« Multicenter, randomized, prospective trial comparing the Efficacy and Safety of Infliximab to that of Cyclophosphamide in severe Behçet's disease»

ITAC : Induction Therapy with Anti-TNFα vs Cyclophosphamide in severe Behçet disease

INTERVENTIONAL RESEARCH PROTOCOL RELATING TO A MEDICINAL PRODUCT FOR HUMAN USE

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Coordinating Investigator: **Pr David SAADOUN**

Department of Internal Medicine and Clinical Immunology
Hospital Pitie Salpetriere
Tel.0142178088
Email david.saadoun@psl.aphp.fr

Scientific Director: **Pr Bertrand WECHSLER**
Centre de référence des maladies autoimmunes et systémiques rares
Department of Internal Medicine and Clinical Immunology
Hospital Pitie Salpetriere
Tel.0142178009
Email bertrand.wechsler@psl.aphp.fr

Sponsor:
AP-HP and by delegation: Clinical Research and Innovation Delegation (DRCI)
Hôpital Saint-Louis
1, avenue Claude Vellefaux
DRCI-Siège project referent: Houria Mebarek

Entity responsible for monitoring the trial:

Unité de Recherche Clinique (URC) du GH saint Louis Lariboisière, site Saint Louis

Address Hôpital Saint Louis
1 avenue Claude Vellefaux
DRCI-URC (Clinical Research Unit) project referent:
Pr Mathieu RESCHE RIGON
Tel. 0142499742
Email : Matthieu.resche-rigon@univ-paris-diderot.fr
Chef de projet : Nabil RAKED
Email : nabil.raked@ univ-paris-diderot.fr
Tel. 0142499749

Clinical Research and Innovation Delegation (DRCI)
Hôpital Saint Louis 75010 PARIS

Entity responsible for the pharmaceutical coordination :

Département des Essais Cliniques
AGEPS
7, rue du Fer à Moulin,
75 005 Paris, France
Pharmaciennes référentes :
Céline Dupré
Tel: 33 1 46 69 14 67 / Fax: 33 1 46 69 95 49
Email: celine.dupre@aphp.fr
Florence Empana-Barat
Tel: 33 1 46 69 90 84 / Fax: 33 1 46 69 95 49
Email: florence.barat@aphp.fr
Chef de projet : Karine Ferrier
Tel: 33 1 46 69 95 43 / Fax: 33 1 46 69 95 49
Email: karine.ferrier@aphp.fr

INTERVENTIONAL RESEARCH PROTOCOL RELATING TO A MEDICINAL PRODUCT FOR HUMAN USE

PROTOCOL SIGNATURE PAGE

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

Coordinating Investigator:
Pr David SAADOUN
Department of Internal Medicine and Clinical Immunology
Hospital Pitie Salpetriere

Date: 01 / 10 / 2020
Signature:

GROUPE HOSPITALIER PITIE-SALPETRIERE
83, Bd de l'Hôpital - 75651 PARIS CEDEX 13
Dép' MEDECINE INTERNE ET IMMUNOLOGIE CLINIQUE
Professeur David SAADOUN
RPPS 10005176275
Secrétariat : 01 42 17 80 09 - Fax : 01 42 17 80 33

Sponsor
AP-HP and by delegation: Clinical Research and Innovation Delegation (DRCI)
Hôpital Saint-Louis

Date: 09 OCT. 2020
Signature:

P° YVACHER

The study was approved by the Ethic committee (CPP) of SUD-EST VI. on 03/11/2017and authorised by the ANSM on 20/09/2017

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SUMMARY

Full title	Multicenter, randomized, prospective trial comparing the Efficacy and Safety of Infliximab to that of Cyclophosphamide in severe Behçet's disease
Acronym	ITAC : Induction Therapy with Anti-TNFα vs Cyclophosphamide in severe Behçet disease
Coordinating Investigator	Pr David SAADOUN Centre de reference des maladies autoimmunes et systémiques rares Department of Internal Medicine and Clinical Immunology 83 bd de l'hôpital 75013 Paris Hospital Pitie Salpetriere Tel.0142178088 Email david.saadoun@psl.aphp.fr
Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	ITAC, is the first randomized prospective, head to head study, comparing infliximab, to that of cyclophophamide in severe manifestations of BD. Behçet's disease (BD) is a systemic vasculitis of arterial and venous vessels of any size, involving young patients (from 12 to 45 years). BD significantly increases morbidity and mortality. Therape utic management of BD depends on the clinical presentation and organ involved. Although colchicine, nonsteroidal antiinflammatory agents and topical treatments are often sufficient for mucocutaneous and joint involvement, more aggressive approach with immunosuppressive agents is warranted for severe manifestations such as retinal vasculitis, cardio-vascular, or neurological involvement. Early recognition and vigorous use of immunosuppressives with high dose steroids have changed the prognosis of patients with severe BD. BD is a severe systemic vasculitis leading to a 5-year mortality rate of 15% in patients with major vessel or neurological involvement. Cyclophosphamide has been used for life-threatening BD for 40 years. However, the outcome of severe complications of BD is still poor. The European League Against Rheumatism (EULAR) recommendation (updated in 2016) for the management of BD advocated cyclophosphamide or anti-TNFα plus glucocorticoids for life-threatening manifestations (i.e neurological and/or major vessel involvement) but recommendations on vascular disease and neurological involvement are based largely on expert opinion and uncontrolled evidence from open trials and observational studies. The need for further properly designed controlled clinical trials is apparent.. TNFa antagonists have been used with success in severe and/or resistant cases. In addition, the incidence of blindness in BD has been dramatically reduced in the recent years with the use of anti-TNF. However, there is no firm evidence or

	randomized controlled trials directly addressing the best induction immunosuppressive therapy in severe BD manifestations. Physicians are still prescribing these compounds off-label use. We therefore aimed to assess the best induction therapy in severe and difficult to treat BD patients.
Main objective and primary endpoint	To assess the benefit of infliximab comparatively to that of cyclophosphamide in severe life-threatening Behçet's disease. Primary assessment criterion will be the complete clinical response at week 22 after randomization
Secondary objectives and endpoints	To estimate and compare the rate and time to occurrence of relapses or worsening To estimate and compare the cumulative dose of steroids To estimate and compare the adverse events To estimate and compare the mean change in SF-36 quality-of-life (see Appendix 3) To estimate and compare the rate of remission according to organs involved To compare the changes in acute-phase reactants, To estimate and compare the changes in CNS involvement To estimate and compare the changes in Cardio-vascular involvement Survival and event free survival To estimate and compare the changes in other BD manifestations To estimate and compare the changes in Behcet's Disease Current Activity Form (see Appendix 2) To assess serum concentration measurement of TNFa inhibitor **Secondary endpoints** - Complete clinical response at week 12 and 48. - Remission of CNS and/or cardiovascular involvement at week 12, 22 and 48. - Measures of corticosteroid sparing : o Percent meeting targets [≤ 0.1 mg/day/kg of prednisone] at week 22 and 48. o Mean dose at week 12, 22 and 48. o Cumulative dose at week 12, 22 and 48. - Time to response onset - Measures of acute-phase reactant : o C-reactive protein [CRP]) every 4 weeks - Relapse : o Time to relapse (Relapse will be defined as the reappearance of clinical and/or paraclinical features of active disease or by the occurrence of new lesions at week 48. o Rate of relapse - Worsening

	o Time to occurrence of worsening. (Worsening will be defined as the progression of preexisting lesions) at week 22 and 48. o Rate of worsening - Gobal survival at week 22 and 48. - Event free survival at week 22 and 48 defined by the occurrence of death, relapse or worsening. - Safety and tolerability of treatments in BD patients as assessed by frequency and severity of adverse clinical events at week 22. - Change in quality of life (QOL) (SF-36V2TM Health Survey) at week 12 and 22. (see Appendix 3) - Changes in CNS involvement on physical exam, and cerebral and/or medullar MRI at week 12 and 22. - Changes in vascular involvement on physical exam, vascular Doppler US, and angio-CT imaging and biologically (normalization of C reactive protein) at week 12 and 22. - Changes in cardiological involvement on physical exam, echocardiography (normalization of left ventricular function and/or disappearance 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 C reactive protein) at week 12 and 22. - Changes in other organs involved in BD - Serum concentration measurement of TNFa inhibitor at week 22 - Change in Behcet's Disease Current Activity Form (see Appendix 2) at week 12 and 22.
Design of the trial	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 to the monitoring for patient safety and evidence of efficacy of small randomized trials
Population of trial subjects	Adult and pediatric patients with severe life-threatening Behçet's disease.
Inclusion criteria	1. Age ≥ 12 years old 2. Written inform consent (Informed Consent should be obtained from the legal guardian in accordance with regional laws or regulations for patients 12 to 17 years of age) 3. Diagnosis of BD according to international criteria for BD (ICBD) (see Appendix 1). 4. Life threatening active BD defined as 1 of the following disease categories and according to the validated international definition: - Major vessel disease: arterial aneurysms or arterial stenosis, myocarditis and/or major deep vein thrombosis (i.e. inferior vena cava, superior vena cava, cardiac cavity thrombosis, pulmonary embolism, supra-hepatic vessels, renal and mesenteric vessels). Diagnosis

	of major vessel involvement will be done using vascular doppler sonography, echocardiography, angio-CT scan and/or cardiac magnetic resonance imaging (MRI). - Central nervous system involvement: encephalitis or meningoencephalitis or myelitis. The diagnosis of neuro-Behçet's (CNS involvement) will be based on objective neurological symptoms that were associated with neuroimaging (CNS and/or medullar MRI) findings suggestive of BD-related CNS involvement. Cerebrospinal fluid (CSF) findings showing aseptic inflammation may be associated. 6. Chest X-ray results (postero-anterior and lateral) within 12 weeks prior to inclusion with no evidence of active Tuberculosis, active infection, or malignancy 7. For female subjects of child-bearing age, a negative pregnancy test 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 6 months after stopping therapy. Adequate contraceptive measures include hormonal methods used for two or more cycles prior to Inclusion (e.g., oral contraceptive pills, contraceptive patch, or contraceptive vaginal ring), barrier methods (e.g., contraceptive sponge, diaphragm used in conjunction with contraceptive foam or jelly, or condom used in conjunction with contraceptive foam or jelly), intrauterine methods (IUD), sterilization (e.g., tubal ligation or a monogamous relationship with a vasectomized partner), and abstinence. 9. A potential subject with a positive interferon-gamma release assay (IGRA) (e.g., QuantiFERON®-TB Gold or T-spot TB® Test) or a positive tuberculin skin test (≤6 months) 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. 10. HIV negative serology and negative HBs Ag test (≤1 month)
Non inclusion criteria	Subjects will be not included from the study if they meet any of the following criteria: 1. Evidence of active Tuberculosis 2. HIV or active HBV infection (HBs Ag+). 3. Pregnancy or lactation 4. Have been taking an oral daily dose of a glucocorticoid of more than 20 mg prednisone equivalent for more than 6 weeks continuously prior to the inclusion visit or taking more than 3000 mg methylprednisolone 4 weeks prior to the inclusion visit 5. Alcohol or drug dependance

