



Call for projects : PHRC N - Janssen

ID RCB : 2018-002569-20

NCT number :

**Title of the study**

**A multicenter phase 2 single-arm proof-of-concept trial assessing the efficacy and safety of ustekinumab in association with prednisone, for the treatment of non-infectious severe uveitis (NISU)**

**Name of the study****USTEKINISU****Version 1.2 dated 05/12/2018****Approved on the 02/01/2019 by the CPP SUD-MEDITERRANEE V****Version 1.1 dated 17/09/2018****Approved on the 25/09/2018 by the ANSM****Phase 2 clinical study****Research category:****Category 1 : Interventional research bearing on drugs**

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**Insurance :**Société Hospitalière d'Assurances Mutuelles (SHAM)  
SponsorPolice n° 129.234

### INVESTIGATORS AND MANAGEMENT STRUCTURE OF THE STUDY

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**Associated units:**

- CRB  
 CIC  
 Others, Specify :

**SUMMARY OF CHANGES TABLE**

MSA number	Protocol version	Modifications	Approval Date CPP	Approval Date ANSM
	V1 – 17/07/2018	Version soumise au CPP et à l'ANSM		
	V1.1 – 17/09/2018	Version 1 corrigée pour répondre à l'ANSM		25/09/2018
	V1.2 – 03/12/2018	Version 1.1 corrigée pour répondre au CPP	02/01/2019	

## SYNOPSIS

<b>Study title</b>	<b>A multicenter phase 2 single-arm proof-of-concept trial assessing the efficacy and safety of ustekinumab in association with prednisone, for the treatment of non-infectious severe uveitis (NISU)</b>
<b>Id</b>	2018-002569-20
<b>Sponsor</b>	Centre Hospitalier Universitaire Dijon Bourgogne
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<b>Rational</b>	<p>Uveitis is characterized by inflammation of the uvea, which is the middle portion of the eye. The greatest challenge for the treatment of uveitis relates to patients who have inflammation involving the posterior segment, either primarily in the vitreous (intermediate uveitis), the choroid or retina (posterior uveitis), or involving the entire eye (panuveitis). The term “Uveitis” describes a heterogeneous collection of diseases including infections, systemic immune-mediated diseases, like sarcoidosis, and immune-mediated syndromes confined to the eye, like sympathetic ophthalmia. Despite the progress in recent decades, uveitis and the related intraocular inflammation are comparable to diabetes or macular degeneration as a cause of lost quality-adjusted life years due to visual morbidity, and as such are a significant public health problem. The Standardization of Uveitis Nomenclature Working Group Guidelines recommend the use of corticosteroids as the first-line therapy for patients with active uveitis. However, long-term corticosteroid treatment can cause serious systemic and ocular side effects, such as hypertension, diabetes, osteoporosis, cataract, and glaucoma that limit its use in the treatment of uveitis. Alternatively, immunomodulatory therapy (IMT) drugs are given as steroid-sparing agents and have shown good clinical results for both systemic diseases and ocular inflammatory diseases. Given the side effects of chronic corticosteroid therapy and better understanding of the mechanisms of autoimmune-mediated uveitis, the aim of the treatment for patients with noninfectious uveitis is steroid-free remission with IMT. While uveitis is a heterogeneous disease with polygenic and environmental factors, most forms of immune-mediated uveitis are thought to be due to an imbalance between regulatory mechanisms that inhibit the immune system and inflammatory mechanisms, which evolved to rid the body of infectious organisms, but which can result in immune-mediated, often chronic disease if they are activated outside the context of the immediate infection. The pathophysiology of non-infectious uveitis involves the rupture of peripheral tolerance, resulting in auto-aggressive Th1 or Th17 lymphocytes reaching the eye. IL-12 and IL-23 are two key cytokines involved in Th1 and Th17 polarization in uveitis, respectively. Furthermore, these two cytokines share a common subunit (p40). Ustekinumab, a humanized anti-p40 monoclonal antibody, is able to target both IL-12 and IL-23 pathways, thus disrupting Th1 and Th17 immune responses.</p> <p>Decreasing the dose as well as the duration of treatment with GC is of particular importance in uveitis, and ustekinumab, which selectively inhibits Th1 and Th17 pathways in the inflammatory cascade, could provide a perfect additional therapy for non-infectious</p>

