicinal products in clinical trials (article 59 of the Regulation (EU) No 536/2014). However, in certain circumstances unauthorised auxiliary medicines may be used. This has to be justified in the protocol. The acceptable reasons for admitting non-authorised auxiliary medicinal products would be related to the availability of authorised auxiliary medicinal products (e.g. no authorised medicinal products exist in the EU, or the amounts available are not sufficient to satisfy the need of the clinical trial). The lower price of non-authorised auxiliary medicinal product shall not be considered as a legitimate justification.

❖ For serious adverse events likely to be related to other study procedure
  ➢ tapering-of corticosteroids: relapse of disease activity.

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

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

10.1.3.2 Analysis and declaration of other safety data

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

The sponsor will report in CTIS platform without delay upon knowledge of any emerging safety issue and, if applicable, describe what measures have been taken.

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

10.1.3.3 Annual safety report

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

- a safety analysis for the research participants,
- a description of the patients included in the trial (demographic profile etc.)
- a list of all the suspected serious adverse reactions that occurred during the period covered by the report,
- summary tables of all the serious adverse events that have occurred since the start of the trial,

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

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

The final annual safety report must be submitted in CTIS no later than 60 days after the end date of the clinical trial.
The end date of the clinical trial is defined as the date of the last visit of the last subject.

10.1.3.4 Data Safety Monitoring Board (DSMB)

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

A DSMB will be established for this trial. The DSMB must hold its first meeting before the first participant is enrolled and ideally before the protocol is submitted to the competent authority and the Ethics Committee.
All missions as well as the specific operating procedures of the DSMB are described in the study's DSMB charter.

The DSMB members are:
- Dr Nabil BELFEKI, Service de médecine interne et immunologie clinique, GHSIF, France
- Pr Marc DE SMET, Cabinet d'Ophtalmologie, Lausanne, Suisse
- Pr Raphaël PORCHER, Centre de Recherche épidémiologie et Statistiques Université de Paris (CRESS-UMR1153), Paris, France

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

11 DATA MANAGEMENT

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

Not applicable

11.2 Right to access source data and documents

11.2.1 Data access

In accordance with GCPs and appendix 1 of the European Regulation N°536-2014:
- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures or inspections by the competent authority

- the Sponsor declares that investigators and participating institutions will ensure the persons in charge of monitoring, quality control and auditing or inspecting the clinical trial have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force.

11.2.2 Source documents

Source documents are defined as any original document or item that can prove the existence or accuracy of a data or a fact recorded during the study. These documents will be kept in accordance with the regulations in force by the investigator or by the hospital in the case of a hospital medical file.

11.2.3 Data confidentiality

The persons responsible for the quality control of clinical trials will take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular their identity and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy.
During and after the clinical trial, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be rendered non-identifying.
Under no circumstances shall the names and addresses of the participants involved be shown. Only the participant's initials will be recorded, accompanied by an encoded number specific to the study indicating the order of enrolment.
The sponsor will ensure that each participant has given written permission for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

11.3 Data processing and storage of research documents and data

Data will be collected on an E-CRF, with data entry performed in each center by Clinical research assistants (CRA) and/or physicians. Monitoring of the data will be performed by CRA under the supervision of the URC and DRCI. Statistical analysis will be performed by Dr Lucie BRIARD Saint Louis hospital, Paris.

- **Data entry**

Data will be entered electronically via a web browser.
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 reference".
All personal data for this trial will be processed in accordance with Chapter IX of the amended French Data Protection Act of 6 January 1978 (articles 53-61).

11.4 Data ownership

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

12 STATISTICAL ASPECTS

12.1 Sample size consideration

The study will use a Bayesian design, where patients will be randomly allocated to two treatment arms. The interest of such randomized approach is to avoid selection of patients. We will first compare the observed probability of each arms to 0.65 then we will compare arms. Given the uncertainty in the Adalimumab benefit over Tocilizumab in Behçet's disease uveitis, and the fact that the severe population focused in this trial is not very large in size, the selection approach to planning sample size was worthy of consideration.
Comparison will use the approach presented by Kawasaki in 2012 (Kawasaki Y, Miyaoka E. A Bayesian inference of for two proportions. Journal of Biopharmaceutical Statistics 2012;22: 425-437). The authors reported throughout a simulation study that the design has good operating characteristics on the basis of a sample of 30 patients in each arm.

12.2 Analysis Populations

The following analysis sets will be considered:
Intent-to-treat (ITT): Includes all randomized subjects. This will refer to the primary analyses.
For the ITT analysis, all patients will be analyzed in their randomization arm regardless of treatment received or post-randomization protocol deviation
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

12.3 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 categorical 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 primary endpoint (complete remission of ocular involvement with prednisone (or prednisolone, only if prednisone is out of stock in the market) lower or equal to 5 mg/day at week 16 after randomization) will be modelled with a binary variable.
The analysis will use a Beta-Binomial model with a non-informative prior (Berry 2006). The posterior probability that the remission rate is at least 0.65 will be estimated in both arms, as

well as the probability that the rate of remission in Arm B is above that in Arm A will be computed, with B being the tocilizumab group and A the adalimumab group.