	6. Severe renal (creatinine clairance <30ml/min/1,73m2) or pre-existing hemorrhagic cystitis or liver insufficiency (hepatic encephalopathy,) or urinary obstruction 7. Heart failure ≥ stage III / IV NYHA, 8. History of malignancy within 5 years prior to Inclusion other than carcinoma in situ of the cervix or excised basal cell or squamous cell carcinoma of the skin. 10. History of multiple sclerosis and/or demyelinating disorder 11. History of severe allergic or anaphylactic reactions to cyclophosphamide or infliximab 12. Infectious disease: - Infection requiring treatment with intravenous antibiotics within 2 weeks prior to Inclusion - History of recurrent infection 14. Laboratory values assessed during Inclusion: - Hemoglobin < 8 g/dL - WBC < 2.0 x 103/mm3 - Platelet count < 70 x 103/mm3 15. Use of the following systemic treatments during the specified periods: - Treatment with systemic biologic therapy or with cyclophosphamide within 3 months prior to Inclusion - if on azathioprine, mycophenolate mofetil, or methotrexate at the time of inclusion, these drugs must be withdrawn prior to receiving the cyclophosphamide or infliximab dose on Day 1 16. Any live (attenuated) vaccine within 4 weeks prior inclusion; recombinant or killed virus vaccines are permitted. 17. Lack of affiliation to a social security benefit plan (as a beneficiary or assignee). Patients affiliated to universal medical coverage (CMU) are eligible for the study
Investigational medicinal product(s)	*Infliximab 5mg/kg intravenously at week 0, 2, 6, 12, and 18*
Comparator treatment	*Cyclophosphamide 0.7g/ m^2 up to 1.2 g/m^2, intravenously at week 0, 4, 8, 12, 16 and 20*
Interventions added for the trial	Evaluations of serum concentration of anti-TNF at week 22
Risks added by the trial	Risk C Intermediate
Scope of the trial	*After the collection of their free and informed consent, eligible patients with active Behçet's disease will be randomized into one of 2 groups at the randomization visit (D0):* • *Arm A Infliximab 5mg/kg intravenously at week 0, 2, 6, 12, and 18* • *Arm B Cyclophosphamide 0.7g/ m^2 up to 1.2 g/ m^2, intravenously at week 0, 4, 8, 12, 16 and 20*

	All patients will receive the same corticosteroid regimen. All patients will have at Inclusion/randomisation visit an oral prednisone at 1 mg/kg/day (up to 80 mg/day). *The following schedule of reduction of prednisone will apply to both groups as long as the disease is inactive:* ▪ *Week 4 : 0.8mg/kg/day* ▪ *Week 6: 0.7mg/kg/day* ▪ *Week 8 : 0.6mg/kg/day* ▪ *Week 10: 0.5mg/kg/day* ▪ *Week 12 : 0.4mg/kg/day* ▪ *Week 14: 0.3mg/kg/day* ▪ *Week 16: 0.2mg/kg/day* ▪ *Week 22 : ≤0.1mg/kg/day*
Number of subjects included	52 patients, 26 patients in each arm
Number of sites	Multicentre national study including 28 centres
Duration of the trial	- *Duration of inclusions: 36 months* - *Duration of participation of each patient:12 months* - *Total duration of the study: 48 months*
Number of enrolments expected per site and per month	0.07 patient/month/centre
Statistical analysis	*The experimental design is a multicentric open multicenter randomized clinical trial stratified on the characteristics of the initial Behçet's disease with evaluation of the primary assessment criteria at 22 weeks. The primary assessment criteria and the final measures of corticosteroid sparing will be reviewed by a scientific committee blinded of the randomization.* *The RCT will use a Bayesian design for phase II randomized national multicentre clinical trial that aims at comparing a new treatment to a reference based on a binary endpoint (i.e. complete clinical response at week 22), which offers greater flexibility and simplicity of inference to the monitoring for patient safety and evidence of efficacy of small randomized trials.*
Sources of funding for the trial	*PHRC*
Trial will have a Data Monitoring Committee	*Yes*

SCIENTIFIC JUSTIFICATION FOR THE TRIAL

1.1 Hypothesis for the study

Behçet's disease (BD) is a systemic vasculitis of arterial and venous vessels of any size, involving young patients (from 12 to 45 years). BD significantly increases morbidity and mortality [1]. Therapeutic management of BD depends on the clinical presentation and organ involved. Although colchicine, nonsteroidal antiinflammatory agents and topical treatments are often sufficient for mucocutaneous and joint involvement, more aggressive approach with immunosuppressive agents is warranted for severe manifestations such as posterior uveitis, retinal vasculitis, cardio-vascular, or neurological involvement [2]. Early recognition and vigorous use of immunosuppressives with high dose steroids have changed the prognosis of patients with severe BD. BD is a severe systemic vasculitis leading to blindness in up to 20% at 4 years and a 5-year mortality rate of 15% in patients with major vessel or neurological involvement [3, 4]. Cyclophosphamide has been used for life-threatening BD for 40 years [5]. The outcomes of severe complications of BD improved but immunosuppressants failed to demonstrate sustainable remission over 70 % of refractory/relapsing BD cases [3, 4, 6-8]. TNFα expression correlate with BD activity and other immunological data provide a strong rationale for targeting BD with biologics. A recent case series have reported up to 85% of complete response with anti-TNFα agents in BD patients with major vessel involvement [9]. The incidence of blindness in BD has been dramatically reduced in the recent years with the use of anti-TNF, raising the question of whether anti-TNFα agents should be used earlier in the treatment of BD. The European League Against Rheumatism (EULAR) recommendation (updated in 2016, paper submitted) for the management of BD advocated cyclophosphamide or anti-TNFα plus glucocorticoids for life-threatening manifestations (i.e neurological and/or major vessel involvement) [10] but recommendations on vascular disease and neurological involvement are based largely on expert opinion and uncontrolled evidence from open trials and observational studies. The need for further properly designed controlled clinical trials is apparent.

Only one randomized, controlled trial, has been performed to date, in mild form of BD and concluded that etanercept (ETA) was efficient on mucocutaneous manifestations and arthritis [11]. However, there is no firm evidence or randomized controlled trials directly addressing the best induction immunosuppressive therapy in severe BD manifestations. Physicians are still prescribing these compounds off-label use. We therefore aimed to assess the best induction therapy in severe and difficult to treat BD patients. ITAC, is the first randomized prospective, head to head study, comparing infliximab, to cyclophophamide in severe manifestations of Behçet's disease (BD).

1.2 Existing knowledge relating to the condition under investigation

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 [2]. Diagnosis is only based on clinical criteria as in BD there is no relevant biological test for diagnosis. BD is especially frequent along the ancient Silk Road, which extends from eastern Asia to the Mediterranean basin. 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.

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Morbidity

BD significantly increases morbidity and mortality [1, 12]. 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. 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. Neuro-BD patients have a poor long-term outcome. In a recent study, 25% of patients had become dependent or died during follow-up [3].

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% [3, 13, 14]. The vasculitis of BD is distinctive because of involvement of both arteries and veins of all sizes [8, 14, 15]. The concept of vasculo-Behçet has been adopted for cases in which vascular complications are present and often dominate the clinical features.

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.

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 15. 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. CD4 and CD8 T cells producing a Th1-type cytokine profile, elevated IL-12 levels and a Th1-type tissue infiltration in intestinal and cutaneous lesions and elevated IL-17 levels in some studies favour the former, whereas the probable primed state of neutrophils, their abundance in BD lesions and the polyclonal gamma delta T cells in BD sera point to the latter. An IL-21 driven Th17 pathway has also been reported [16]. 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.

Criteria of disease activity

There are no definitive criteria for progression of Behçet's disease. The complete clinical response will be defined by the remission of all affected organs involved at baseline and the absence of clinical relapse.

- 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) [17].
- 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) [18].
- Remission of neurological involvement is defined as a complete clinical, and imaging (as evaluated by MRI) remission, biologically (normalization of inflammatory syndrome) and the absence of neurological sequelae (defined as a Rankin score <1) [3].
- 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). 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 grading [19] associated with 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.

Treatment Options

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. Recent improvements in the understanding of the pathogenic mechanisms have led to the identification of potential targets and future therapies for BD. In contrast to current non-specific immunosuppressive agents, the emergence of immunomodulatory drugs provides the possibility of interfering with specific pathogenic pathways. Early treatment with azathioprine is recommended as the initial agent for ocular involvement and favorably affects the long-term prognosis of BD. AZA (2.5 mg/kg/day) combined with prednisone at an initial dose of 0.5–1 mg/kg/day in 157 consecutive BD with active posterior uveitis or panuveitis, significantly improved the visual acuity and decreased the percentage of patients who had loss of useful vision compared to baseline values[20]. Patients having retinal vasculitis and severe visual loss at baseline were less likely to be complete responders. Azathioprine represents an effective therapy in BD patients without retinal vasculitis or severe vision loss. Ciclosporin A (CsA) has been studied in several controlled studies regarding its efficacy in ocular BD. CsA 5-10 mg/kg in comparison to corticosteroids and chlorambucil significantly reduced the number of relapses and improved most rapidly visual acuity. In 2010, Yamada et al showed in a retrospective study that infliximab (given in monotherapy in 17 patients) was more effective in reducing acute episodes of uveitis in BD compared to CsA (given in 20 patients) 21. Moreover, its use in BD is limited by its toxicity (mainly nephrotoxicity). In 2 independent retrospective studies, CsA appears to cause neurotoxicity and accelerate the development of CNS symptoms in BD. Thus, CsA is not recommended for patients with present or previous CNS involvement[10].
Novel targeted immunosuppressive therapies might be used in the future for BD. Proinflammatory cytokines, and T-cells play an important role in the pathogenesis of BD. Therefore, immunomodulatory approaches with biotherapies such as modulation of NFκB expression, inhibition of TNFα, IL-1 or IL-6 signaling, or T-cells depletion has been proposed as therapeutic option for BD. In patients presenting with severe BD disease, more targeted therapies offer the potential advantage of faster delay of action as compared the generally slow response to conventional immunosuppressive drugs. Anti-IL-1 (i.e. gevokizumab or anakinra) and anti-IL-6 (tocilizumab), are inhibitors of IL-1 and IL-6, respectively, approved for rheumatoid arthritis (RA) that have also been used for the treatment of BD in a small number of patients.

Treatment of major vessel and neurological involvement
BD can affect the heart and both venous and arterial vessels. Venous, arterial and cardiac lesions are observed in about 30%, 10% and 5% of patients with BD, respectively. Neurological manifestations occur in 30% of cases in BD, including parenchymal (i.e. meningo-encephalitis and pseudotumoral inflammation) and non-parenchymal forms (i.e. dural sinus thrombosis and cerebral arterial aneurysm). There is no firm evidence to guide us in managing major vessel and neurological disease in BD. However, the 2008 EULAR recommendations for the management of Behçet's disease [10] serve as a reminder that there are no controlled data to guide the therapeutic choice in major vessel and neurological disease in BD. The updated EULAR recommendations of 2016 (submitted) advocated cyclophosphamide or anti-TNFa plus glucocorticoids for life-threatening manifestations (i.e neurological and/or major vessel involvement). The use of steroids alone or in combination with cyclophosphamide was proved effective in retrospective studies [3 , 6, 7]. Since that time, the efficacy of anti-TNF agents (mainly infliximab 5mg/kg) was reported in cases series in patients with central nervous system [22, 23], and major vessel involvement [24, 25]. Complete remission was observed in 82% of patients with CNS involvement [26] with infiliximab. A recent study, have reported up to 85% of complete response with anti-TNFα agents in BD patients with major vessel involvement [9]. Overall clinical response is evidenced in up to 90% of BD with refractory ocular and extra-ocular manifestations of BD. The standard therapeutic induction protocol largely used in life threatening manifestations of BD (i.e. major vessel and CNS involvement) includes three 1 g pulses of methylprednisolone followed by prednisolone 1 mg/kg/day, tapered and if possible stopped over 6 months. Intravenous cyclophosphamide – 1 g – is given monthly for 6 months and infliximab is given at a dose of 5mg/kg at week 0, 2, 4, then every 6 weeks [25]. There is no consensus concerning anticoagulation in patients with BD and venous thrombosis.

Regarding anticoagulation, there are no controlled data or evidence of benefit from uncontrolled studies on anticoagulants in the management of deep vein thrombosis of BD. Some authors recommend anticoagulants for major vein thrombosis, while others suggest they be avoided owing to the increased risk of fatal bleeding from coexisting pulmonary arterial aneurysm and to the estimated low risk of pulmonary embolism in BD. In the largest study published to date, almost all 296 BD patients with deep vein thrombosis received anticoagulation therapy despite a high number (n=44, 14.9%) of associated arterial aneurysms of whom 8 had pulmonary arterial aneurysms. The tolerance was satisfactory, with 2% of hemorrhagic complications [18].