	<p>severe uveitis (NISU) to reach this objective.</p> <p>Therefore, in the present study, we propose to evaluate the efficacy and safety of ustekinumab for the treatment of NISU.</p>
<p><b>Objectives</b></p>	<ul style="list-style-type: none"> <li>• <b><u>PRIMARY OBJECTIVE :</u></b> To determine the proportion of patients failing to achieve remission within 6 weeks or relapsing from a non-infectious severe uveitis during the 24 weeks of treatment with both corticosteroids, with a mandatory tapering schedule, and ustekinumab, with a loading dose of 90 mg at week 0 and week 4 followed by one maintenance injection of 90 mg at week 16.</li> <li>• <b><u>SECONDARY OBJECTIVES:</u></b> <b>EFFICACY:</b> <ul style="list-style-type: none"> <li>• To determine the proportion of patients failing to achieve remission at W6</li> <li>• To determine the proportion of patients achieving remission at W6 and relapsing between W6 and W24</li> <li>• To determine the relapse rate at W52</li> <li>• To determine the time to relapse</li> <li>• To evaluate the quality of life of patients treated with ustekinumab for NISU</li> </ul> </li> <li>• <b>SAFETY:</b> <ul style="list-style-type: none"> <li>• To assess the safety of ustekinumab in patients with NISU, when combined with corticosteroids</li> </ul> </li> <li>• <b>IMMUNOMONITORING :</b> <b>To assess the efficacy of ustekinumab on:</b> <ul style="list-style-type: none"> <li>• Th1, Th2, Th17 and Treg polarization</li> </ul>                     The concentrations of inflammatory and anti-inflammatory cytokines                 </li> </ul>
<p><b>End points</b></p>	<p><b><u>PRIMARY ENDPOINT</u></b> Composite end-point comprising:</p> <ul style="list-style-type: none"> <li>• Remission at week 6: patients will be considered remitting in the absence of any one of the following criteria in at least one eye:                     <ul style="list-style-type: none"> <li>- new inflammatory lesions relative to baseline,</li> <li>- or anterior chamber cell or vitreous haze grade that did not decrease to 0.5+ or lower</li> <li>- or worsening of best-corrected visual acuity by 15 or more letters on the early treatment diabetic retinopathy study chart, relative to the best state previously achieved</li> <li>- presence of macular edema, same or worse than baseline</li> <li>- any deviation from the scheduled prednisone tapering because of uveitis activity</li> </ul> </li> <li>• AND patients free of relapse between week 6 and week 24, patients will be considered to have disease relapse if they have:                     <ul style="list-style-type: none"> <li>- new active, inflammatory lesions relative to baseline</li> <li>- or a two-step increase in anterior chamber cell or vitreous haze grade, or a worsening of best-corrected visual acuity by 15 or more letters on the early treatment diabetic retinopathy study chart relative to the best state previously achieved, in at least one eye</li> <li>- presence of macular edema at a value greater than the OCT machine-specific, pre-defined upper limit of normal for central retinal thickness</li> <li>- any deviation from the scheduled prednisone tapering because of uveitis activity</li> </ul> </li> </ul> <p><b><u>SECONDARY ENDPOINTS</u></b> <b>EFFICACY:</b></p> <ul style="list-style-type: none"> <li>• Proportion of patients failing to achieve remission at W6: the failure to achieve remission at week 6 is defined by:                     <ul style="list-style-type: none"> <li>- new inflammatory lesions relative to baseline,</li> <li>- Or anterior chamber cell or vitreous haze grade that did not decrease to 0.5+ or lower</li> </ul> </li> </ul>