We will use a Bayesian inference framework, where $\pi_A = P(Y = 1|A)$ denotes the probability of remission in the arm A. After inclusion of n_A patient in Arm A and y_A complete response observed. Using a beta Be(a_A, b_A) prior for π_A, the posterior probability of π_A is still a beta distribution given by Be(a_A+y_A, b_A+$n_A - y_A$) due to the natural conjugate property of the beta family for binomial sampling.
In our setting, the efficacy of the drug in arm A will be first assessed by comparison to some historical minimal value of interest, sometimes called the "minimum required treatment remission rate". It has been set at 0.65 in this trial. Thus, we will compute

$$P(\pi_A > 0.65|y_A, n_A)$$

Similarly,

We will use a Bayesian inference framework, where $\pi_B = P(Y = 1|B)$ denotes the probability of remission in the arm B. After inclusion of n_B patient in Arm B and y_B complete response observed. Using a beta Be(a_B, b_B) prior for π_B, the posterior probability of π_B is still a beta distribution given by Be(a_B+y_B, b_B+$n_B - y_B$) due to the natural conjugate property of the beta family for binomial sampling.
In our setting, the efficacy of the drug in arm B will be first assessed by comparison to 0.65 in this trial. Thus, we will compute for each arm:

$$P(\pi_B > 0.65|y_B, n_B)$$

However, in randomized phase II settings, the selection of a new drug is mostly based on evaluating the potential benefits of experimental treatments. Thus, one may consider dropping a new drug from further studies only if there is a rather low posterior probability that this drug is beneficial over the other by some targeted minimal level. This will be assessed by computing the value of the posterior probability of the difference in remission rates between the two experimental arms (Kawasaki in 2012) being greater than zero, with B being the tocilizumab group and A the adalimumab group:

$$P(\pi_B - \pi_A > 0|y_A, y_B, n_A, n_B)$$

As we consider a Bayesian design an interim analysis will be performed without any "alpha spending" after inclusion of 30 patients.
If $P(\pi_A > 0.65|y_A, n_A)$ >0.80, $P(\pi_B > 0.65|y_B, n_B)$ >0.80 and if $P(\pi_B - \pi_A > 0|y_A, y_B, n_A, n_B)$ >0.80, the trial will be stopped.
If $P(\pi_A > 0.65|y_A, n_A)$ <0.10 **or** $P(\pi_B > 0.65|y_B, n_B)$ <0.10 the corresponding arm will be stopped and the following patients will be included in the other arm.
If $P(\pi_A > 0.65|y_A, n_A)$ <0.10 **and** $P(\pi_B > 0.65|y_B, n_B)$ <0.10, the trial will be stopped.

- Analysis of Secondary Endpoints

Still with B the tocilizumab group and A the adalimumab group:

- Measures of corticosteroid sparing (mean dose at week 16, and cumulative dose) for subjects randomized to each arm will be estimated then compared across arms using normal Bayesian models with non-informative priors. The probability of the posterior difference in means (μ_B-μ_A) between the two experimental arms being greater than 0 will be computed.

$$P(\mu_B - \mu_A > 0|n_A, n_B)$$

- Time to response onset will be estimated in each arm by Kaplan Meier estimator and compared using log-rank test.
- Mean acute-phase reactants (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], 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. The probability of the posterior difference in means (μ_B-μ_A) between the two experimental arms being greater than 0 will be computed.

$$P(\mu_B - \mu_A > 0 | n_A, n_B)$$

- Rate and Time to occurrence of relapse or worsening while on study. (Relapse will be defined as the reappearance of clinical and/or paraclinical features of active disease or by the occurrence of new lesions or progression of preexisting lesions) will be estimated in each arms by Kaplan Meier estimator or appropriate usual estimator depending on the existence of competing risks. They will be compared using either log-rank test or Gray's test.
- Means changes in Behcet's Disease Current Activity Form and Behcet's Syndrome Activity Score at week 8, 16 and 24 will be estimated then compared across arms using Normal Bayesian models with non-informative priors. The probability of the posterior difference in means (μ_B-μ_A) between the two experimental arms being greater than 0 will be computed.

$$P(\mu_B - \mu_A > 0 | n_A, n_B)$$

- Means changes in other organs involved by BD at week 4, 8, 12, 16 and 24 will be estimated then compared across arms using Normal Bayesian models with non-informative priors. The probability of the posterior difference in means (μ_B-μ_A) between the two experimental arms being greater than 0 will be computed.

$$P(\mu_B - \mu_A > 0 | n_A, n_B)$$

- Means changes in quality of life (QOL) scales at week 16 and 24 will be estimated then compared across arms using Normal Bayesian models with non-informative priors.
- The probability of the posterior difference in means (μ_B-μ_A) between the two experimental arms being greater than 0 will be computed.

$$P(\mu_B - \mu_A > 0 | n_A, n_B)$$

- Safety and tolerability of treatments in BD patients as assessed by frequency and severity of adverse clinical events at week 4, 8, 12, 16 and 24 will be analysed as the primary endpoint
- Means changes in Tyndall, flare and Vitreous Haze at week 8, 16 and 24 will be estimated then compared across arms using Normal Bayesian models with non-informative priors.
- The probability of the posterior difference in means (μ_B-μ_A) between the two experimental arms being greater than 0 will be computed.

$$P(\mu_B - \mu_A > 0 | n_A, n_B)$$

- Means changes in Best corrected visual acuity (SNELLEN score) at week 8, 16 and 24 will be estimated then compared across arms using Normal Bayesian models with non-informative priors. The probability of the posterior difference in means (μ_B-μ_A) between the two experimental arms being greater than 0 will be computed.

$$P(\mu_B - \mu_A > 0 | n_A, n_B)$$

- Means changes in central retinal thickness measured with Optical Coherence Tomography (OCT) at week 8, 16 and 24 be estimated then compared across arms using Normal Bayesian models with non-informative priors. The probability of the posterior difference in means (μ_B-μ_A) between the two experimental arms being greater than 0 will be computed.

$$P(\mu_B - \mu_A > 0 | n_A, n_B)$$

- Percentage of patients with central retinal thickness <300 microns at week 8, 16 and 24 will be analysed as the primary endpoint
- Percentage of patients without retinal vessel leakage on retinal angiography at week 16, and at week 24, 36 and 48, in case of retinal vasculitis will be analysed as the primary endpoint

12.4 Analysis of Safety

Safety analyses will involve examination of the incidence, severity, and type of treatment of reported adverse events, 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.