Overview of different drugs

Cyclophosphamide

Cyclophosphamide has been used for life-threatening BD for 40 years [5]. The outcomes of severe complications of BD improved but immunosuppressants failed to demonstrate sustainable remission over 70 % of refractory/relapsing BD cases [3, 4, 6-8]. Complete remission have been described in refractory cases and for various manifestations, such as cutaneous, ocular, arterial aneurysms and gastrointestinal or neurological involvements. Currently the main use of cyclophosphamide in BD is in major
vascular involvement. Two retrospective studies by Hamuryudan et al emphasised its role in treating pulmonary artery aneurysms. In the first report, which evaluated patients registered until 1992, 17 of 24 patients were treated with cyclophosphamide. A total of 12 patients, 6 of whom had not had time to use immunosuppressives, had died after a mean (SD) of 9.5 months after the onset of haemoptysis. In the second report, which evaluated patients registered from 1992 to 2003, 25 of 26 patients with a mean follow-up after the diagnosis of pulmonary artery aneurysms of 48.8 (41.4) months, were treated with cyclophosphamide and only 6 of them died. In 2012, Seyahi et al reported 47 BD patients with pulmonary artery aneurysms. After a median follow up of 7 years, 12 of 47 (26%) patients were died 7. The protocol used by many expert groups includes three 1 g pulses of methylprednisolone followed by prednisolone 1 mg/kg/day, tapered and if possible stopped over 6 months. Intravenous cyclophosphamide – 1 g – is given monthly for 6 months 8. , In a large series of neuro-Behçet's cyclophosphamide has been shown to be more effective than azathioprine especially in severe cases (i.e. rankin's score>2) [3]. These results tend to support the assumption of the EULAR recommendations, which suggest that IV cyclophosphamide could be better than azathioprine in patients with neuro-Behçet's.

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 controls [27]. Other group 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). IFX has been used in more than 300 cases, mainly for refractory ocular BD, and was associated with clinical improvement in 89% of patients who were resistant to conventional thera¬pies TNFα-antagonists are increasingly used for patients with BD, especially infliximab and in a lesser extent adalimumab [28]. Few cases report have shown efficacy of certolizumab or golimumab in BD. Only 1 randomized, double-blind, placebo-control trial assessed the effect of etanercept on mucocutaneous manifestations and arthritis [62]. The relapse rate of uveitis and daily corticosteroid doses were significantly lower during infliximab treatment in patients with BD in whom uveitis was resistant to combination therapy with corticosteroids, azathioprine, and cyclosporine 28. Complete remission were observed in 83% and 82% of patients with gastrointestinal and CNS involvement, respectively 26, 29. Rapid onset of action and steroid-sparing effect characterize the efficacy of TNFα-antagonists, mainly

reported in patients resistant to conventional therapies [25, 28]. The switching of anti-TNF-α agents after a failure of a first anti-TNF-α agent can be an alternative therapeutic option but the two monoclonal antibodies, infliximab and adalimumab, seem more effective than the soluble antibodies, etanercept notably for uveitis. However, repeated long term infusions are warranted to sustain remission as TNFα-antagonists are likely suspensive 25, 28. The standard regimen of infliximab use in severe BD is usually infusions of 5mg/kg at week 0, 2, 4, then every 6 weeks [25]. Since that time, the efficacy of anti-TNF agents (mainly infliximab 5mg/kg) was reported in cases series in patients with central nervous system 22, 23, and major vessel involvement [24, 25]. A recent study has reported up to 85% of complete response with anti-TNFα agents in BD patients with major vessel involvement [9].

1.3 Summary of relevant pre-clinical and clinical trials

A recent case series have reported up to 85% of complete response with anti-TNFα agents in BD patients with major vessel involvement [9].
Only one randomized, controlled trial has been performed to date, in mild form of BD and concluded that etanercept (ETA) was efficient on mucocutaneous manifestations and arthritis [11].

1.4 Description of the population of trial subjects and justification for the choice of subjects

This is a Bayesian Phase II randomized clinical trial that aims at evaluating the best treatment strategy of severe Behçet's disease, based on difference in the response rate as measured at week 22 after randomization.

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 chose 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 (as described below).
Given the uncertainty in the infliximab benefit over cyclophosphamide in severe Behçet's disease 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 hypothesize that up to 70% of the patients receiving cyclophosphamide and 85% of those treated by anti-TNF will achieve a complete remission of BD at 6 months and with less than 0.1 mg/kg/day of prednisone. Thus, based on binomial distributions under the assumed response rate of the control arm (here, p=0.70), this allowed to randomly allocate two groups of 26 patients to detect a 0.15 difference in response rates with a 0.90 probability

1.5 Name and description of the investigational medicinal product(s)

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

- Arm A Infliximab 5mg/kg intravenously at week 0, 2, 6, 12, and 18
- Arm B Cyclophosphamide 0.7g/ m^2 up to 1.2 g/ m^2, intravenously at week 0, 4, 8, 12, 16 and 20

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

- Arm A Infliximab 5mg/kg intravenously at week 0, 2, 6, 12, and 18
- Arm B Cyclophosphamide 0.7g/m^2 up to 1.2 g/ m^2, intravenously at week 0, 4, 8, 12, 16 and 20

1.7 Summary of the known and foreseeable benefits and risks for the study participants

Current treatment of BD is guided by organ involvement and the severity of the disease. Intravenous cyclophosphamide is still recommended for management of patient with life-threatening manifestations of BD. However, this treatment fails to control inflammation or maintain remissions in up to 30% of patients who develop relapse, or irreversible organ damage or severe and even life-threatening complications. Rapid onset of action and steroid-sparing effect characterize the efficacy of TNFα-antagonists, mainly reported in patients resistant to conventional therapies. Although the results of several studies have suggested that anti-TNF therapy with infliximab (5mg/kg) for severe BD could be effective and rescue refractory case to cyclophosphamide, therapeutic trial comparing cyclophosphamide to infliximab 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 BD. It will allow the validation of the treatment of difficult to treat Behçet's disease patients. This study may confirm the efficacy of a biologic therapy in terms of efficacy and steroid sparing. This study may assess the benefit of anti-TNF therapy over cyclophosphamide in terms of safety, efficacy, fertility in women with reproductive potential and steroid sparing. It could thus improve the care of patients with BD. The expected benefit is both individual, in reduced morbidity for patients with BD, and collective, in reducing costs of hospitalization, and surgery or endovascular procedures.

OBJECTIVES

1.8 Primary objective

To assess the benefit of infliximab comparatively to that of cyclophosphamide in severe life - threatening Behçet's disease.

1.9 Secondary objectives

- To estimate and compare the rate and time to occurrence of relapses or worsening
- To estimate and compare the cumulative dose of steroids
- To estimate and compare the adverse events
- To estimate and compare the mean change in SF-36 quality-of-life
- To estimate and compare the rate of remission according to organs involved
- To compare the changes in acute-phase reactants,
- To estimate and compare the changes in CNS involvement
- To estimate and compare the changes in Cardio-vascular involvement
- To estimate and compare the changes in other BD manifestations;
- Survival and event free survival
- To estimate and compare the changes in Behcet's Disease Current Activity Form (see Appendix 2)
- To assess serum concentration measurement of TNFa inhibitor

DESCRIPTION OF THE TRIAL

1.10 Concise description of the primary and secondary endpoints

Primary endpoint

Primary assessment criterion will be the complete clinical response at week 22 after randomization.

The complete clinical response is defined by the remission of all affected organs involved at baseline with a prednisone ≤ 0.1mg/kg per day :

Life threatening manifestations; CNS and/or cardiovascular involvement:
- 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 C reactive protein and ESR) [17].
- 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) [18].
- Remission of neurological involvement is defined as a complete clinical, and imaging (as evaluated by CNS MRI) remission, and the absence of neurological sequelae (defined as a Rankin score <1) [3].

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), and by endoscopy (improvement of potential gastrointestinal lesions seen at baseline).
- 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 grading 19 associated with 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.

Secondary endpoints

- Complete clinical response at week 12 and 48.
- Remission of CNS and/or cardiovascular involvement at week 12, 22 and 48.
- Measures of corticosteroid sparing :
o Percent meeting targets [≤ 0.1 mg/day/kg of prednisone] at week 22 and 48.
o Mean dose at week 12, 22 and 48.
o Cumulative dose at week 12, 22 and 48.
- Time to response onset
- Measures of acute-phase reactants :
o C-reactive protein [CRP]) every 4 weeks
- Relapse :
o Time to relapse (Relapse will be defined as the reappearance of clinical and/or paraclinical features of active disease or by the occurrence of new lesions) at week 48.
o Rate of relapse
- Worsening
o Time to occurrence of worsening. (Worsening will be defined as the progression of preexisting lesions) at week 22 and 48.
o Rate of worsening
- Gobal survival at week 22 and 48.
- Event free survival at week 22 and 48 defined by the occurrence of death, relapse or worsening.
- Safety and tolerability of treatments in BD patients as assessed by frequency and severity of adverse clinical events at week 22.
- Change in quality of life (QOL) (SF-36V2TM Health Survey) at week 12 and 22.(see Appendix 3)
- Changes in CNS involvement on physical exam, and cerebral and/or medullar MRI at week 12 and 22.
- Changes in vascular involvement on physical exam, vascular Doppler US, and angio-CT or MRI imaging and biologically (normalization of C reactive protein) at week 12 and 22.
- Changes in cardiological involvement on physical exam, 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 C reactive protein) at week 12 and 22.
- Changes in other organs involved in BD
- Serum concentration measurement of TNFa inhibitor at week 22
- Change in Behcet's Disease Current Activity Form (see Appendix 2) at week 12 and 22.

1.11 Research methodology

Design of the trial

The experimental design is a multicentric open multicenter randomized clinical trial stratified on the characteristics of the initial Behçet's disease with evaluation of the primary assessment criteria at week 22.

The primary assessment criteria and the final measures of corticosteroid sparing will be reviewed by a endpoint adjudication committee blinded of the randomization. This committee will have the role of validating under blind conditions the following assignments: complete remission, treatment failure and relapse of the disease. It will consist of persons external to the Study: Clinicians specializing in the pathology under consideration: Prof B Wechsler (Pitié-Salpétrière Hospital). Radiologist: Dr S Boussouar (Pitié-Salpétrière Hospital) and Dr D Leclercq (Pitié-Salpétrière Hospital). It will meet at the end of the study.

The RCT will use an adaptive Bayesian design for phase II randomized national multicentre clinical trial that aims at comparing a new treatment to a reference based on a binary endpoint (i.e. complete clinical response at week 22), which offers greater flexibility and simplicity of inference to the monitoring for patient safety and evidence of efficacy of small randomized trials.

• 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 Infliximab 5mg/kg intravenously at week 0, 2, 6, 12, and 18

Arm B Cyclophosphamide 0.7g/ m^2 up to 1.2 g/ m^2, intravenously at week 0, 4, 8, 12, 16 and 20

All patients will receive the same corticosteroid regimen. All patients will receive oral prednisone at 1 mg/kg/day (up to 80 mg/day) at randomization.