	<ul style="list-style-type: none"> <li>- Or worsening of best-corrected visual acuity by 15 or more letters on the early treatment diabetic retinopathy study chart, relative to the best state previously achieved</li> <li>• Proportion of patients achieving remission at W6 and relapsing between W6 and W24. Disease relapse between W6 and W24 is defined by:             <ul style="list-style-type: none"> <li>- new active, inflammatory lesions relative to baseline</li> <li>- or a two-step increase in anterior chamber cell or vitreous haze grade,</li> <li>- or a worsening of best-corrected visual acuity by 15 or more letters on the early treatment diabetic retinopathy study chart relative to the best state previously achieved, in at least one eye.</li> </ul> </li> <li>• Relapse rate at W52 Disease relapse before W52 is defined by:             <ul style="list-style-type: none"> <li>- new active, inflammatory lesions relative to baseline</li> <li>- or a two-step increase in anterior chamber cell or vitreous haze grade,</li> <li>- or a worsening of best-corrected visual acuity by 15 or more letters on the early treatment diabetic retinopathy study chart relative to the best state previously achieved, in at least one eye.</li> </ul> </li> <li>• Time to relapse: time (in days) from corticosteroid initiation to relapse, as defined above. Among patients who fail to achieve remission at the W6 visit, time to relapse will be arbitrarily set at 42 days (6 weeks) plus the duration of corticosteroid treatment before the first ustekinumab injection</li> <li>• quality of life of patients treated with ustekinumab for NISU             <ul style="list-style-type: none"> <li>○ French version of the VFQ-25</li> <li>○ generic SF-36 questionnaire</li> </ul> </li> </ul> <p><b>SAFETY:</b></p> <ul style="list-style-type: none"> <li>• Frequency and type of side effects (infection, cancer...) related to ustekinumab within 1 year after inclusion</li> </ul> <p><b>IMMUNOMONITORING:</b></p> <ul style="list-style-type: none"> <li>• For the immunomonitoring study, blood samples will be taken at W0, W6, W24 (=M6) and W52 (=M12) and sent to Pr. Bonnotte's team, INSERM U1098, Dijon.</li> <li>1) Flow cytometry analysis (for patients included in Dijon only): percentages of Th1, Th2, Th17, and cytotoxic CD8 T cells.</li> <li>2) Serum concentrations of IL-1<math>\beta</math>, IL-2, IL-6, IL-6Rs, soluble gp130, IL-12p35, IL-12/23p40, IL-17, IL-23p19, IL-17A, TNF-<math>\alpha</math>, IFN-<math>\gamma</math> (all centers)</li> </ul>
<p><b>Number of subjects</b></p>	<p>29 patients are expected to participate in this research</p>
<p><b>Study population</b></p>	<p><b>INCLUSION CRITERIA</b></p> <ul style="list-style-type: none"> <li>- Patients with newly diagnosed active NISU:             <ul style="list-style-type: none"> <li>○ evidence of activity within the 3 months prior to the screening visit as per:                 <ul style="list-style-type: none"> <li>▪ VH (visual haze) <math>\geq 4</math> on the Miami 9-step scale (or VH <math>&gt;1+</math> according to SUN classification)</li> <li>▪ and/or macular edema on OCT (Central retinal thickness <math>\geq 300</math> microns)</li> <li>▪ and/or other signs of intraocular inflammation (e.g. perivascular sheathing of retinal vessels or leakage of retinal vessels on fluorescein angiography (FA)).</li> </ul> </li> </ul> </li> <li>- Patients judged to be in good health as determined by the Principal Investigator based upon the results of medical history, laboratory profile, physical examination, chest x-ray (CXR), and a 12-lead electrocardiogram (ECG) performed during Screening.</li> <li>- For men and women of childbearing age, effective contraception must be used by the patient and/or his/her partner throughout the duration of treatment with ustekinumab and until 23 weeks after the end of treatment. Breastfeeding is allowed 23 weeks after the end of treatment. Women considered without risk of pregnancy are those with :</li> </ul>