12.5 Adverse Events

Adverse events reported during the study will be recorded. Incidence of treatment-emergent adverse events will be summarized by treatment group.

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.

13 QUALITY CONTROL AND ASSURANCE

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

13.1 General organisation

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

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

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

13.1.1 Strategy for center opening

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

13.1.2 Scope of center monitoring

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

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

13.1.3 Quality control

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

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

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

13.2 Case Report Form

All information required by the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Any missing data must be coded.
Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given a document offering guidance on using this tool.
When the investigators complete the case report form via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. To this end, the investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment.
The investigator must archive a copy of the authenticated document that was issued to the sponsor.

13.3 Management of non-compliances

Any events that occur as a result of non-compliance – by the investigator or any other individual involved in running the study – with the protocol, standard operating procedures, good clinical

practices or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.

These non-compliances will be managed in accordance with the sponsor's procedures.

The sponsor shall notify the Member States concerned about a serious breach of this Regulation or of the version of the protocol applicable at the time of the breach through the EU portal without undue delay but not later than seven days of becoming aware of that breach.

13.4 Audits/inspections

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

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

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

13.5 Principal Investigator's commitment to assume responsibility

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

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

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

13.6 Suitability of the facilities

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

14 ETHICAL AND LEGAL CONSIDERATIONS

14.1 Methods for informing research participants and obtaining their consent

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

A reflection period is given to the individual between the time when he or she is informed and when he or she signs the consent form.

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

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

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

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

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

An exclusion period will apply during the trial. and 3 months after the participant has finished this study treatment.

Whilst participating in this trial, subjects may not take part in any other clinical trial without first speaking to the doctor in charge of this trial.
Participation in an observational protocol is not prohibited.

14.3 Legal obligations

14.3.1 Role of the sponsor

Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this study and, by delegation, the DRCI (Clinical Research and Innovation Department) carries out the study's missions in accordance with with regulation (EU) No 536/2014 of the European Parliament and of the council of 16 April 2014 and all national Laws. Assistance Publique - Hôpitaux de Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case, notification will be sent to the investigator.

14.3.2 Request for authorisation

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

14.3.3 Procedures relating to data protection regulations

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

For France:

- Commitment to comply with "Reference Methodology" MR-001

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

14.3.4 Start of the Clinical Trial

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

14.3.5 Amendments to the Clinical trial

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, approval from the Ethics Committee and authorisation from the competent authority within the scope of their respective authorities, before the amendment can be implemented.
The information note and the consent form can be revised, if necessary, in particular in case of a substantial amendment to the study or if adverse reactions occur.

14.3.6 End of the Clinical Trial

The end of the Clinical Trial corresponds to the end of the participation of the last person who participate to the Clinicaltrial.
The end of the recruitment of subjects for the clinical trial and the end of the clinical trial should be notified in CTIS. That notification shall be made within 15 days from the end of the clinical trial in relation to that Member State.

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

14.3.7 Archiving

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

- A sealed envelope for the investigator containing a copy of all the information notes and consent forms signed by all individuals at the center who participated in the study;
- A sealed envelope for the sponsor, containing a copy of all the information notes and consent forms signed by all individuals at the center who participated in the study;
- "Study" binders for the Investigator and the sponsor, including (non-exhaustive list) :
  - the successive versions of the protocol (identified by the version number and its date), and any appendices

- the competent authority authorisations and Ethics Committee decisions
- any correspondence
- the enrolment list or register
- the appendices specific to the research
- final study report

- The data collection documents

15 FUNDING AND INSURANCE

15.1 Funding sources

PHRC (Hospital Funding for Clinical Research)

15.2 Insurance

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

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

16 PUBLICATION RULES

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

16.1 Mention of AP-HP affiliation for projects sponsored by AP-HP

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

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

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

16.3 Mention of the financial backer in the acknowledgements of the text

The study was funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC 2019 (French Ministry of Health)"

This study has been registered on the website http://clinicaltrials.gov/ website under NCT05874505