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

- *Week 4 : 0.8mg/kg/day*
- *Week 6: 0.7mg/kg/day*
- *Week 8 : 0.6mg/kg/day*
- *Week 10: 0.5mg/kg/day*
- *Week 12 : 0.4mg/kg/day*
- *Week 14: 0.3mg/kg/day*
- *Week 16: 0.2mg/kg/day*
- *Week 22 : ≤0.1mg/kg/day*

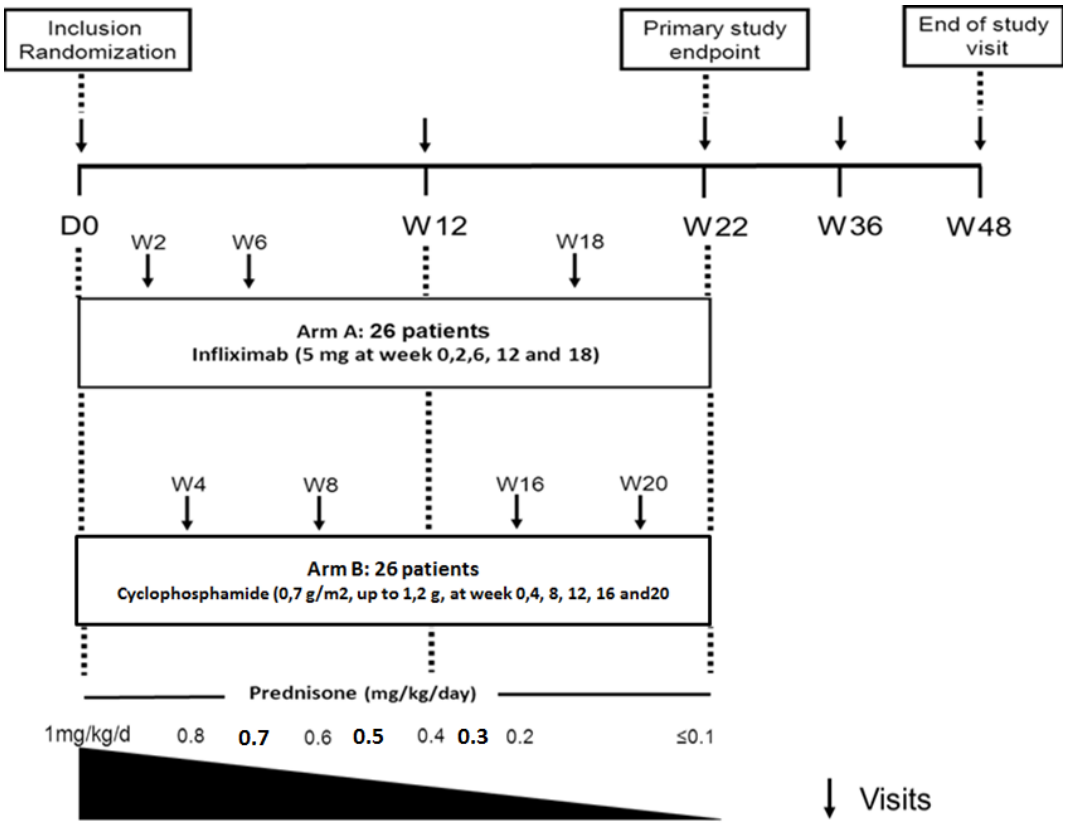
For patients with a positive interferon-gamma release assay (IGRA) (e.g., QuantiFERON® -TB Gold or T-spot TB® Test) or a positive tuberculosis skin test before inclusion and receiving rifampicin (300mg/day) and isoniazid (150mg/day) (prophylactic TB treatment) for 3 months the prednisone dosage will be increase of 20% (due to interaction between isoniazid and prednisone) during the prophylactic TB treatment period (i.e 3 months).

- Week 12, and 22: Evaluation of secondary assessment criteria
- Week 22: Evaluation of primary assessment criteria
- Week 36 and 48: Evaluation of secondary assessment criteria

All patients will be reviewed for systemic physical examination at the visits Day 0 (inclusion and randomization) and the follow-up visits at :
- Arm A Infliximab 5mg/kg at week 2, 6, 12, 18, 22, 36 and 48
- Arm B Cyclophosphamide 0.7g/ m^2 up to 1.2 g/ m^2, 4, 8, 12, 16, 20, 22, 36 and 48.

Monitoring will also include laboratory testing every month and imaging (echocardiography, vascular Doppler US, angiographic CT scan, cardiac MRI, and/or cerebral and/or medullar MRI) at week 12 and week 22 after randomization.
Additional visits will take place in case of any clinical or laboratory findings suggestive of a flare-up of the disease.

Figure 1. Scheme of the study



Number of participating sites

Multicentre national study including 28 centres.

Identification of the subjects

The subjects participating in this study will be identified as follows:
Site number (3 digits) - Sequential selection number for the site (4 digits) - surname initial - first name initial
This reference is unique and will be retained for the entire duration of the trial.

Randomisation

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 (major vessel involvement and CNS involvement) and according to newly diagnosed vs 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.
All inclusion and non-inclusion criteria will be checked before randomization

PROCEDURE FOR THE TRIAL

1.12 Inclusion/randomisation visit

The Inclusion/randomisation visit takes place *at day 0*.

Whose consent must be obtained	Who informs the individual and collects their consent	When is the individual informed	When is the individual's consent collected
the subject participating in the trial and the legal guardian in accordance with regional laws or regulations for patients 12 to 17 years of age	*the investigator internal medicine, pneumologist, pediatrician or Rheumatologist*	*During Inclusion visit*	*After time reflexion during Inclusion/randomisation visit*

The Inclusion/randomisation 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,
- histories of undercurrent disease and current treatments,
- perform a physical examination including a search for active lesions of Behçet's disease
- assess the investigations looking for signs of cardiac, major vessel involvement or neurological lesions of Behçet's disease.
- perform complete blood count with platelets, serum electrolytes, liver function tests (AST, ALT, GGT, total bilirubin, albumin), CRP, creatinine, and for women, ßHCG (urinary or plasmatic) and ECG.
- inform the patient about the protocol, and give them the information and consent form
- collect the free and informed written consent of the patient
- assess the results of the cardiovascular and/or neurological exams obtained within 1 month prior inclusion and of chest xray of less than 12 weeks.
- Assess other exams according to others active BD manifestations (i.e. GI endoscopy, ophthalmologic exam…) have to be obtained within 3 months prior inclusion.

- If all eligibility criteria are met the investigator will complete the Study Inclusion Form listing the eligibility criteria
- Assure the randomization on CleanWeb, an online randomization system
- Quality of life assessment
- Provide the first treatment

.

1.13 Follow-up visits

Monitoring should continue for all patients until the end of the Study according to the schedule, even if they discontinue. Consultations at these visits will be with the patient's usual Study doctor. Patients in Arm A Infliximab 5mg/kg will be reviewed at week 2, 6, 12, 18, 22, 36 and 48, and patients in Arm B Cyclophosphamide at 0.7g/ m^2 up to 1.2 g/ m^2, at week 4, 8, 12, 16, 20, 22, 36 and 48.

- A physical examination will be performed by the patient's Study physician at each visit.
- Laboratory tests will be carried between visits at local laboratories and include monthly monitoring of blood count, platelets, liver functions and urea and creatinine.
- At each visit a complete blood count with platelets, serum electrolytes, liver function tests (AST, ALT, GGT, total bilirubin, albumin), CRP, creatinine, will be measured and ECG.
- Imaging studies [cardiac (echocardiography and cardiac MRI) and/or vascular (vascular Doppler US, and angio-CT or MRI imaging) and/or central nervous system (CNS or medullar MRI imaging] will be performed at week 12 and 22, 36 et 48.
- Other exams according to others active BD manifestations (i.e. GI endoscopy, ophthalmologic exam…) have to be done at week 22.
- For women with reproductive potential urinary ßHCG at each visit **and monthly until 6 months after the end of treatment**. Kits for urinary pregnancy test will be given at visit week 22 for women with reproductive potential as well as a diary for the notification of the result which will be reported at visit week 36 and week 48
- Serum concentration measurement of TNFa inhibitor at week 22.

Anonymous cardiovascular and neurologic imaging will be collected at baseline, week 12 and 22.
Additional visits will take place according to the treatment arm for treatment administration (Day hospitatlization).

Arm A (n=26 patients) : Infliximab 5mg/kg intravenously at week 0, 2, 6, 12, and 18

Arm B (n=26 patients) : Cyclophosphamide 0.7g/ m^2 up to 1.2 g/ m^2, intravenously at week 0, 4, 8, 12, 16, and 20
Additional visits will take place if there are clinical signs indicating a possible flare up of the disease.

1.14 End of study visit

After Month 12, all subjects will be followed after the study according to their usual routine hospital care every 3 months until one year.

1.15 Expected length of participation, 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 18 weeks for Arm A (Infliximab) and 20 weeks for Arm B (Cyclophosphamide**)**. After 6 months the treatment will be left to the discretion of the physician in charge of the patient.

1.16 Table or diagram summarising the chronology of the study

	D0	W2	W4	W6	W8	W12	W16	W18	W20	**W22§**	W36	W48
Verification of inclusion and non inclusion criteria	**☒/**Δ ®											
Inclusion/randomization visit (Oral and written Information about the protocol and Signature of informed consent)	**☒/**Δ ®											
Clinical examination	☒/Δ	☒	Δ	☒	Δ	☒/Δ	Δ	☒	Δ	☒/Δ	☒/Δ	☒/Δ
Biological tests *	☒/Δ	☒	Δ	☒	Δ	☒/Δ	Δ	☒	Δ	☒/Δ	☒/Δ	☒/Δ
Latent tuberculosis tests, HIV, HBV, serologies †	☒/Δ											
bhCG**	☒/Δ	☒	Δ	☒	Δ	☒/Δ	Δ	**☒**	Δ	☒/Δ		
ECG	☒/Δ	☒	Δ	☒	Δ	☒/Δ	Δ	**☒**	Δ	☒/Δ		
Chest X Ray (within 12 weeks)	☒/Δ											
QOL questionnaires	**☒/**Δ ®					**☒/**Δ ®				**☒/**Δ ®		
Angio CT scan or MRI, and vascular doppler US ‡	☒/Δ					☒/Δ				☒/Δ	☒/Δ	☒/Δ
Echocardiography, troponin, cardiac MRI ‡	☒/Δ					☒/Δ				☒/Δ	☒/Δ	☒/Δ
Central nervous system MRI ‡	☒/Δ					☒/Δ				☒/Δ	☒/Δ	☒/Δ
Other exams≠	☒/Δ									☒/Δ		
Serum concentration of anti-TNF										**☒/**Δ ®		
Treatment delivery	☒/Δ	☒	Δ	☒	Δ	☒/Δ	Δ	**☒**	Δ			

☒ : Arm (A) Infliximab 5mg, Δ: Arm (B) Cyclophosphamide at 0.7g/ m^2 up to 1.2 g/ m^2,

® = Specific for research

§ Primary end point

† Latent tuberculosis tests have to be obtained within 6 months prior inclusion and HIV and HBV serologies of less than 1 month prior inclusion

‡The baseline cardiovascular and/or neurological exams have to be obtained within 1 month prior inclusion.

≠ other exams according to others active BD manifestations (i.e. GI endoscopy, ophthalmologic exam…) have to be obtained within 3 months prior inclusion and at week 22.

**For women with reproductive potential urinary ßHCG at each visit and monthly until 6 months after the end of treatment. Kits for urinary pregnancy test will be given at visit week 22 for women with reproductive potential as well as a diary for the notification of the result which will be reported at visit week 36 and week 48

1.17 Distinction between standard care and research

Procedures and treatments carried out as part of the research	Procedures and treatments associated with care	Procedures and treatments added because of the research
Treatments	- oral prednisone - Reduction of corticosteroid regimen - supportive treatment to reduce the adverse effects associated with the use of steroids	- Infliximab 5mg/kg at week 0, 2, 6, 12 and 18 intravenously - Cyclophosphamide 0.7g/ m^2 up to 1.2 g/ m^2, intravenously at week 0, 4, 8, 12, 16, and 20
Consultations	- one visit per month (±2 weeks)	
Blood samples	- blood sampling at each visit - BHCG (plasmatic or urinary) at baseline	- Serum concentration of anti-TNF at week 22 - BHCG (urinary) at each visit during treatment and monthly until 6 months after the end of treatment
Imaging	- ECG: before starting treatment - Chest X Ray before starting treatment - Central nervous system and/or medullar MRI and/or Echocardiography, troponin, cardiac MRI and/or Angio CT scan or MRI, and vascular doppler US at week 12 and 22	- Collect anonymous cardiovascular and neurologic imaging at baseline, week 12 and 22.
Others		- QOL questionnaires at D0, 12 and 22 weeks

1.18 Termination and exit rules

Criteria and procedures for prematurely terminating the study treatment

1.18.1 Different situations

- -
- Temporary suspension of treatment: the investigator must document the reason for suspending and resuming the treatment in the subject's source file and the case report form (eCRF)
- Premature termination of treatment, but the subject remains enrolled in the study until the end of the subject's participation: the investigator must document the reason
- Premature termination of treatment and exit from the study.

The investigator must:

- Document the reason(s)

- Collect all endpoints at the moment the subject exits from the study, if the subject agrees
- Schedule further follow-up visits, especially in case of a serious adverse event.