	<ul style="list-style-type: none"> <li>▪ combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)</li> <li>▪ progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)</li> <li>▪ intrauterine device (IUD)</li> <li>▪ intrauterine hormone-releasing system ( IUS)</li> <li>▪ bilateral tubal occlusion</li> <li>▪ vasectomised partner</li> <li>▪ sexual abstinence</li> <li>▪ or those surgically sterile (, bilateral oophorectomy or hysterectomy).</li> <li>▪ or at least one year of menopause (amenorrhea for at least 12 months)</li> </ul> <p>—</p> <ul style="list-style-type: none"> <li>- Patients over 18 years of age</li> <li>- Affiliation to the french social security system</li> <li>- Patients who have given their consent</li> </ul> <ul style="list-style-type: none"> <li>- <b><u>NON-INCLUSION CRITERIA</u></b></li> <li>- Subjects considered by the Investigator, for any reason, to be unsuitable candidates for the study.</li> <li>- Surgery scheduled within 12 months</li> <li>- Patients with dementia</li> <li>- Non-compliant patients</li> <li>- Weight &lt;45 kg or &gt; 100 kg</li> <li>- Patients under ward of court, tutelage or legal guardianship</li> <li>- Pregnant or breast-feeding women</li> </ul> <p><u>Non-inclusion criteria related to uveitis:</u></p> <ul style="list-style-type: none"> <li>- Infectious uveitis, masquerade syndromes, or uveitis due to causes other than non-infectious uveitis disease (idiopathic uveitis is permitted)</li> <li>- Isolated anterior uveitis</li> <li>- Presence of cataract or posterior capsular opacification so severe that an assessment of the posterior segment of either eye is inadequate or impossible</li> <li>- Contraindication to mydriasis in either eye or presence of posterior synechiae in the study eye such that mydriasis is inadequate for posterior segment examination</li> <li>- Intraocular pressure <math>\geq 25</math>mmHg by Goldmann tonometry or advanced glaucoma (e.g., cup-to-disc ratio &gt; 0.9, split fixation on visual field, or need for &gt; 3 intraocular pressure lowering medications to keep IOP &lt; 22 mmHg) in either eye</li> <li>- Monocular patient</li> <li>- Sarcoidosis-related uveitis</li> </ul> <p><u>Non-inclusion criteria related to ustekinumab:</u></p> <ul style="list-style-type: none"> <li>- History of congenital or acquired immunodeficiency (e.g. common variable immunodeficiency disease).</li> <li>- History of prior treatment with ustekinumab</li> <li>- Hypersensitivity to ustekinumab, one of its excipients or another human or murine monoclonal antibody or latex</li> <li>- Evidence of active infection at the time of baseline visit, or other Infectious contraindication to ustekinumab</li> <li>- Neoplasia &lt; 5 years, (except for in situ cervical cancer and skin carcinoma with R0 resection)</li> <li>- Active tuberculosis or sign of latent tuberculosis (based on a history of untreated contact, a history of opacity of more than 1 cm in diameter on the chest x-ray, or an in vitro test positive[Quantiferon® or T-spot-TB®]). A history of TB disease or latent TB whose treatment was completed is not an exclusion criteria, regardless the Quantiferon® or T-spot-TB® is positive or not.</li> </ul>
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	<ul style="list-style-type: none"> <li>- Known positive syphilis serology, HIV antibody, hepatitis B surface antigen or anti-nucleocapsid antibody of hepatitis B virus, and/or hepatitis C antibody.</li> <li>- History of multiple sclerosis and/or demyelinating disorder</li> <li>- Infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the Baseline Visit or oral anti-infectives within 14 days prior to the Baseline Visit.</li> <li>- Screening laboratory and other analyses showing any of the following abnormal results:             <ul style="list-style-type: none"> <li>▪ AST, ALT &gt; 1.75 x upper limit of the reference range;</li> <li>▪ WBC count &lt; 3.0 x 10<sup>9</sup>/L;</li> </ul> </li> </ul> <p><u>Other treatments:</u></p> <ul style="list-style-type: none"> <li>• Corticosteroids             <ul style="list-style-type: none"> <li>▪ History of ≥3 systemic corticosteroid therapies (topical or inhaled treatments allowed) for another disease (e.g. asthma) within the last 6 months before screening visit</li> <li>▪ Subjects who have received IV corticosteroids within 2 weeks prior to the screening Visit</li> <li>▪ Dexamethasone intravitreal implant less than 6 months prior to study</li> </ul> </li> <li>• Patients receiving (or having stopped for less than 6 months or 5 elimination half-lives) an immunosuppressive or immunomodulatory drug or biotherapy:             <ul style="list-style-type: none"> <li>▪ • anti TNF-α,</li> <li>▪ • tocilizumab,</li> <li>▪ • abatacept,</li> <li>▪ • anakinra,</li> <li>▪ • methotrexate,</li> <li>▪ • azathioprine,</li> <li>▪ • ciclosporine,</li> <li>▪ • cyclophosphamide,</li> <li>▪ • dapsone</li> <li>▪ • or corticosteroid pulses</li> </ul> </li> </ul> <p>Live vaccine administered within 30 days preceding inclusion</p>
<p><b>Risk-benefit Analyse</b></p>	<p><u>Benefit:</u> Individual benefit resulting from the decreased duration and cumulative dose of GC received during NISU treatment</p> <p><u>Risk:</u> Risk related to ustekinumab (see paragraph 8.3).</p> <p>Due to the low incidence of serious adverse effects related to ustekinumab and short-term morbidity associated with GC, the risk/benefit ratio appears favorable.</p>
<p><b>Study procedure</b></p>	<ul style="list-style-type: none"> <li>- <b><u>COURSE OF THE STUDY</u></b></li> <li><b><u>1- Pre-screening of patients</u></b></li> <li><b><u>2- Screening visit (W-2)</u></b> <ul style="list-style-type: none"> <li>- Information is provided</li> <li>- Written consent is obtained</li> <li>- Checking for inclusion and non-inclusion criteria</li> <li>- Medical history, physical examination, vital signs</li> <li>- Routine lab tests: hematology (FBC), blood chemistry, C-reactive protein, fibrinogen, ESR</li> <li>- Ophthalmologic examination : best corrected visual acuity (BCVA) testing, Slit Lamp Exam, tonometry, dilated indirect ophthalmoscopy, optical coherence tomography (OCT)</li> <li>- A pre-therapeutic appraisal will be performed (ECG, Chest X Ray, Quantiferon test®, urine analysis, SGOT, SGPT, alkaline phosphatase, gamma GT, Serology for HIV, B and C hepatitis, Serum protein electrophoresis, Pregnancy test)</li> <li>- Prednisone will be started at 60 mg/day 2 weeks before inclusion</li> <li>- Vaccination against pneumococcus (Pneumo23®) can be proposed</li> </ul> </li> </ul>