17 BIBLIOGRAPHY

1. Saadoun D, Wechsler B, Desseaux K, Le Thi Huong D, Amoura Z, Resche-Rigon M, et al. Mortality in Behçet's disease. Arthritis Rheum. sept 2010;62(9):2806-12.
2. Kitaichi N, Miyazaki A, Iwata D, Ohno S, Stanford MR, Chams H. Ocular features of Behcet's disease: an international collaborative study. Br J Ophthalmol. déc 2007;91(12):1579-82.
3. Tugal-Tutkun I, Onal S, Altan-Yaycioglu R, Huseyin Altunbas H, Urgancioglu M. Uveitis in Behçet disease: an analysis of 880 patients. Am J Ophthalmol. sept 2004;138(3):373-80.
4. Okada AA, Goto H, Ohno S, Mochizuki M, Ocular Behçet's Disease Research Group Of Japan. Multicenter study of infliximab for refractory uveoretinitis in Behçet disease. Arch Ophthalmol Chic Ill 1960. mai 2012;130(5):592-8.
5. Hatemi G, Christensen R, Bang D, Bodaghi B, Celik AF, Fortune F, et al. 2018 update of the EULAR recommendations for the management of Behçet's syndrome. Ann Rheum Dis. juin 2018;77(6):808-18.
6. Vallet H, Seve P, Biard L, Baptiste Fraison J, Bielefeld P, Perard L, et al. Infliximab Versus Adalimumab in the Treatment of Refractory Inflammatory Uveitis: A Multicenter Study From the French Uveitis Network. Arthritis Rheumatol Hoboken NJ. 2016;68(6):1522-30.
7. Vallet H, Riviere S, Sanna A, Deroux A, Moulis G, Addimanda O, et al. Efficacy of anti-TNF alpha in severe and/or refractory Behçet's disease: Multicenter study of 124 patients. J Autoimmun. août 2015;62:67-74.
8. Levy-Clarke G, Jabs DA, Read RW, Rosenbaum JT, Vitale A, Van Gelder RN. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. Ophthalmology. mars 2014;121(3):785-796.e3.
9. Jaffe GJ, Dick AD, Brézin AP, Nguyen QD, Thorne JE, Kestelyn P, et al. Adalimumab in Patients with Active Noninfectious Uveitis. N Engl J Med. 8 sept 2016;375(10):932-43.
10. Nguyen QD, Merrill PT, Jaffe GJ, Dick AD, Kurup SK, Sheppard J, et al. Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. Lancet Lond Engl. 17 sept 2016;388(10050):1183-92.
11. Calvaruso V, Mazza M, Almasio PL. Pegylated-interferon-α(2a) in clinical practice: how to manage patients suffering from side effects. Expert Opin Drug Saf. mai 2011;10(3):429-35.
12. Yamada Y, Sugita S, Tanaka H, Kamoi K, Kawaguchi T, Mochizuki M. Comparison of infliximab versus ciclosporin during the initial 6-month treatment period in Behçet disease. Br J Ophthalmol. mars 2010;94(3):284-8.
13. Atienza-Mateo B, Calvo-Río V, Beltrán E, Martínez-Costa L, Valls-Pascual E, Hernández-Garfella M, et al. Anti-interleukin 6 receptor tocilizumab in refractory uveitis associated with Behçet's disease: multicentre retrospective study. Rheumatol Oxf Engl. 01 2018;57(5):856-64.
14. Eser Ozturk H, Oray M, Tugal-Tutkun I. Tocilizumab for the Treatment of Behçet Uveitis that Failed Interferon Alpha and Anti-Tumor Necrosis Factor-Alpha Therapy. Ocul Immunol Inflamm. 11 oct 2017;1-10.
15. Chen J, Chen S, He J. A case of refractory intestinal Behçet's disease treated with tocilizumab, a humanised anti-interleukin-6 receptor antibody. Clin Exp Rheumatol. déc 2017;35 Suppl 108(6):116-8.
16. Alokaily F, Al Saati A, Jawad A. Successful treatment of Behçet's uveitis with Tocilizumab. Saudi J Ophthalmol Off J Saudi Ophthalmol Soc. mars 2017;31(1):42-4.
17. Santos-Gómez M, Calvo-Río V, Blanco R, Beltrán E, Mesquida M, Adán A, et al. The effect of biologic therapy different from infliximab or adalimumab in patients with refractory uveitis due to Behçet's disease: results of a multicentre open-label study. Clin Exp Rheumatol. oct 2016;34(6 Suppl 102):S34-40.
18. Deroux A, Chiquet C, Bouillet L. Tocilizumab in severe and refractory Behcet's disease: Four cases and literature review. Semin Arthritis Rheum. 2016;45(6):733-7.
19. Chang HK, Jang WC, Park SB, Han SM, Nam YH, Lee SS, et al. Association between interleukin 6 gene polymorphisms and Behcet's disease in Korean people. Ann Rheum Dis.