1.18.2 Criteria and procedure for premature withdrawals and exits from the study

- Subjects may exit the study at any time and for any reason.
- The investigator can temporarily or permanently withdraw a subject from the study for any safety reason or if it is in the subject's best interests.

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

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

- The case report form must list the various reasons why the subject exited or was withdrawn from the study:
- Lack of efficacy
- Adverse reaction
- Other medical problem
- Subject's personal reasons
- Explicit withdrawal of consent
- Lost to follow-up

Monitoring subjects after the premature termination of treatment

If a subject exits the trial this will in no way affect the standard care received for his/her condition.
In case of severe adverse events, the investigator must notify the sponsor and monitor the subject for 12 months following the premature termination of treatment. If treatment is stopped prematurely due to a serious adverse event, a serious adverse event notification form will be sent by fax (01 44 84 17 99) to the sponsor. The serious adverse reaction will be monitored until it is resolved.
The Data Monitoring Committee can specify and/or validate the monitoring methods.

Full or partial cancellation of the study

AP-HP as sponsor or the Competent Authority (ANSM) can prematurely terminate all or part of the research, temporarily or permanently, upon the recommendation of a data monitoring Committee 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, AH-HP, as the sponsor, or the Competent Authority (ANSM) may prematurely cancel the trial due to the discovery of unexpected facts 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 the sponsor, reserves the right to permanently suspend enrolment at any time if the enrolment targets have not been met.

If the study is cancelled prematurely, AP-HP will inform the Competent Authority (ANSM) and the Institutional Review Board of its decision within 15 days, together with justification for the decision and any recommendations from the Data Monitoring Committee.

ELIGIBILITY CRITERIA

1.19 Inclusion criteria

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

1. Age ≥ 12 years old
2. Written inform consent (Informed Consent should be obtained from the legal guardian in accordance with regional laws or regulations for patients 12 to 17 years of age)
3. Diagnosis of BD according to international criteria for BD (ICBD) (see Appendix 1).
4. Life threatening active BD defined as 1 of the following disease categories and according to the validated international definition:

- Major vessel disease: arterial aneurysms or arterial stenosis, myocarditis and/or major deep vein thrombosis (i.e. inferior vena cava, superior vena cava, cardiac cavity thrombosis, pulmonary embolism, supra-hepatic vessels, renal and mesenteric vessels). Diagnosis of major vessel involvement will be done using vascular doppler sonography, echocardiography, angio-CT scan and/or cardiac magnetic resonance imaging (MRI).
- Central nervous system involvement: encephalitis or meningoencephalitis or myelitis. The diagnosis of neuro-Behçet's (CNS involvement) will be based on objective neurological symptoms that were associated with neuroimaging (CNS and/or medullar MRI) findings suggestive of BD-related CNS involvement. Cerebrospinal fluid (CSF) findings showing aseptic inflammation may be associated.

6. Chest X-ray results (postero-anterior and lateral) within 12 weeks prior to inclusion with no evidence of active Tuberculosis, active infection, or malignancy
7. For female subjects of child-bearing age, a negative pregnancy test
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 6 months after stopping therapy. Adequate contraceptive measures include hormonal methods used for two or more cycles prior to Inclusion (e.g., oral contraceptive pills, contraceptive patch, or contraceptive vaginal ring), barrier methods (e.g., contraceptive sponge, diaphragm used in conjunction with contraceptive foam or jelly, or condom used in conjunction with contraceptive foam or jelly), intrauterine methods (IUD), sterilization (e.g., tubal ligation or a monogamous relationship with a vasectomized partner), and abstinence.
9. A potential subject with a positive interferon-gamma release assay (IGRA) (e.g., QuantiFERON®-TB Gold or T-spot TB® Test) or a positive tuberculin skin test (≤6 months) 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.
10. HIV negative serology and negative HBs Ag test (≤1 month)

1.20 Exclusion criteria

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

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

1. Evidence of active Tuberculosis
2. HIV or active HBV infection (HBs Ag+).
3. Pregnancy or lactation
4. Have been taking an oral daily dose of a glucocorticoid of more than 20 mg prednisone equivalent for more than 6 weeks continuously prior to the inclusion visit or taking more than 3000 mg methylprednisolone 4 weeks prior to the inclusion visit
5. Alcohol or drug dependance
6. Severe renal (creatinine clairance <30ml/min/1,73m2) or pre-existing hemorrhagic cystitis or liver insufficiency (hepatic encephalopathy) or urinary obstruction
7. Heart failure ≥ stage III / IV NYHA,
8. History of malignancy within 5 years prior to Inclusion other than carcinoma in situ of the cervix or excised basal cell or squamous cell carcinoma of the skin.
10. History of multiple sclerosis and/or demyelinating disorder
11. History of severe allergic or anaphylactic reactions to cyclophosphamide or infliximab
12. Infectious disease:

- Infection requiring treatment with intravenous antibiotics within 2 weeks prior to Inclusion
- History of recurrent infection

14. Laboratory values assessed during Inclusion:

- Hemoglobin < 8 g/dL
- WBC < 2.0 x 103/mm3
- Platelet count < 70 x 103/mm3

15. Use of the following systemic treatments during the specified periods:

- Treatment with systemic biologic therapy or with cyclophosphamide within 3 months prior to Inclusion
- if on azathioprine, mycophenolate mofetil, or methotrexate at the time of inclusion, these drugs must be withdrawn prior to receiving the cyclophosphamide or infliximab dose on Day 1

16. Any live (attenuated) vaccine within 4 weeks prior inclusion; recombinant or killed virus vaccines are permitted.
17. Lack of affiliation to a social security benefit plan (as a beneficiary or assignee). Patients affiliated to universal medical coverage (CMU) are eligible for the study

1.21 Recruitment methods

The French national reference center for rare systemic and autoimmune 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 1000 patients. 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 [20]. 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 and autoimmune diseases. We are working in close collaboration with French neurologist, cardiologist and vascular surgeon including those from Pitie Salpetriere hospital, in Paris.

	Number of subjects
Total number of subjects to be included	*52*
Number of centres	*28*
Inclusion period (months)	*36*
Number of subjects/centre	*1.8*
Number of subjects/centre/month	***0.07***

TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

1.22 The investigational medicinal product(s)

Investigational medicinal product 1

Arm A

Infliximab (Remicade®), powder for concentrate for solution for infusion, 5mg/kg intravenously for 3 hours in 250 ml of physiologic serum (0.9%) at week 0, 2, 6, 12, and 18. A systematic premedication with paracetamol 1g and polaramin 5mg will be prescribed. **All patients will be followed 1 to 2 hours after the infusion to ensure the absence of hypersensibility reaction. Emergency equipment will be mandatory.**

Investigational medicinal product 2

Arm B

Cyclophosphamide (0.7g/m^2 up to 1.2 g/m^2) intravenously for 1 hour with 500 ml of physiologic serum (0.9%) at week 0, 4, 8, 12, 16, and 20. Associated medications will include orally or intravenously ondansetron or another setron, and mesna (Uromitexan®) at hours 0, 4 and 8.

1.23 Additional medicinal products (treatments required for the trial)

Additional medicinal product 1

Corticosteroids

All patients will receive the same corticosteroid regimen. All patients will have at Inclusion/randomisation visit an oral prednisone at 1 mg/kg/day (up to 80 mg/day).

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

- Week 4 : 0.8mg/kg/day
- Week 6: 0.7mg/kg/day
- Week 8 : 0.6mg/kg/day
- Week 10 : 0.5mg/kg/day
- Week 12 : 0.4mg/kg/day
- Week 14: 0.3mg/kg/day
- Week 16: 0.2mg/kg/day
- Week 22 : ≤0.1mg/kg/day

For patients with a positive interferon-gamma release assay (IGRA) (e.g., QuantiFERON® -TB Gold or T-spot TB® Test) or a positive tuberculosis skin test before inclusion and receiving rifampicin (300mg/day) and isoniazid (150mg/day) (prophylactic TB treatment) for 3 months the prednisone dosage will be increase of 20% (due to interaction between isoniazid and prednisone) during the prophylactic TB treatment period (i.e 3 months).
In severe pediatric form of BD the dose and frequencies of administration of steroids, cyclophosphamide and infliximab are similar to those used in adult's patients [31,32].

- ***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

Additional medicinal product 2

A systematic premedication with paracetamol 1g *will be prescribed* in accordance with SmPC *in association with infliximab*. *This drug may cause* an allergic reaction, which can cause a rash and swelling, and flushing, thrombocytopenia and leukopenia. In case of overdose liver failure may arise.

Additional medicinal product 3

Polaramin 5mg will be prescribed in accordance with SmPC in association with infliximab. . This drug may cause nausea, rash, blurred vision, chest tightness, chills, constipation, coordination impaired, dizziness, dry nose, difficulty in urination, early menstrual periods, headache, loss of appetite, nasal congestion, sedation, sleepiness, frequent urge to urinate, vertigo, wheezing, dry mouth,and fatigue.

1.23.1 Additional medicinal product 4

Ondansetron or another setron will be prescribed in accordance with SmPC, in association with cyclophosphamide. This drug may cause headache, fatigue, constipation, diarrhea, dizziness, rash and flushing.

Additional medicinal product 5

Mesna (Uromitexan®) per os or IV will be prescribed in accordance with SmPC, in association with cyclophosphamide at hour 0, 4 and 8. Isolated cases of partially hypersensitivity reactions (itching, redness, vesiculation), local tissue swelling (urticarial oedema), rare cases of drop in blood pressure and tachycardia due to severe anaphylactoid reactions, and also a transient rise in certain liver function tests (transaminases) have been reported.

Additional medicinal product 6

Rifampicin (300mg/day) (prophylactic TB treatment) will be prescribed for 3 months in case of latent tuberculosis. This drug may cause upset stomach, heartburn, nausea, headache, drowsiness, or dizziness. This medication may produce a reddish coloration of urine, sweat, saliva, or tears. Soft contact lenses may be permanently stained.
Rifampin may rarely cause elevation of transaminases.

Additional medicinal product 7

Isoniazid (150mg/day) (prophylactic TB treatment) will be prescribed for 3 months in case of latent tuberculosis. This drug may cause clumsiness or unsteadiness, dark urine, loss of appetite, nausea or vomiting, numbness, tingling, burning, or pain in hands and feet, skin rash, unusual tiredness or weakness and elevation of transaminases.

1.24 Traceability information for the investigational medicinal product(s)

7.3.1. Origins and storage conditions :

- **Infliximab**

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

- **Cyclophosphamide**

Origin : supply and labelling by DEC-AGEPS
Storage : Do not store above 25°C.

7.3.3 Reconstitution of investigational drugs

The hospital pharmacy will be in charge of reconstitution of the IMP.
Infusion bags will be prepared by the hospital pharmacy with respect to patient's randomization group.

The preparation of infusion will be made in accordance with the SMPC :

- **Infliximab**

Infliximab infusion will be prepared with 250 ml of physiological serum (0.9%).

- **Cyclophosphamide**

Cyclophosphamide infusion will be prepared with 500 ml of physiologic serum (0.9%)

Each bag will be labelled with all mandatory mentions), and its shelf life.
Infusion bags should be stored between 2 and 8°C until administration.

7.3.4 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.

7.3.5 Administration and follow up

Each administration should be recorded on a specific traceability document.

Infliximab and cyclophosphamide should be administered under the close supervision of an experienced healthcare professional, and in an environment where full resuscitation facilities are immediately available, after premedication.

7.3.6. Methods for monitoring compliance with the treatment

Infliximab and cyclophosphamide will be administered intravenously and will be easily monitored for compliance.

7.3.7. Accountability and destruction

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

1.25 Authorised and prohibited treatments (medicinal, non-medicinal, surgical), including emergency medications

Authorised treatments

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

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

- a potassium supplement (DIFFU K, 1 capsule 3 times/day)

- a calcium/vitamin D supplement (CACIT D3, 1 g/day)
- a bisphosphonate, in the absence of contra-indications, either Actonel (risedronate) at 35 mg/week or Fosamax (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.