**3- Inclusion visit (W0)**

- Medical history, physical examination, vital signs, and collection of clinical and biological data
- Ophthalmologic examination : BCVA testing, Slit Lamp Exam, tonometry, dilated indirect ophthalmoscopy, OCT
- Self-administered questionnaires: VFQ-25, SF-36
- Blood samples:
  - o Routine lab tests: hematology (FBC), blood chemistry, serum creatinine, C-reactive protein, fibrinogen, ESR, SGOT, SGPT, , gamma GT, Pregnancy test
  - o Research samples:
    - *Centers of Dijon*: total blood (8 heparin tubes of 6 mL) to isolate peripheral blood mononuclear cells (PBMC), to be sent within 24 hours to Pr. Bonnotte's team, INSERM U1098, Dijon
    - *All centers*: serum (1 dry tube of 5 mL) and DNA storage (1 EDTA tube of 6 mL) These samples will be stored at -20°C in each center and sent later to Pr. Bonnotte's team, INSERM U1098, Dijon.
- Delivery of a diary for patients
- Prescription of corticosteroid therapy (Cortancyl®, non-substitutable) and of associated measures detailed in the protocol.
- Subcutaneous administration of 90 mg of ustekinumab

**4- Follow-up visits (W4, W6, W8, W12, W16, W20, W24, W32, W40, W48)**

- Medical history, physical examination, vital signs, and collection of clinical and biological data
- Ophthalmologic examination : BCVA testing, Slit Lamp Exam, tonometry, dilated indirect ophthalmoscopy, OCT
- inflammatory activity of uveitis: achievement of remission (W6), occurrence of relapse
- Monitoring of occurrence of skin tumors : skin examination in order to detect potential onset of skin cancer
- Self-administered questionnaires: VFQ-25 and SF-36 (W6, W24 and W52 only)
- Blood samples:
  - Routine lab tests:  
Hematology (FBC), blood chemistry, C-reactive protein, fibrinogen, ESR SGOT, SGPT (until W24), Pregnancy test
  - Research samples (W6 and W24 only)  
Dijon center: total blood for PBMC isolation (8 heparin tubes 6 mL): to be sent within 24 hours to Pr. Bonnotte's team, INSERM U1098, Dijon  
All centers: serum storage (1 dry tube of 5 mL). Serum will be stored at -20°C in each center and then sent to Pr. Bonnotte's team, INSERM U1098, Dijon.
- Tapering of prednisone according to the protocol (Table 1).
- If applicable, tapering of topical corticosteroid according to table 2
- Completion of the patient's

Subcutaneous injection of ustekinumab (90 mg) will be administered at W4 and W16.

**5- End of visit (W52)**

- Medical history, physical examination, vital signs and collection of clinical and biological data
- Ophthalmologic examination : BCVA testing, Slit Lamp Exam, tonometry, dilated indirect ophthalmoscopy, OCT Completion of the patient's diary
- inflammatory activity of uveitis: occurrence of relapse
- Monitoring of occurrence of skin tumors
- Self-administered questionnaires: VFQ-25, SF-36
- Routine lab tests: Hematology (FBC), blood chemistry, C-reactive protein, fibrinogen, ESR
- Research samples

	<ul style="list-style-type: none"> <li>▪ Dijon center: total blood for PBMC isolation (8 heparin tubes 6 mL): to be sent within 24 hours to Pr. Bonnotte's team, INSERM U1098, Dijon</li> <li>▪ All centers: serum storage (1 dry tube of 5 mL). Serum will be stored at -20°C in each center and then sent to Pr. Bonnotte's team, INSERM U1098, Dijon.</li> </ul>
<b>Collection of biological samples</b>	<p>4 biological sample(s) collected / patients with use of these biological samples in the context of the research with the preservation and subsequent use of this collection</p> <p>Duration of preservation beyond the study: until biological material is exhausted Stored at: CR INSERM U1098, Pr. BONNOTTE's Team, bâtiment B3, CHU de Dijon, rue Angélique Ducoudray, 21000 Dijon.</p>
<b>Treatment</b>	Prednisone + ustekinumab (Stelara®) (90mg) at W0, W4 and W16
<b>Dose, Route, Duration</b>	Ustekinumab: Patients will receive one subcutaneous injection of Ustekinumab (90 mg) at W0, W4 and W16
<b>Statistical analyses</b>	<ul style="list-style-type: none"> <li>• <b>CALCULATION OF THE NUMBER OF SUBJECTS REQUIRED</b></li> </ul> <p>In the VISUAL 1 study, the median time to treatment failure (defined by uveitis relapse) was 24 weeks (plus at least two weeks of corticosteroid prior to the beginning of the study) in the adalimumab group and 13 weeks. An approximate relapse rate of 75% in corticosteroid arm (25% relapse-free patients) and 50% in adalimumab plus corticoid arm (50% relapse-free patients) [12] was observed 24 weeks after the beginning of the treatment.</p> <p>We calculated the sample size using the following hypothesis:</p> <ul style="list-style-type: none"> <li>- More than 25% relapse-free patients at W24 are expected (less than 75% relapse, as observed under corticosteroid alone)</li> <li>- At least 50% relapse-free patients at W24 are needed to confirm the significant clinical efficacy of Ustekinumab (less than 50% relapse, as observed under adalimumab + corticosteroids)</li> <li>- An alpha risk of 0.05 and a power of 0.8</li> </ul> <p>Sample size was determined using Fleming's single-stage phase II design.[42,43] We hypothesized that ustekinumab would be considered clinically inactive if more than 75% of patients with NISU experience relapse W24 (<math>\leq 25\%</math> relapse-free patients), whereas ustekinumab would be considered clinically active if less than 50% of patients experienced relapse (<math>&gt;50\%</math> relapse-free patients). Based on these hypotheses, with a one-sided alpha risk of 0.05 and a power of 90%, 26 patients are required. Allowing for 10% of drop-outs, <b>29 patients will be included in this study</b></p> <ul style="list-style-type: none"> <li>• <b>STATISTICAL TESTS</b></li> </ul> <p>If 11 or more patients out of the total of 29 patients treated with ustekinumab are relapse-free with no deviation from the scheduled prednisone tapering because of NISU activity at W24, it will be concluded that the clinical activity of ustekinumab warrants further investigation.</p> <p>If 10 or fewer patients out of the total of 29 patients treated with ustekinumab are relapse-free with no deviation from the scheduled prednisone tapering because of NISU activity at W24, ustekinumab will be deemed not worthy of any further investigation in this patient population, unless clinical considerations suggest otherwise.</p> <p>The 95% confidence interval for the proportion of patients who experienced relapse or any deviation from the scheduled prednisone tapering at W24 will be calculated on the basis of an exact binomial probability.</p>