févr 2005;64(2):339-40.
20. Lin P. Targeting interleukin-6 for noninfectious uveitis. Clin Ophthalmol Auckl NZ. 2015;9:1697-702.
21. Calvo-Río V, de la Hera D, Beltrán-Catalán E, Blanco R, Hernandez M, Martínez-Costa L, et al. Tocilizumab in uveitis refractory to other biologic drugs: a study of 3 cases and a literature review. Clin Exp Rheumatol. août 2014;32(4 Suppl 84):S54-57.
22. Papo M, Bielefeld P, Vallet H, Seve P, Wechsler B, Cacoub P, et al. Tocilizumab in severe and refractory non-infectious uveitis. Clin Exp Rheumatol. août 2014;32(4 Suppl 84):S75-79.
23. Silpa-Archa S, Oray M, Preble JM, Foster CS. Outcome of tocilizumab treatment in refractory ocular inflammatory diseases. Acta Ophthalmol (Copenh). sept 2016;94(6):e400-406.
24. Calvo-Río V, Blanco R, Santos-Gómez M, Díaz-Valle D, Pato E, Loricera J, et al. Efficacy of Anti-IL6-Receptor Tocilizumab in Refractory Cystoid Macular Edema of Birdshot Retinochoroidopathy Report of Two Cases and Literature Review. Ocul Immunol Inflamm. oct 2017;25(5):604-9.
25. Sakane T, Takeno M, Suzuki N, Inaba G. Behçet's disease. N Engl J Med. 21 oct 1999;341(17):1284-91.
26. Mishima S, Masuda K, Izawa Y, Mochizuki M, Namba K. The eighth Frederick H. Verhoeff Lecture. presented by saiichi mishima, MD Behçet's disease in Japan: ophthalmologic aspects. Trans Am Ophthalmol Soc. 1979;77:225-79.
27. Benezra D, Cohen E. Treatment and visual prognosis in Behçet's disease. Br J Ophthalmol. août 1986;70(8):589-92.
28. Kural-Seyahi E, Fresko I, Seyahi N, Ozyazgan Y, Mat C, Hamuryudan V, et al. The long-term mortality and morbidity of Behçet syndrome: a 2-decade outcome survey of 387 patients followed at a dedicated center. Medicine (Baltimore). janv 2003;82(1):60-76.
29. Noel N, Bernard R, Wechsler B, Resche-Rigon M, Depaz R, Le Thi Huong Boutin D, et al. Long-term outcome of neuro-Behçet's disease. Arthritis Rheumatol Hoboken NJ. mai 2014;66(5):1306-14.
30. Akman-Demir G, Serdaroglu P, Tasçi B. Clinical patterns of neurological involvement in Behçet's disease: evaluation of 200 patients. The Neuro-Behçet Study Group. Brain J Neurol. nov 1999;122 (Pt 11):2171-82.
31. Akman-Demir G, Tüzün E, Içöz S, Yeşilot N, Yentür SP, Kürtüncü M, et al. Interleukin-6 in neuro-Behçet's disease: association with disease subsets and long-term outcome. Cytokine. déc 2008;44(3):373-6.
32. Borhani Haghighi A, Ittehadi H, Nikseresht AR, Rahmati J, Poorjahromi SG, Pourabbas B, et al. CSF levels of cytokines in neuro-Behçet's disease. Clin Neurol Neurosurg. juill 2009;111(6):507-10.
33. Jabs DA, Nussenblatt RB, Rosenbaum JT, Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. sept 2005;140(3):509-16.
34. Geri G, Wechsler B, Thi Huong DL, Isnard R, Piette J-C, Amoura Z, et al. Spectrum of cardiac lesions in Behçet disease: a series of 52 patients and review of the literature. Medicine (Baltimore). janv 2012;91(1):25-34.
35. Desbois AC, Wechsler B, Resche-Rigon M, Piette JC, Huong DLT, Amoura Z, et al. Immunosuppressants reduce venous thrombosis relapse in Behçet's disease. Arthritis Rheum. août 2012;64(8):2753-60.
36. Lindstedt EW, Baarsma GS, Kuijpers RW a. M, van Hagen PM. Anti-TNF-alpha therapy for sight threatening uveitis. Br J Ophthalmol. mai 2005;89(5):533-6.
37. Bodaghi B, Gendron G, Wechsler B, Terrada C, Cassoux N, Huong DLT, et al. Efficacy of interferon alpha in the treatment of refractory and sight threatening uveitis: a retrospective monocentric study of 45 patients. Br J Ophthalmol. mars 2007;91(3):335-9.
38. Hamzaoui K, Hamzaoui A, Guemira F, Bessioud M, Hamza M, Ayed K. Cytokine profile in Behçet's disease patients. Relationship with disease activity. Scand J Rheumatol. 2002;31(4):205-10.

39. Tugal-Tutkun I, Pavesio C, De Cordoue A, Bernard-Poenaru O, Gül A. Use of Gevokizumab in Patients with Behçet's Disease Uveitis: An International, Randomized, Double-Masked, Placebo-Controlled Study and Open-Label Extension Study. Ocul Immunol Inflamm. 25 janv 2018;1-11.
40. Dick AD, Tugal-Tutkun I, Foster S, Zierhut M, Melissa Liew SH, Bezlyak V, et al. Secukinumab in the treatment of noninfectious uveitis: results of three randomized, controlled clinical trials. Ophthalmology. avr 2013;120(4):777-87.
41. Fabiani C, Vitale A, Emmi G, Vannozzi L, Lopalco G, Guerriero S, Orlando I, Franceschini R, Bacherini D, Cimino L, Soriano A, Frediani B, Galeazzi M, Iannone F, Tosi GM, Salvarani C, Cantarini L. Efficacy and safety of adalimumab in Behçet's disease-related uveitis: a multicenter retrospective observational study. Clin Rheumatol (2017) 36:183–189
42. Atienza-Mateo B, Martín-Varillas JL, Calvo-Río V, Demetrio-Pablo R, Beltrán E, Sánchez-Bursón J, Mesquida M, Adan A, Hernández MV, Hernández-Garfella M, Valls-Pascual E, Martínez-Costa L, Sellas-Fernández A, Cordero-Coma M, Díaz-Llopis M, Gallego R,García-Serrano JL, Ortego-Centeno N, Herreras JM, Fonollosa A, Garcia-Aparicio AM, Maíz-Alonso O, Blanco A, Torre-Salaberri I, Fernandez-Espartero C, Jovaní V, Peiteado D, Pato E, Cruz J, Férnandez-Cid C, Aurrecoechea E, García-Arias M, Castañeda S, Caracuel-Ruiz MA, Montilla-Morales CA, Atanes-Sandoval A, Francisco F, Insua S, González-Suárez S, Sanchez-Andrade A, Gamero Linares Ferrando LF, Romero-Bueno F, García-González AJ, Almodóvar González R, Muro EM, Carrasco-Cubero C, Olive A, Prior A,Vázquez J, Ruiz-Moreno O, Jiménez-Zorzo F, Manero J, Muñoz Fernandez S, Fernández-Carballido C, Rubio-Romero E, Pages FA, Toyos-Sáenz de Miera FJ, Gandia Martinez M, Díaz-Valle D, López Longo FJ, Nolla JM, Álvarez ER, Revenga Martínez M,González-LópezJJ,Rodríguez-Cundin P, Hernández JL, González-Gay MA, Blanco R. Comparative Study of Infliximab Versus Adalimumab in Refractory Uveitis due to Behçet's Disease: National Multicenter Study of 177 Cases. Arthritis & Rheumatology Vol. 71, No. 12, December 2019, pp 2081–2089
43. Atienza-Mateo B, Beltrán E, Hernández-Garfella M, Valls Pascual E, Martínez-Costa L, Atanes A, Moriano C, Cordero-Coma M, Nolla JM, Carrasco Cubero C, Sánchez Martín J, Calvo-Río V, Demetrio R, Palmou-Fontana N, González-Gay MA, Blanco R. Tocilizumab in Behçet's disease with refractory ocular and/or neurological involvement: response according to different clinical phenotypes. Clinical and Experimental Rheumatology 2021; 39 (Suppl. 132): S37-S42.
44. Akiyama M, Kaneko Y, Takeuchi T. Effectiveness of tocilizumab in Behcet's disease: A systematic literature review. Seminars in Arthritis and Rheumatism, Volume 50, Issue 4, August 2020, Pages 797-804

18 LIST OF ADDENDA / APPENDIX

Each addendum and the log of addenda versions are attached, independently of the protocol. Each addendum can be modified (change of addendum version) without modifying the protocol version.