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

Prohibited treatments

Immununosuppressive or immunomodulatory therapies (azathioprine, mycophenolate mofetil, methotrexate, ciclosporin, tacrolimus, plaquenil) are contraindicated during treatment by investigational medicinal product(s)
Any live (attenuated) vaccine is contraindicated for the duration of the study.

EFFICACY ASSESSMENT

1.26 Description of parameters for assessing efficacy endpoints

- ***Complete clinical remission***

The complete clinical response will be defined by the remission of all affected organs involved at baseline and the absence of clinical relapse.

- **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) [17].
- **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) [18].
- **Remission of neurological involvement** is defined as a complete clinical, and imaging (as evaluated by MRI) remission, biologically (normalization of inflammatory syndrome) and the absence of neurological sequelae (defined as a Rankin score $\leq$1) [3].
- **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). 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 grading [19] associated with 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.

- ***Treatment failure***

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

- Death related to persistent disease activity

- Lack of remission at 1 month. Such a patient will be considered an early treatment failure (treatment resistant) and included in the intention to treat analysis. They will receive ongoing clinical care according to good medical practice.
- A severe disease flare which requires (additional) immunosuppressive therapy and/or increased doses of corticosteroids. These patients will be considered treatment failures and included in the intention to treat analysis. They will receive ongoing clinical care according to good medical practice.
- Inability to tolerate decreasing doses of corticosteroids at the M1, M3 or M6 (steroid discontinuation) visits because of persistent or recurrent disease.
- Relapse of disease activity

- Relapse

A relapse is defined by the reappearance of at least one of the following activity criteria:
- Relapse of cardiovascular, neurological or ocular clinical manifestations of Behçet's disease
- Typical imaging features: new vascular or neurological lesions (in previously unaffected territories) or the progression of preexisting lesions detected on serial imaging studies.

SPECIFIC COMMITTEES FOR THE TRIAL

1.27 Scientific Committee

This committee will consist of the Coordinating Investigator (Pr Saadoun CHU Pitié-Salpétrière), a representative of the associated centers (Pr Gilles Kaplanski, CHU La Conception, Marseille), and a representative of the sponsor (Pr Mathieu Resche Rigon, 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.

1.28 Steering Committee

Members: Coordinating Investigator, one of more other investigators, biostatistician, the sponsor's appointed representatives for the trial.

- Members of the committee: Pr D Saadoun, Pr M Resche-Rigon, N Raked, H Mebarek.
- Missions:*Define the overall structure of the study, coordinate information, determine the initial methodology and oversee the trial.*
- Operating procedures: *Propose procedures to be followed every 6 months during the study, acknowledging any recommendations from the Data Monitoring Committee. The sponsor retains the decision-making authority.*

1.29 Endpoint Adjudication Committee

This committee will have the role of validating under blind conditions the following assignments: complete remission, treatment failure and relapse of the disease. It will consist of persons external to the Study: Physicians specializing in the pathology under consideration: Prof B Wechsler (Pitié-Salpétrière Hospital). Radiologist: Dr S Boussouar (Pitié-Salpétrière Hospital) and Dr D Leclercq (Pitié-Salpétrière Hospital). It will meet at the end of the study. The will reviewed cardiovascular and neurological imaging collected anonymously at baseline, and at week 12 and 22.

SAFETY ASSESSMENT - RISKS AND RESTRICTIONS ADDED BY THE STUDY

1.30 Recording and reporting adverse events

Definitions

According to Article R1123-46 of the French Public Health Code:
Adverse event
Any untoward medical occurrence in a trial subject, which does not necessarily have a causal relationship with the clinical trial or with the investigational product.

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

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

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

According to Article R.1123-46 of the Code de la Santé Publique and the guidelines for clinical trial sponsors (ANSM):

Emerging safety issue
Any new safety information that may lead to a reassessment of the risk/benefit ratio of the trial or the investigational medicinal product, modifications in the investigational medicinal product use, the conduct of the clinical trial, or the clinical trial documents, or a suspension, interruption or modification of the protocol of the clinical trial or other similar trials..
For the clinical trials involving the first administration or use of an investigational medicinal product in healthy volunteers, any serious adverse reaction.
Examples:
a) any clinically significant increase in the frequency of an expected serious adverse reaction
b) suspected unexpected serious adverse reactions in patients who have terminated their participation in the clinical trial that are notified by the investigator to the sponsor together with follow-up reports
c) any new safety issue relating to the conduct of the clinical trial or the development of the investigational medicinal product, that may impact the safety of the trial subjects.
Examples:
- a serious adverse event likely to be related to the interventions and the trial’s diagnostic procedures and which may impact the conduct of the clinical trial,
- a significant risk on the trial subjects such as ineffectiveness of the investigational medicinal product in treating a life-threatening illness under investigation,

- significant safety results from a recently completed non-clinical study (such as a carcinogenicity study),
- the premature termination, or temporary suspension, of a trial conducted on the same investigational medicinal product in another country, for safety reasons,
- an unexpected serious adverse reaction associated with a non-experimental medication required for the conduct of the clinical trial, (e.g. challenge agents, rescue treatment)
d) recommendations from the Data Safety Monitoring Board (DSMB), if applicable, that may affect the safety of the trial subjects
e) any suspected unexpected serious adverse reaction (SUSAR) reported to the sponsor by another sponsor of a trial carried out in a different country but relating to the same medication.

The role of the investigator

The investigator must notify the sponsor, **immediately on the day when the investigator becomes aware**, of all the serious adverse events, except those that are listed in the protocol (see. section 10.3.3.1) or in the investigator's brochure as not requiring immediate notification.

These serious adverse events are recorded in the "adverse event" section of the case report form and the investigator must immediately notify the sponsor's Vigilance division (see 10.3.4).

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

- The investigator assesses the severity of the adverse events by using the *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 the study procedure(s).

The method used by the investigator is based on the WHO Uppsala Monitoring Centre method and uses the following causality terms:

- Certain
- Probable/likely
- Possible
- Unlikely (not ruled out).

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

Specific features of the protocol

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

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

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

*All points should be reasonably complied with

** Or study procedures

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

As per article R.1123-49 of the French Public Health Code (CSP), the investigator must notify the sponsor **without delay on the day when the investigator becomes aware** of any serious adverse event which occurs during a trial as described in Article L.1121-1(1) CSP, except those which are listed in the protocol (see section xxx) and, if applicable, in the investigator's brochure as not requiring a notification without delay.

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

1.30.1.2 Specific features of the protocol

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

- Adverse events judged as being "medically significant"

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

- Adverse events of particular interest

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

- **In utero** exposure

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

Notification is required if the exposure involves:
- the mother,
- the father if the experimental medication is genotoxic.

- Exposure **via breastfeeding**

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

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

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

The common side effects of infliximab are:
- Gastrointestinal toxicity : abdominal or stomach pain, nausea, vomiting, diarrhea (< grade 3)
- Hypersensitivity reaction: fever, chills, chest pain, flushing of the face, nasal congestion (< grade 3)
- Skin rash (< grade 3)
- Headache(< grade 3)
- Dizziness(< grade 3)
- Upper respiratory tract and urinary tract infections
- Cytopenias (leucopenia and neutropenia, lymphopenia, thrombocytopenia, anemia) (< grade 3)

- Elevation of liver enzymes, GGT, bilirubin (< grade 3)

The common side effects of cyclophosphamide are:
- Gastrointestinal toxicity: nausea, vomiting, anorexia, abdominal or stomach pain, mucositis, diarrhea (< grade 3)
- Hypersensitivity reaction: fever, chills, chest pain, flushing of the face, nasal congestion (< grade 3)
- Cytopenias (leucopenia and neutropenia, lymphopenia, thrombocytopenia, anemia) (< grade 3)
- Elevation of liver enzymes, GGT, bilirubin (< grade 3)
- Hair loss (< grade 3)

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)
- Relapse:

A relapse is defined by the reappearance of at least one of the following activity criteria:
- Relapse of cardiovascular, neurological or ocular clinical manifestations of Behçet's disease
- Typical imaging features: new vascular or neurological lesions (in previously unaffected territories) or the progression of preexisting lesions detected on serial imaging studies.

- Treatment failure

Changes in therapy may be required in case of treatment failure which will be defined by the presence of at least one of the following:
- Death related to persistent disease activity
- Lack of remission at 1 month. Such a patient will be considered an early treatment failure (treatment resistant) and included in the intention to treat analysis. They will receive ongoing clinical care according to good medical practice.
- A severe disease flare which requires (additional) immunosuppressive therapy and/or increased doses of corticosteroids. These patients will be considered treatment failures and included in the intention to treat analysis. They will receive ongoing clinical care according to good medical practice.
- Inability to tolerate decreasing doses of corticosteroids at the M1, M3 or M6 (steroid discontinuation) visits because of persistent or recurrent disease.
- Relapse of disease activity
- **Relapse and treatment failure do not require the investigator to notify the sponsor without delay. However, these serious adverse events are recorded in the case report form and a CRF extraction of these serious adverse events will be realized every 3**

months by clinical research unit and transmitted to Vigilance department at expertisecsi.drc@aphp.fr

Special circumstances

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

- *Adverse events during the trial possibly related with the treatments prescribed as part of the patient's standard care*

The investigator must report these events to his *Centre Régional de Pharmacovigilance* (CRPV).

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

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

- starting from the date on which the subject signs the consent form
- throughout the whole follow-up period intended by the trial
- 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)

1.30.1.4 Procedures and deadlines for notifying the sponsor

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

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

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

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

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

The reception of the SAE form to the vigilance department is centralized to allow immediate processing of SAE as soon as they are received. The initial SAE notification, the SAE monitoring reports and any other document will be sent to the sponsor represented by its Vigilance department by fax (+33 1 44 84 17 99). It is possible to transmit the SAE form to the Vigilance department by e-mail (eig-vigilance.drc@aphp.fr) **only in case of unsuccessful attempt** to send the SAE form by fax.

NB: Do not transmit by e-mail the documents initially successfully transmitted by fax to avoid duplication.

For trials which use e-CRF
- the investigator completes the SAE report form in the e-CRF, then validates, prints and signs the form before sending it by fax;
- In case of failure to connect to the e-CRF, the investigator should complete, sign and send the SAE report form to the safety Department. As soon as the connection is restored, the investigator must complete the SAE report form in the e-CRF.

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

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

Special rules for trials involving the administration of a radioactive product (e.g. PET scan): if a subject develops secondary cancer/cancer or develops a hereditary deficiency following exposure to ionising radiation, the investigator shall complete the special form for reporting cancer

Role of the sponsor

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

1.30.1.5 Analysis and declaration of serious adverse events

The sponsor assesses:
- the **seriousness** of all reported adverse events,
- the **causal relationship** between these adverse events and investigational medicinal product and/or study procedures and any other treatments,
  All serious adverse events for which the investigator and/or the sponsor suspect a causal relationship with the investigational medicinal product are classed as suspected serious adverse reactions.
- the **expectedness assessment** of the serious adverse reactions
  Any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the summary of product characteristics, or in the investigator's brochure if the product is not authorised, is considered unexpected.
  The sponsor, acting through its safety Department, assesses the expectedness of the serious adverse reaction based on the information described below**.**

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

- refer to the SmPC for Infliximab and Cyclophosphamide

❖ For serious adverse events likely to be related to additional medicinal products (treatments required for the trial):

- refer to the SmPC for Prednisone, Polaramin®, Uromitexan®, Zofran®, and the specialities of paracetamol, isoniazid and rifampicin administred.

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

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

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

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

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

Specific rules for serious adverse events of special interest The sponsor may be required to declare serious adverse events of special interest, with the same procedures and within the same timelines as for SUSARs.

1.30.1.6 Analysis and declaration of other safety data

This relates to any new safety data that may lead to a reassessment of the risk/benefit ratio of the trial or the investigational medicinal product, modifications in the investigational medicinal product use, the conduct of the clinical trial, or the clinical trial documents, or a suspension, interruption or modification of the protocol of the clinical trial or other similar trials.
[Include or delete the following paragraph as applicable] For the clinical trials involving the first administration of a medicinal product in healthy volunteers, emerging safety issue is defined as all serious adverse reactions occurring in trial subjects.