<b>Expected Results and alternatives</b>	We hypothesized that ustekinumab could have a dramatic GC-sparing effect and thus lead to better control of the disease as defined by a high remission rate at W6 and a low relapse risk at W24.
<b>Study planning</b>	Estimated start date of the study: February 2019 Duration of inclusion period: 18 mois - - total duration of participation for a person taking part in the study: 12 mois total duration of the study (inclusion + follow-up): 30 mois Period of exclusivity for a participant: <input type="checkbox"/> non <input checked="" type="checkbox"/> oui Period of exclusion for a participant: <input checked="" type="checkbox"/> non <input type="checkbox"/> oui duration :            days

### STUDY PLAN

	Screening	W0	W4	W6	W8	W12	W16	W20	W24	W32	W40	W48	W52
	<b>W-2</b>												
Written Informed Consent	X												
Medical history	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	
Side effects		X	X	X	X	X	X	X	X	X	X	X	
Compilation of eCRF	X	X	X	X	X	X	X	X	X	X	X	X	
ECG	X												
Chest X-rays	X												
Pneumo 23® injection (optional)	X												
Search for any contraindications to ustekinumab		X	X				X						
Ustekinumab (90 mg) subcutaneous injection		X	X				X						
<b>Ophthalmologic examination</b>													
BCVA	X	X	X	X	X	X	X	X	X	X	X	X	X
Slip Lamp Exam	X	X	X	X	X	X	X	X	X	X	X	X	X
Tonometry	X	X	X	X	X	X	X	X	X	X	X	X	X
Dilated indirect ophthalmoscopy	X	X	X	X	X	X	X	X	X	X	X	X	X
Fundus photography	X	X		X					X				
Optical Coherence Tomography	X	X	X	X	X	X	X	X	X	X	X	X	X
Fluorescein angiography		X		X					X				
Indocyanin green angiography		X		X					X				
<b>Questionnaires for patients</b>													
VFQ-25		X		X					X				X
SF-36		X		X					X				X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X
Administration of treatment		X											
<b>Routine labs tests</b>													
FBC (NFS)	X	X	X	X	X	X	X	X	X	X	X	X	X
Quantiferon test	X												
Blood Chemistry (ionogram)	X	X	X	X	X	X	X	X	X	X	X	X	X
SGOT, SGPT	X	X	X	X	X	X	X	X	X				
Alkaline phosphatase, Gamma GT	X	X											
C-reactive protein	X	X	X	X	X	X	X	X	X	X	X	X	X
Fibrinogen	X	X	X	X	X	X	X	X	X	X	X	X	X
ESR	X	X	X	X	X	X	X	X	X	X	X	X	X
Serology (HIV, B and C hepatitis)	X												
Serum protein electrophoresis	X												

β HCG	X	X	X	X	X	X	X	X	X	X	X	X	X	X
<b>Research samples</b>														
Serum storage (5 mL)		X		X						X				X
PBMC (8x6 mL, heparin) *		X		X						X				X
DNA storage (6 mL, EDTA)		X												

\*PBMCs will be sampled in Dijon patients and sent within 24 hours to Pr. Bonnotte's team, INSERM U1098, Dijon.

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations	Meaning
AMM	Marketing authorization
ANSM	Agence Nationale de Sécurité des Médicaments et des produits de santé (drug safety agency)
CA	Competent Authority
CPP	Comité de Protection des Personnes (ethical review board)
SAE	Severe adverse event/effect
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Event
JIA	juvenile idiopathic arthritis
BD	Behcet's disease
VKH	Vogt-Koyanagi-Harada (VKH) syndrome
NISU	non-infectious severe uveitis
EAU	experimental autoimmune uveoretinitis (EAU)
CS	corticosteroid
IMT	Immunomodulatory therapy
APC	antigen-presenting cell
DC	dendritic cell
LPS	Lipopolysaccharide
PMNL	polymorphonuclear lymphocyte
Th	T helper type
Treg	T regulatory cell
IL	Interleukine
TNF	Tumour necrosis factor
CS	Corticosteroids
GCA	Giant Cell Arteritis
OCT	Optical Coherence Tomography
SUN	Standardization of Uveitis Nomenclature Working Group
NEI	National Eye Institute
VFQ-25	National Eye Institute Visual Functioning Questionnaire 25
SF-36	Medical Outcome Study Short Form-36
INSERM	French National Institute of Health and Medical Research
ECG	Electrocardiogram
CXR	Chest X-Ray
IOP	Intra-ocular pressure
IV	Intravenous
SC	Subcutaneous
CMIO	Club Médecine Interne et Œil
FBC	Full blood count
ESR	Erythrocyte sedimentation rate
CRP	C-reactive protein
BCVA	Best Corrected Visual Acuity Testing
AREDS	Age-Related Eye Disease Study
ITT	Intention-To-Treat
PP	Per Protocol