18.1 List of Investigators

See enclosed document.

18.2 SAE notification form

18.3 Pregnancy notification form

18.4 International criteria for the classification of Behçet's disease revised in 2013

The diagnostic of Behçet's disease is held if ≥ 4 points

Symptoms	Points
Oral ulcers	**2**
Genital ulcers	**2**
Ocular involvement	**2**
Skin involvement	**1**
Vascular involvement	**1**
Neurological involvement	**1**
Positive Pathergy test	**1**

18.5 BEHÇET'S DISEASE CURRENT ACTIVITY FORM 2006

ISBD
International Society for Behcet's Disease

BEHÇET'S DISEASE CURRENT ACTIVITY FORM 2006

Date: Name: Sex: M/F
Centre: Telephone Date of birth:
Country:
Clinician: Address:

All scoring depends on the symptoms present over the **4 weeks** prior to assessment.
Only clinical features that the **clinician feels are due to Behçet's Disease** should be scored.

PATIENT'S PERCEPTION OF DISEASE ACTIVITY
(Ask the patient the following question:)

"Thinking about your Behçet's disease only, which of these faces expresses how you have been feeling over the last four weeks? "(Tick one face)

HEADACHE, MOUTH ULCERS, GENITAL ULCERS, SKIN LESIONS, JOINT INVOLVEMENT AND GASTROINTESTINAL SYMPTOMS

Ask the patient the following questions and fill in the related boxes **"Over the past 4 weeks have you had?"**

(please tick one box per line)

	not at all	Present for up to 4 weeks
Headache		
Mouth Ulceration		
Genital Ulceration		
Erythema		
Skin Pustules		
Joints - Arthralgia		
Joints - Arthritis		
Nausea/vomiting/abdominal pain		
Diarrhoea+altered/frank blood per rectum		

EYE INVOLVEMENT
(Ask questions below)

		(please circle) Right Eye		Left Eye	
"Over the last 4 weeks have you had?"	a red eye	No	Yes	No	Yes
	a painful eye	No	Yes	No	Yes
	blurred or reduced vision	No	Yes	No	Yes

If any of the above is present: "Is this new"? No Yes
(circle the correct answer)

NERVOUS SYSTEM INVOLVEMENT (include intracranial vascular disease)

New Symptoms in nervous system and major vessel involvement are defined as those not previously documented or reported by the patient
(Ask questions below)

Over the last 4 weeks have you had any of the following?	*please circle*		tick if new
blackouts	No	Yes	
difficulty with speech	No	Yes	
difficulty with hearing	No	Yes	
blurring of/double vision	No	Yes	
weakness/loss of feeling of face	No	Yes	
weakness/loss of feeling of arm	No	Yes	
weakness/loss of feeling of leg	No	Yes	
memory loss	No	Yes	
loss of balance	No	Yes	

Is there any evidence of <u>new</u> active nervous system involvement? No Yes

MAJOR VESSEL INVOLVEMENT(exclude intracranial vascular disease)
(Ask question below)

"Over the last 4 weeks have you had any of the following?"	*please circle*		tick if new
had chest pain	No	Yes	
had breathlessness	No	Yes	
coughed up blood	No	Yes	
had pain/swelling/discolouration of the face	No	Yes	
had pain/swelling/discolouration of the arm	No	Yes	
had pain/swelling/discolouration of the leg	No	Yes	

Is there evidence of new active major vessel inflammation? No Yes

CLINICIAN'S OVERALL PERCEPTION OF DISEASE ACTIVITY

Tick one face that expresses how you feel the patient's disease has been over the last 4 weeks.

BEHÇET'S DISEASE ACTIVITY INDEX

Add up all the scores which are highlighted in <u>blue</u> (front page items, one tick = score of 1 on index, all other items score 'yes' = 1. You should now have a score out of 12 which is the patient's Behçet's Disease Activity Index Score.

SCORE

Patients index score	0	1	2	3	4	5	6	7	8	9	10	11	12
Transformed index score on interval scale	0	3	5	7	8	9	10	11	12	13	15	17	20

18.6 Questionnaire SF36

Questionnaire de santé SF-36

1. **Dans l'ensemble, pensez-vous que votre santé est** : (entourez la bonne réponse)

Excellente	1
Très bonne	2
Bonne	3
Médiocre	4
Mauvaise	5

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

Bien meilleur que l'an dernier	1
Plutôt meilleur	2
A peu près pareil	3
Plutôt moins bon	4
Beaucoup moins bon	5

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 limit(é) en raison de votre état de santé actuel.** (Entourez la réponse de 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	1	2	3
b. Efforts physiques modérés tels que déplacer une table, passer l'aspirateur, jouer aux boules	1	2	3
c. Soulever et porter des courses	1	2	3
d. Monter plusieurs étages par l'escalier	1	2	3
e. Monter un étage par escalier	1	2	3
f. se pencher en avant, se mettre à genoux, s'accroupir	1	2	3
g. Marcher plus d'un km à pied	1	2	3
h. Marcher plusieurs centaines de mètres	1	2	3
i. Marcher une centaine de mètres	1	2	3
j. Prendre un bain, une douche ou s'habiller	1	2	3