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

Following the initial declaration of emerging safety issue, the sponsor will declare to ANSM any additional relevant information about the new 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.

1.30.1.7 Annual safety report

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

- cumulative summary tabulation of all the serious adverse events that have occurred since the beginning of the clinical trial,

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

Data Safety Monitoring Board (DSMB)

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

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

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

<u>General information about the DSMB</u>
The DSMB makes recommendations to the sponsor about the continuation, modification or termination of the research. The recommendations that the DSMB can make are:

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

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

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

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

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

- Validation of the research methodology:

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

- nature of the evaluated parameters
- frequency of the evaluations, consultation schedule

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

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

DATA MANAGEMENT

Data collection

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

1.32 Right to access source data and documents

1.32.1.1 Access to data

In accordance with GCP:
- 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.
- the investigators will ensure the persons in charge of monitoring and auditing the clinical trial and of quality control have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

1.32.1.2 Source documents

The source documents are any original document or item that proves the existence or accuracy of a data-point or fact recorded during the trial. Source documents will be kept by the investigator, or by the hospital in the case of hospital medical records, for the statutory period.

List the types of source documents relevant to the trial (medical files, original laboratory test results, medical imaging reports, etc.).

1.32.1.3 Data confidentiality

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the French Public Health Code) will take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular the identity of the participants and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the French Criminal Code).
During and after the clinical study, all data collected about the study participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be anonymised.
Under no circumstances will the names and addresses of the subjects be shown.
Only the subject's initials will be recorded, along with an identification code specific to the study indicating the order of enrolment.
The sponsor will ensure that each subject has agreed in writing for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

1.33 Data processing and storage of documents and data

Identification of the data processing manager and the location(s)

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

Data entry

Data entry will be carried out on electronic media 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”.

Archiving

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

This indexed archival includes, in particular:

- A sealed envelope containing the original copies of all information sheets and consent forms signed for all individuals at the centre that participated in the research for the investigator
- A copy of all the information notes and consent forms signed for all subjects at the centre that participated in the research for the sponsor

- "Research" binders for the Investigator and the sponsor, including:
  - the successive versions of the protocol (identified by the version no. and date), and the appendices
  - the ANSM authorisations and CPP favourable opinions
  - letters of correspondence
  - the inclusion list or register
  - the appendices specific to the research
  - the final research report
- The data collection documents

1.34 Ownership of the data

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

The computer file used for this research is implemented in accordance with the French (loi Informatique et Libertés modifiée) and European (General Data Protection Regulation - GDPR) regulations.

Commitment to compliance with the MR 001 "Méthodologie de Reference"
This study falls under the framework of the "Reference Methodology for personal data processing operated in the context of research" (MR-001 modified). As study sponsor, the AP-HP has signed a commitment to comply with this "Reference Methodology"

STATISTICAL ASPECTS

1.35 Planned statistical methods, including the timetable for any planned interim analyses

This is a Bayesian Phase II randomized clinical trial that aims at evaluating the best treatment strategy of severe Behçet's disease, based on difference in the response rate as measured at week 22 after randomization.

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 chose 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 (as described below).

1.36 Hypotheses for calculating the required number of subjects, and the result

Given the uncertainty in the infliximab benefit over cyclophosphamide in severe Behçet's disease 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. Based on binomial distributions under the assumed response rate of the control arm (here, p=0.70), this allowed to randomly allocate two groups of 26 patients to detect a 0.15 difference in response rates with a 0.90 probability. This appeared preferable to planning a trial on hypotheses either non-consistent with the literature based on a too pejorative success rate on control arm, or overoptimistic regarding the expected effect size in the experimental arm.

1.37 In the case of a comparative randomised study, the calculation is based on a hypothesis of a difference between the two groups for the primary endpoint, and is a function of the accepted ALPHA and BETA risks, of the uni-or bilateral formulation and of the variance (in the case of a quantitative variable).

Given the uncertainty in the infliximab benefit over cyclophosphamide in severe Behçet's disease 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. Based on binomial distributions under the assumed response rate of the control arm (here, p=0.70), this allowed to randomly allocate two groups of 26 patients to detect a 0.15 difference in response rates with a 0.90 probability. This appeared preferable to planning a trial on hypotheses either non-consistent with the literature based on a too pejorative success rate on control arm, or overoptimistic regarding the expected effect size in the experimental arm.

1.38 State whether subjects who exit the study prematurely will be replaced and in what proportion.

All patients withdrawn will be considered as treatment failures.

1.39 Anticipated level of statistical significance

1.40 Statistical criteria for termination of the study.

An interim analysis will be performed once one-half of the projected numbers of patients have been recruited into the study. It will use a Beta-Binomial model with a non-informative prior (Berry 2006). The posterior probability that the response rate is at least 0.70, and that the rate of response in the experimental arm is above that observed in the control will be computed.

We will use a Bayesian inference framework, where $\pi_k = P(Y = 1|A = k)$ denotes the probability of response in the arm A=k (k=1,2). Using a beta Be(a_k, b_k) prior for π_k, the posterior probability of π_k is still a beta distribution given by Be(a_k+y_k, b_k+$n_k - y_k$) due to the natural conjugate property of the beta family for binomial sampling.
In our setting, the inefficacy of the drug will be first assessed by comparison to some historical minimal value of interest, sometimes called the "minimum required treatment response rate". It has been set at 0.70 in this trial. Thus, we will compute for each arm:

$$P(\pi_k < 0.70 | y_{ki}, n_{ki}) \quad (1)$$

However, in randomized phase II settings, the selection of a new drug is mostly based on evaluating the potential benefits of the experimental treatment over the control arm (Whitehead 2014). 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 control by some targeted minimal level. This will be done by computing the value of the posterior probability of the difference in response rates between the experimental arm and the control (Xie 2012):

$$P(\pi_k - \pi_0 > \Delta | y_{ki}, n_{ki}) \quad (2)$$

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

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

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

All modifications of the initial plan will be submitted.

1.43 Selection of populations

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

QUALITY CONTROL AND ASSURANCE

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

1.44 General organisation

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the trial. The sponsor must have a quality assurance system for monitoring the implementation of the study at the research centres.

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

- the research subjects are safe, protected and their rights are being met
- the data being recorded is accurate, complete and consistent with the source documents
- the study is carried out in accordance with the current version of the protocol, with GCP and with all statutory and regulatory requirements.

Strategy for site opening

The strategy for opening the centres established for this research is determined using the appropriate monitoring plan. It will be performed by the CRA from the URC-DRC from Saint Louis hospital.

Scope of site monitoring

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

1.45 Quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the proper running of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI and in accordance with Good Clinical Practice as well as with 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 by the Clinical Research Associate. During these visits, the following elements will be reviewed:

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

1.46 Case Report Form

Electronic CRF:

All information required by the protocol must be entered in the case report forms. The data must be collected as and when it is 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 instructions for using this tool.

Using on-line case report forms means 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, there are consistency checks to ensure the data are verified immediately upon being entered. 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. A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the study. The investigator must archive a copy of the authenticated document that was delivered to the sponsor.

1.47 Management of non-compliances

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

The sponsor has its own procedures for managing these non-compliances.

1.48 Audits/inspections

The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. These audits and inspections cannot be refused on the basis of medical secrecy.

An audit can be carried out at any time by independent individuals appointed by the sponsor. 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 trial 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 and the storage of the data used or produced as part of the study.

1.49 Principal Investigator's declaration of responsibility

Before starting the trial, each investigator will give the sponsor's representative a signed and dated copy of his/her curriculum vitæ and RPPS number (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals).

Each investigator will agree to comply with legislation and to conduct the trial in line with GCP, in accordance with the Declaration of Helsinki.

The Principal Investigator at each participating site will sign a declaration of responsibility (standard DRCI document) which will be sent to the sponsor's representative.
The investigators and their co-workers will sign a delegation form specifying each person's role.

ETHICAL AND LEGAL CONSIDERATIONS

1.50 Methods for informing and obtaining consent from the research participants

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

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

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

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

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

1.51 Prohibition of concomitant clinical studies participation and exclusion period after the trial, if applicable

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

Whilst participating in this trial, subjects may not take part in any other clinical study without first speaking to the doctor in charge of this trial.

1.52 Legal obligations

The sponsor's role

Assistance Publique Hôpitaux de Paris (AP-HP) is the sponsor of this study and has delegated powers to its Clinical Research and Innovation Delegation (DRCI) in order to conduct the study in accordance with Article L.1121-1 of the French Public Health Code. AP-HP reserves the right to terminate the study at any time for medical or administrative reasons. In this case, the investigator will be informed accordingly.

1.53 Request for approval from the Institutional Review Board

AP-HP, as sponsor, obtains prior approval from the Institutional s Review Board for its clinical trials of medicinal products for human use, within the scope of the Board's authority and in accordance with statutory and regulatory requirements.

1.54 Request for approval from the ANSM

AP-HP, as sponsor, obtains prior authorisation from the ANSM for its clinical trials of medicinal products for human use, within the scope of the ANSM's authority and in accordance with statutory and regulatory requirements.

1.55 Modifications to the trial

Any substantial amendment made to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, prior to implementing the amendment, approval from the Institutional Review Board and authorisation from the ANSM, within the scope of their respective authorities.
The information sheet and the consent form can be revised if necessary, in particular if there is substantial amendment to the study or if adverse reactions occur.

1.56 Final study report

The final study report referred to in CSP Article R.1123-67 is written and signed by the sponsor and the investigator. A report summary, meeting the competent authority’s guidelines, has to be sent to the competent authority and Institutional Review Board within one year of the end of the trial i.e. the end of the participation of the last study participant..

FUNDING AND INSURANCE

1.57 Insurance

For the duration of the research, the Sponsor will take out an insurance policy covering the sponsor's own civil liability as well as the civil liability of all the doctors involved in carrying out the research. The sponsor will also provide full compensation for all harmful consequences of the research for the research subjects and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any agent. The act of a third party or the voluntary withdrawal of the person who initially consented to participate in the research cannot be invoked against said compensation.

Assistance Publique- Hôpitaux de Paris (AP-HP) has taken out insurance from HDI-GERLING through BIOMEDIC-INSURE for the full research period, covering its own civil liability and that

of any agent (doctor or research staff), in accordance with Article L.1121-10 of the French Public Health Code.

PUBLICATION

The author(s) of any publication relating to this study must include the AP-HP among their affiliations and 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 the sponsor and funders).