## 1 STATE OF THE ART AND RATIONALE FOR THE STUDY

### 1.1. Uveitis

Uveitis is characterized by inflammation of the uvea, which is the middle portion of the eye; the anterior portion of the uvea includes the iris and ciliary body, and the posterior portion of the uvea is known as the choroid [1]. Epidemiological studies estimate the population adult prevalence of non-infectious uveitis in the United States at 121 cases per 100 000 persons, and indicate that about 80% of uveitis are anterior in location [2], which generally permits successful therapy with topical medication alone. The greatest challenge for the treatment of uveitis relates to patients who have inflammation involving the posterior segment, either primarily in the vitreous (intermediate uveitis), the choroid or retina (posterior uveitis), or involving the entire eye (panuveitis).

The term “Uveitis” describes a heterogeneous collection of diseases including infections, systemic immune-mediated diseases, like sarcoidosis, and immune-mediated syndromes confined to the eye, like sympathetic ophthalmia. Despite the progress in recent decades, uveitis and related intraocular inflammation is comparable to diabetes or macular degeneration as a cause of lost quality-adjusted life years due to visual morbidity, and as such is a significant public health problem [3,4]. Uveitis can occur either alone or as part of a systemic syndrome (systemic disease-associated autoimmune uveitis), such as one of the spondyloarthritides (including those complicating inflammatory bowel disorders and ankylosing spondylitis), juvenile idiopathic arthritis (JIA), Behcet’s disease (BD), Vogt–Koyanagi–Harada (VKH) syndrome, systemic lupus erythematosus, sarcoidosis, autoimmune hepatitis, and multiple sclerosis, in which the eye is one of several organs involved.

Since the description of experimental autoimmune uveoretinitis (EAU) induced in mice by provoking an immune response [5] and because the treatment for non-infectious severe uveitis (NISU) commonly respond to systemic immunomodulation [6], most forms of uveitis are presumed to be due to the immune response. The treatment of autoimmune-mediated uveitis is divided into acute-phase and maintenance therapy. The acute stage can be controlled with corticosteroid (CS) therapy because of their immediate efficacy. In point of fact, the Standardization of Uveitis Nomenclature Working Group (SUN) Guidelines recommend the use of corticosteroids as the first-line therapy for patients with active uveitis [1,7]. However, long-term corticosteroid treatment can cause serious systemic and ocular side effects, such as hypertension, diabetes, osteoporosis, cataract, and glaucoma, that limit its use in the treatment of uveitis [7,8]. Alternatively, immunomodulatory therapy (IMT) drugs are given as steroid-sparing agents and have shown good clinical results for both systemic diseases and ocular inflammatory diseases. Given the side effects of chronic corticosteroid therapy and better understanding of the mechanisms of autoimmune-mediated uveitis, the aim of the treatment for patients with noninfectious uveitis is steroid-free remission with IMT. A stepladder approach is a common practice in immune-mediated uveitis: nonsteroidal anti-inflammatory drugs and conventional immunomodulatory agents are usually used before proceeding with biological response modifiers. Before 2016, the only drugs approved for treatment of uveitis in France were corticosteroids for systemic or local administration, and the immunosuppressive agent cyclosporine. The registered indication of cyclosporine comprises the treatment of intermediate or posterior uveitis and Behcet’s disease [9]. Most IMT agents have been used in uveitis despite the absence of randomized clinical trials. The off-label use of antimetabolites including methotrexate, azathioprine, and mycophenolate mofetil; alkylating agents, which include cyclophosphamide; or biologics are proposed to patients requiring for doses of systemic corticosteroids that are highly likely to result in corticosteroid complications. Recently, the results of two randomized controlled trial demonstrated that the use of Adalimumab, a subcutaneous monoclonal anti-TNF-alpha antibody, was associated with statistically significant and clinically meaningful improvements in clinical and patient-reported visual functioning for patients with noninfectious intermediate uveitis, posterior uveitis [10–12]. A French marketing authorization was thus granted in 2016 to Adalimumab for the treatment of noninfectious intermediate uveitis, posterior uveitis in patients in patient that did not respond to CS, as a CS-sparing agent or in case of contraindication to CS.



In conclusion, CS-sparing agents are effective in many patients as they allow a reduction in steroid dose and preserve visual function. Aggressive treatment may result in fewer complications and less recurrence.

### 1.2. Why target the IL-12 and IL-23 pathway specifically in uveitis patients?

Targeted approaches to treating uveitis require an understanding of the pathogenesis of uveitis. While uveitis is a heterogeneous disease with polygenic and environmental factors, most forms of immune-mediated uveitis are thought to be due to an imbalance between regulatory mechanisms that inhibit the immune system and inflammatory mechanisms, which evolved to rid the body of infectious organisms, but which can result in immune-mediated, often chronic disease if they are activated outside the context of the immediate infection. This aberrant immune activation appears to be a combination of an environmental trigger and genetic risk factors that tip the balance away from immune regulation and towards unchecked inflammation.