4. **Au cours de ces 4 dernières semaines, et en raison de votre état physique**
(Entourez la réponse de votre choix, une par ligne)

	Oui	Non
a. Avez-vous réduit le temps passé à votre travail ou à vos activités habituelles	1	2
b. Avez-vous accompli moins de choses que vous auriez souhaité ?	1	2
c. Avez-vous du arrêter de faire certaines choses ?	1	2
d. Avez-vous eu des difficultés à faire votre travail ou toute autre activité ? (par exemple, cela vous a demandé un effort supplémentaire)	1	2

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

	Oui	Non
a. Avez-vous réduit le temps passé à votre travail ou à vos activités habituelles	1	2
b. Avez-vous accompli moins de choses que vous auriez souhaité ?	1	2
c Avez-vous eu des difficultés à faire ce que vous aviez à faire avec autant de soin et d'attention que d'habitude ?	1	2

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

Pas du tout	1
Un petit peu	2
Moyennement	3
Beaucoup	4
Enormément	5

7. **Au cours de ces 4 dernières semaines, quelle a été l'intensité de vos douleurs (physiques) ?** (Entourez la réponse de votre choix)

Nulle	1
Très faible	2
Faible	3
Moyenne	4
Grande	5
Très grande	6

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 ?** (Entourez la réponse de votre choix)

Pas du tout	1
Un petit peu	2
Moyennement	3
Beaucoup	4
Enormément	5

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 :**
(Entourez la réponse de votre choix, une par ligne)

Liste d'activités	En permanence	Très souvent	Souvent	Quelques fois	Rarement	Jamais
a. vous vous êtes senti(e) dynamique ?	1	2	3	4	5	6
b. vous vous êtes senti(e) très nerveux(se) ?	1	2	3	4	5	6
c. Vous vous êtes senti(e) si découragé(e) que rien ne pouvait vous remonter le moral	1	2	3	4	5	6
d. vous vous êtes senti(e) calme et détendu(e) ?	1	2	3	4	5	6
e. vous vous êtes senti(e) débordant(e) d'énergie?	1	2	3	4	5	6
f. vous vous êtes senti(e) triste et abattu(e) ?	1	2	3	4	5	6
g. vous vous êtes senti(e) épuisé(e) ?	1	2	3	4	5	
h. vous vous êtes senti(e) heureux(e)	1	2	3	4	5	6
i. vous vous êtes senti(e) fatigué(e) ?	1	2	3	4	5	6

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

En permanence	1
Une bonne partie du temps	2
De temps en temps	3
Rarement	4
Jamais	5

11. **Indiquez pour chacune des phrases suivantes dans quelle mesure elles sont vraies ou fausses dans votre cas :**
(Entourez la réponse de votre choix, une par ligne)

Liste d'activités	Totalement vrai	Plutôt vrai	Je ne sais pas	Plutôt fausse	Totalement fausse
a. je tombe malade plus facilement que les autres	1	2	3	4	5
b. je me porte aussi bien que n'importe qui	1	2	3	4	5
c. je m'attends à ce que ma santé se dégrade	1	2	3	4	5
d. je suis en excellent santé	1	2	3	4	5

→ **Score (0 à 100) : l__l__l__l**

18.7 BSAS

Evaluation de l'activité de la maladie par le patient dans le syndrome de Behçet

Behçet's Syndrome Activity Score (BSAS)

Nom : .....
Age : ..... ans
Sexe : □ Homme □ Femme

Date : ..... / ..... / .....

1. Dans quelle mesure les **ulcères buccaux** vous ont-ils gêné au cours des quatre dernières semaines ? Veuillez indiquer ci-dessous

PAS D'ULCÈRES — LES ULCÈRES ONT ÉTÉ UN PROBLÈME MAJEUR

0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10

2. Combien **d'ulcères (nouveaux ou anciens)** avez-vous eus dans votre **bouche** au cours des 4 dernières semaines ?

0 ☐
1-3 ☐
Plus que 3 ☐

3. Dans quelle mesure **les ulcères de la région génitale** vous ont-ils gêné au cours des 4 dernières semaines ? Veuillez indiquer ci-dessous

PAS D'ULCÈRES — LES ULCÈRES ONT ÉTÉ UN PROBLÈME MAJEUR

0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10

4. Combien **d'ulcères (nouveaux ou anciens)** avez-vous eus dans votre **région génitale** au cours des 4 dernières semaines ?

0 ☐
1-3 ☐
Plus que 3 ☐

5. Dans quelle mesure **l'acné ou les lésions cutanées semblables à l'acné (nouvelles ou anciennes)** vous ont-elles dérangé au cours des 4 dernières semaines ?

PAS DE LÉSION CUTANÉE — LES LÉSION CUTANÉE ONT ÉTÉ UN PROBLÈME MAJEUR

0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10

6. Combien de **lésions cutanées acnéiques ou de lésions cutanées semblables à l'acné (nouvelles ou anciennes)** avez-vous eues au cours des 4 dernières semaines ?

0 ☐
1-5 ☐
Plus que 5 ☐

7. Avez-vous eu des **douleurs abdominales et des diarrhées** durant la majeure partie de la journée et la plupart des jours de la semaine au cours des 4 dernières semaines ?

Non ☐ **Oui** ☐

8. Avez-vous eu des **yeux douloureux ou rouges et/ou une vision floue ou réduite** au cours des 4 dernières semaines ?

Non ☐ **Oui** ☐

9. Avez-vous eu un **gonflement/décoloration de vos membres inférieurs, ou un caillot sanguin** au cours des 4 dernières semaines ?