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

- If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is not important
- However, if the trial is funded by an internal call for tenders at the AP-HP, the first affiliation must be "AP-HP"
- Each of these affiliations must be identified by an address and separated by a semicolon
*- The AP-HP institution must feature under the acronym "**AP-HP**" first in the address, specifically followed by: **AP-HP**, hospital, department, city, postcode, France*

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

- "The sponsor was *Assistance Publique – Hôpitaux de Paris* (Department of Research and Clinical Innovation)"

1.60 Mention of the funder in the acknowledgements of the text

- *The study was funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC 2016 (Ministry of Health)*

This study has been registered on the http://clinicaltrials.gov/ website under *registration number* NCT03371095

BIBLIOGRAPHY

1. Saadoun D, Wechsler B, Desseaux K, Le Thi Huong D, Amoura Z, Resche-Rigon M, Cacoub P. Mortality in Behcet's disease. Arthritis Rheum 2010;62:2806-12.
2. Sakane T, Takeno M, Suzuki N, Inaba G. Behcet's disease. N Engl J Med 1999;341:1284-91.
3. Noel N, Bernard R, Wechsler B, Resche-Rigon M, Depaz R, Boutin DL, Piette JC, Drier A, Dormont D, Cacoub P, Saadoun D. Long-Term Outcome of Neuro-Behcet's Disease. Arthritis Rheum 2014.
4. Saadoun D, Asli B, Wechsler B, Houman H, Geri G, Desseaux K, Piette JC, Huong DL, Amoura Z, Salem TB, Cluzel P, Koskas F, Resche-Rigon M, Cacoub P. Long-Term Outcome of Arterial Lesions in Behcet Disease: A Series of 101 Patients. Medicine (Baltimore) 2012;91:18-24.
5. Le Thi Huong D, Vidailhet MJ, Wechsler B, Piette JC, Ziza JM, Chapelon C, Bletry O, Godeau P. [Value of the cyclophosphamide bolus in severe systemic diseases. Preliminary results]. Presse Med 1988;17:524-7.
6. Hamuryudan V, Er T, Seyahi E, Akman C, Tuzun H, Fresko I, Yurdakul S, Numan F, Yazici H. Pulmonary artery aneurysms in Behcet syndrome. Am J Med 2004;117:867-70.
7. Seyahi E, Melikoglu M, Akman C, Hamuryudan V, Ozer H, Hatemi G, Yurdakul S, Tuzun H, Oz B, Yazici H. Pulmonary artery involvement and associated lung disease in Behcet disease: a series of 47 patients. Medicine (Baltimore) 2012;91:35-48.
8. Seyahi E, Yazici H. Behcet's syndrome: pulmonary vascular disease. Curr Opin Rheumatol 2015;27:18-23.
9. Hamuryudan V, Seyahi E, Ugurlu S, Melikoglu M, Hatemi G, Ozguler Y, Akman C, Tuzun H, Yurdakul S, Yazici H. Pulmonary artery involvement in Behcets syndrome: Effects of anti-Tnf treatment. Semin Arthritis Rheum 2015;45:369-73.
10. Hatemi G, Silman A, Bang D, Bodaghi B, Chamberlain AM, Gul A, Houman MH, Kotter I, Olivieri I, Salvarani C, Sfikakis PP, Siva A, Stanford MR, Stubiger N, Yurdakul S, Yazici H. EULAR recommendations for the management of Behcet disease. Ann Rheum Dis 2008;67:1656-62.
11. Melikoglu M, Fresko I, Mat C, Ozyazgan Y, Gogus F, Yurdakul S, Hamuryudan V, Yazici H. Short-term trial of etanercept in Behcet's disease: a double blind, placebo controlled study. J Rheumatol 2005;32:98-105.
12. Yazici H, Basaran G, Hamuryudan V, Hizli N, Yurdakul S, Mat C, Tuzun Y, Ozyazgan Y, Dimitriyadis I. The ten-year mortality in Behcet's syndrome. Br J Rheumatol 1996;35:139-41.
13. Akman-Demir G, Serdaroglu P, Tasci B. Clinical patterns of neurological involvement in Behcet's disease: evaluation of 200 patients. The Neuro-Behcet Study Group. Brain 1999;122 (Pt 11):2171-82.
14. Siva A, Kantarci OH, Saip S, Altintas A, Hamuryudan V, Islak C, Kocer N, Yazici H. Behcet's disease: diagnostic and prognostic aspects of neurological involvement. J Neurol 2001;248:95-103.
15. Remmers EF, Cosan F, Kirino Y, Ombrello MJ, Abaci N, Satorius C, Le JM, Yang B, Korman BD, Cakiris A, Aglar O, Emrence Z, Azakli H, Ustek D, Tugal-Tutkun I, Akman-Demir G, Chen W, Amos CI, Dizon MB, Kose AA, Azizlerli G, Erer B, Brand OJ, Kaklamani VG, Kaklamanis P, Ben-Chetrit E, Stanford M, Fortune F, Ghabra M, Ollier WE, Cho YH, Bang D, O'Shea J, Wallace GR, Gadina M, Kastner DL, Gul A. Genome-wide association study identifies variants in the MHC class I, IL10, and IL23R-IL12RB2 regions associated with Behcet's disease. Nat Genet 2010;42:698-702.
16. Geri G, Terrier B, Rosenzwajg M, Wechsler B, Touzot M, Seilhean D, Tran TA, Bodaghi B, Musset L, Soumelis V, Klatzmann D, Cacoub P, Saadoun D. Critical role of IL-21 in modulating TH17 and regulatory T cells in Behcet disease. J Allergy Clin Immunol 2011;128:655-64.

17. Geri G, Wechsler B, Thi Huong du L, Isnard R, Piette JC, Amoura Z, Resche-Rigon M, Cacoub P, Saadoun D. Spectrum of cardiac lesions in behcet disease: a series of 52 patients and review of the literature. Medicine (Baltimore) 2012;91:25-34.
18. Desbois AC, Wechsler B, Resche-Rigon M, Piette JC, Huong Dle T, Amoura Z, Koskas F, Desseaux K, Cacoub P, Saadoun D. Immunosuppressants reduce venous thrombosis relapse in Behcet's disease. Arthritis Rheum 2012;64:2753-60.
19. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol 2005;140:509-16.
20. Saadoun D, Wechsler B, Terrada C, Hajage D, Le Thi Huong D, Resche-Rigon M, Cassoux N, Le Hoang P, Amoura Z, Bodaghi B, Cacoub P. Azathioprine in severe uveitis of Behcet's disease. Arthritis Care Res (Hoboken) 2010;62:1733-8.
21. 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 Behcet disease. Br J Ophthalmol 2010;94:284-8.
22. Pipitone N, Olivieri I, Padula A, D'Angelo S, Nigro A, Zuccoli G, Boiardi L, Salvarani C. Infliximab for the treatment of Neuro-Behcet's disease: a case series and review of the literature. Arthritis Rheum 2008;59:285-90.
23. Desbois AC, Addimanda O, Bertrand A, Deroux A, Perard L, Depaz R, Hachulla E, Lambert M, Launay D, Subran B, Ackerman F, Mariette X, Cohen F, Marie I, Salvarini C, Cacoub P, Saadoun D. Efficacy of Anti-TNFalpha in Severe and Refractory Neuro-Behcet Disease: An Observational Study. Medicine (Baltimore);95:e3550.
24. Schreiber BE, Noor N, Juli CF, Haskard DO. Resolution of Behcet's syndrome associated pulmonary arterial aneurysms with infliximab. Semin Arthritis Rheum 2011;41:482-7.
25. Vallet H, Riviere S, Sanna A, Deroux A, Moulis G, Addimanda O, Salvarani C, Lambert M, Bielefeld P, Seve P, Sibilia J, Pasquali J, Fraison J, Marie I, Perard L, Bouillet L, Cohen F, Sene D, Schoindre Y, Lidove O, Le Hoang P, Hachulla E, Fain O, Mariette X, Papo T, Wechsler B, Bodaghi B, Rigon MR, Cacoub P, Saadoun D. Efficacy of anti-TNF alpha in severe and/or refractory Behcet's disease: Multicenter study of 124 patients. J Autoimmun 2015;62:67-74.
26. Iwata S, Saito K, Yamaoka K, Tsujimura S, Nawata M, Suzuki K, Tanaka Y. Effects of anti-TNF-alpha antibody infliximab in refractory entero-Behcet's disease. Rheumatology (Oxford) 2009;48:1012-3.
27. Mege JL, Dilsen N, Sanguedolce V, Gul A, Bongrand P, Roux H, Ocal L, Inanc M, Capo C. Overproduction of monocyte derived tumor necrosis factor alpha, interleukin (IL) 6, IL-8 and increased neutrophil superoxide generation in Behcet's disease. A comparative study with familial Mediterranean fever and healthy subjects. J Rheumatol 1993;20:1544-9.
28. Arida A, Fragiadaki K, Giavri E, Sfikakis PP. Anti-TNF agents for Behcet's disease: analysis of published data on 369 patients. Semin Arthritis Rheum 2011;41:61-70.
29. Giardina A, Ferrante A, Ciccia F, Vadala M, Giardina E, Triolo G. One year study of efficacy and safety of infliximab in the treatment of patients with ocular and neurological Behcet's disease refractory to standard immunosuppressive drugs. Rheumatol Int 2011;31:33-7.
30. The International Criteria for Behcet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. J Eur Acad Dermatol Venereol 2014;28:338-47.
31. Saulsbury FT, Mann JA. Treatment with infliximab for a child with Behcet's disease. Arthritis Rheum. 2003;49(4):599-600.
32. Yazici H, Barnes CG. Practical treatment recommendations for pharmacotherapy of Behcet's syndrome. Drugs. 1991;42(5):796-804.

LIST OF ADDENDA

1.61 List of Investigators

	Name	Town	Country	Hospital	Speciality
Pr	Saadoun	Paris	France	Pitie Salpetriere	internal medicine
Dr	Jamilloux	Lyon	France	Croix Rousse	internal medicine
Pr	Lambert	Lille	France	CHRU LILLE	internal medicine
Pr	Fain	Paris	France	Saint Antoine	internal medicine
~~Dr~~	~~Riviere~~	~~Montpellier~~	~~France~~	~~CHU St Eloi~~	~~Internal medicine~~
Dr	Schmidt	Amiens	France	CHRU AMIENS	internal medicine
Pr	Benhamou	Rouen	France	Bois-Guillaume	internal medicine
Pr	Hot	Lyon	France	E Herriot	internal medicine
Pr	Aouba	Caen	France	CHU Caen	internal medicine
Dr	Martin	Poitiers	France	CHU Poitiers	internal medicine
Pr	Sene	Paris	France	Lariboisiere	internal medicine
Pr	Bouillet	Grenoble	France	CHU Grenoble	Internal medicine
~~Pr~~	~~Granel~~	~~Marseille~~	~~France~~	~~CHU Nord~~	~~internal medicine~~
Dr	Bielefeld	Dijon	France	CHU Dijon	internal medicine
Pr	Viallard	Bordeaux	France	CHU Bordeaux	internal medicine
Pr	Sacre	Paris	France	CHU Bichat	internal medicine
Pr	Alric	Toulouse	France	CHU Purpan	internal medicine
Pr	Kone Paut	Bicetre	France	CHU Bicetre	Pediatric rheumatologist
Dr	Abad	Bobigny	France	Avicenne	internal medicine
Dr	Lhote	Saint Denis	France	CHR St Denis	internal medicine
Dr	Noel	Bicetre	France	CHU Bicetre	Internal medicine
Dr	Parrot	Tenon	France	CHU Tenon	Pneumology
Dr	Maurier	Metz	France	CH Metz	internal medicine
Dr	Quemeneur	Valenciennes	France	CH Valenciennes	internal medicine
Dr	Trad	Boulogne	France	CHU A Paré	internal medicine
Dr	Lioger	Paris	France	Saint Louis	Internal medicine
Dr	Ackermann	Paris	France	Foch	Internal medicine
Dr	Limal	Paris	France	Henri Mondor	Internal medicine
Dr	Ribeiro	Bordeaux	France	Hopital Saint-Andre	Internal medicine
Dr	Ebbo	Marseille	France	Hôpital de la Timone	Internal medicine

1.62 Serious Adverse Events report form

1.63 Include the SCP or Investigator's Brochure

Specify here that the SCP must have been obtained from the EMA website (http://www.ema.europa.eu/ema/), or from the ANSM website (http://agence-prd.ansm.sante.fr/php/ecodex/index.php); otherwise, use the SCP from Vidal.

1.64 Questionnaire or scale

APPENDIX

- Appendix 1

International criteria for the classification of Behçet's disease revised in 2013 [7]

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**

- Appendix 2

BEHÇET'S DISEASE CURRENT ACTIVITY FORM 2006

International Society for Behcet's Disease

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

- Appendix 3

9 Echelles de qualité de vie

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

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

Auteur(s) : Ware et al.

Type : Echelle d'auto-évaluation

Objectifs : Evaluer la qualité de vie liée à la santé

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

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

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

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

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

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

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

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

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

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

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

Bibliographie :

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

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

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

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

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

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

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

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

Questionnaire : SF-36

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

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

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

Excellente

Très bonne

Bonne

Médiocre

Mauvaise

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

Bien meilleur que l'an dernier

Plutôt meilleur

A peu près pareil

Plutôt moins bon

Beaucoup moins bon

SF36

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

Cochez la case qui correspond à votre choix

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

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

Cochez la case qui correspond à votre choix

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

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

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

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

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

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

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

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

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

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

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

Cochez la case qui correspond à votre choix

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

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

Cochez la case qui correspond à votre choix

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

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

Cochez la case qui correspond à votre choix

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

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

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

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

(Suite de la question 9)

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

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

Cochez la case qui correspond à votre choix

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

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

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

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