Non ☐ **Oui** ☐

10. En ce qui concerne l'activité de votre maladie de Behçet (ulcères buccaux, ulcères génitaux, problèmes de peau, douleurs articulaires, problèmes oculaires et neurologiques), dans quelle mesure diriez-vous que votre maladie a été active au cours des 4 dernières semaines ?

PAS DU TOUT ACTIF — EXTRÊMEMENT ACTIF

0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10

Scores :
Les questions 1, 3, 5 et 10 sont notées de 0 à 10.
Les questions 2, 4 et 6 sont notées 0, 5 ou 10 en fonction des 3 cases cochées.
Les questions 7, 8 et 9 sont notées 0 ou 10.

Pour une note totale de 100

18.8 Bahçet disease Quality of Life

BD-QoL

Questionnaire de Qualité de Vie de la Maladie de Behçet

Nom : .....

Age : ..... ans

Sexe : □ Homme □ Femme

Date : ..... / ..... / .....

Consignes : Ce questionnaire comporte 30 affirmations. Veuillez lire attentivement chaque affirmation, puis choisissez **Vrai** si l'affirmation s'applique à vous et choisissez **Pas vrai** si elle ne s'applique pas à vous à l'heure actuelle. Entourez le chiffre approprié.

1. Ma vie tourne autour des visites à l'hôpital 1 Vrai 0 Pas vrai	**7. Mon état interfère avec ma vie** 1 Vrai 0 Pas vrai
2. Rien ne m'intéresse 1 Vrai 0 Pas vrai	**8. Il est difficile de se lever du lit** 1 Vrai 0 Pas vrai
3. C'est trop d'efforts pour sortir et voir des gens 1 Vrai 0 Pas vrai	**9. Je me sens mal à cause de mon apparence** 1 Vrai 0 Pas vrai
4. Marcher est douloureux 1 Vrai 0 Pas vrai	**10. Parler est stressant** 1 Vrai 0 Pas vrai
5. Il me faut plus de temps pour faire les choses 1 Vrai 0 Pas vrai	**11. Je me sens dépendant des autres** 1 Vrai 0 Pas vrai
6. Je ne peux pas rester debout longtemps 1 Vrai 0 Pas vrai	**12. Je me sens plus vieux que mon âge** 1 Vrai 0 Pas vrai

13. Cela limite les endroits où je peux aller

1 Vrai

0 Pas vrai

14. Je trouve qu'il est difficile de prendre soin des personnes dont je suis proche.

1 Vrai

0 Pas vrai

15. Je ne peux pas compter sur comment je serai demain

1 Vrai

0 Pas vrai

16. Mon état de santé affecte considérablement ma vie

1 Vrai

0 Pas vrai

17. Je suis souvent frustré(e)

1 Vrai

0 Pas vrai

18. Je me sens comme un prisonnier dans ma propre maison

1 Vrai

0 Pas vrai

19. Ma maladie affecte les décisions importantes dans ma vie

1 Vrai

0 Pas vrai

20. Je n'aime pas être touché(e)

1 Vrai

0 Pas vrai

21. Je ne peux pas parler correctement

1 Vrai

0 Pas vrai

22. Cela met à mal mes relations personnelles

1 Vrai

0 Pas vrai

23. Je me sens inutile

1 Vrai

0 Pas vrai

24. Je crains de freiner les autres

1 Vrai

0 Pas vrai

25. Mes proches ont été perdants à cause de mon état

1 Vrai

0 Pas vrai

26. Je me sens incapable de faire face à ma maladie

1 Vrai

0 Pas vrai

27. J'ai perdu le contact avec les gens

1 Vrai

0 Pas vrai

28. Je m'inquiète des effets sur les autres

1 Vrai

0 Pas vrai

29. Tout me pèse aujourd'hui

1 Vrai

0 Pas vrai

30. Je me sens seul(e)

1 Vrai

0 Pas vrai

18.9 Description of the Clinical Trial in the AP-HP Trials Register

La maladie de Behçet est une maladie inflammatoire des vaisseaux qui peut toucher les veines et les artères de tout calibre. L'inflammation peut affecter les muqueuses (aphtes), les articulations, la peau, le système nerveux central, les vaisseaux ou l'oeil.
L'atteinte oculaire est fréquente au cours de la maladie de Behçet et peut être associée à un mauvais pronostic fonctionnel. Dans de nombreux cas, les deux yeux sont impliqués et les symptômes peuvent inclure diminution de la vision, douleur oculaire, rougeur oculaire, larmoiement, photophobie (douleur et / ou sensibilité à la lumière), la pression intraoculaire élevée, des cicatrices intraoculaire, oedème maculaire, et même une occlusion vasculaire.
Les uvéites peuvent entraîner une perte visuelle sévère et jusqu'à 25% de cécité. Les corticoïdes et immunosuppresseurs conventionnels (imurel, methotrexate, cellcept…) ne permettent pas d'obtenir de réponse durable dans les uvéites sévères ou réfractaires de la maladie de Behçet. Au cours des dernières années avec l'utilisation des produits biologiques (anti-TNF, anti-interleukines 6) le pronostic des uvéites a été nettement amélioré. Ces produits agissent rapidement et sont très efficaces pour diminuer la cortisone évitant ainsi l'apparition de la cataracte et / ou du glaucome.
Le but de notre étude est d'évaluer et de comparer l'efficacité des produits biologiques : anti-TNF (Adalimumab) et anti-interleukine 6 (tocilizumab) dans les uvéites sévères de la maladie de Behçet.
Pour répondre à la question posée dans la recherche, il est prévu d'inclure 60 personnes présentant une **uvéite sévère dans la** maladie de Behçet dans des établissements de soins situés en France (étude multicentrique).