Incomplete thymic elimination of effector T cell precursors, which are able to recognize retinal antigens, combined with deficient peripheral tolerance results in the persistence of circulating, non-tolerized T cells. These cells become activated by exposure to retina-derived or cross-reactive antigens in conjunction with exogenous or endogenous inflammatory signals, and differentiate into an auto-aggressive Th1 or Th17 phenotype. Although natural Treg cells exported from the thymus inhibit activation and clonal expansion of these precursors, some activated effector T cells still reach the eye. Recognition of the cognate ocular antigen initiates a cascade of inflammatory events resulting in breakdown of the blood–retinal barrier, the recruitment of leukocytes and the onset of uveitis. However, retina-derived antigens released from the damaged tissue can induce the generation of antigen-specific Treg cells via a spleen-dependent process, helping to terminate the inflammatory process and limit the ocular pathology [13–16]

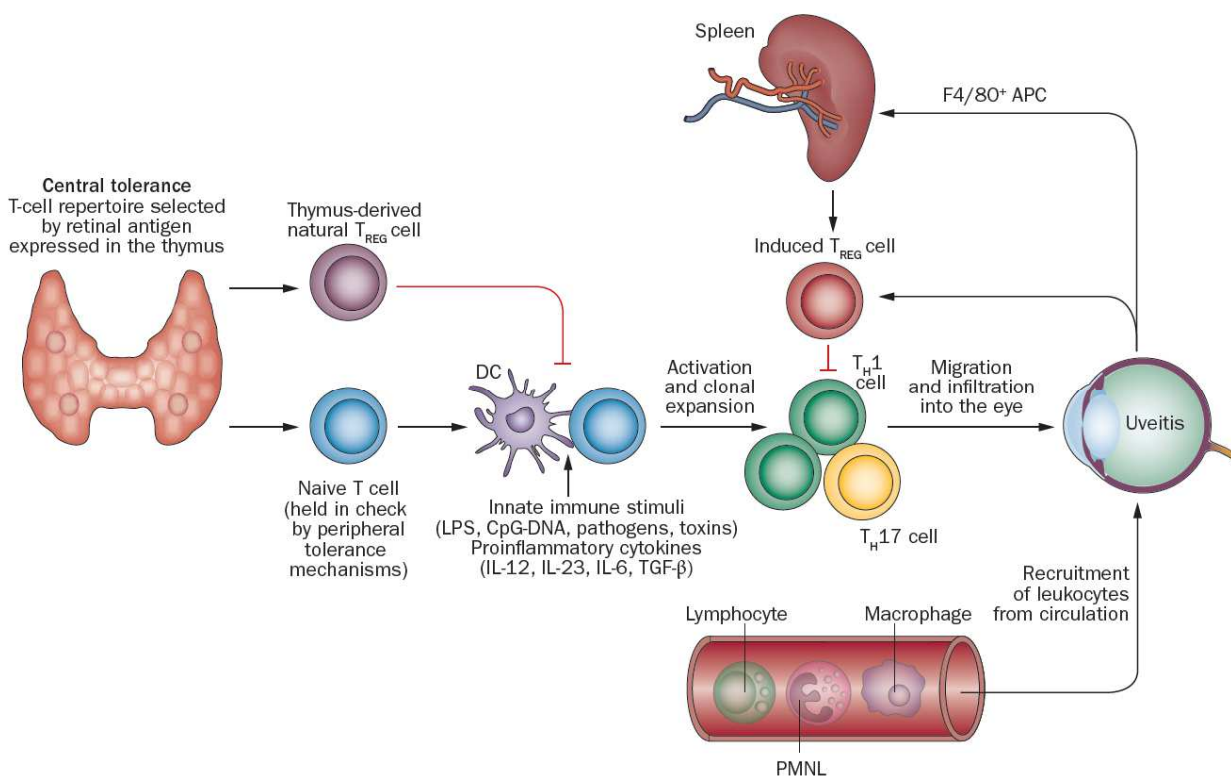


Figure 1. Immunopathogenesis of uveitis [15]

Tissue damage in uveitis is thus linked with Th1 and Th17 lymphocytes, which produce cytokines such as IL-17, IL-23, and TNF $\alpha$ , recruiting leukocytes from the circulation. Some of the key inflammatory cytokines that can either act on the inflammatory subgroups of cells or are produced by these cells and are being studied as potential targets to treat uveitis. For example, although IL-17 is broadly recognized as an inflammatory cytokine contributing to the pathogenesis of uveitis, one study showed that recombinant human IL-17 given systemically protected against inflammation in two different animal models of experimental uveitis [17]. Moreover, initial attempts at targeting IL-17A with the monoclonal antibody secukinumab (Novartis) have resulted in a disappointing benefit in Phase 3 clinical trials for uveitis [18], despite a large body of pre-clinical and clinical data supporting the significant role of this cytokine and its downstream effectors in certain types of immune-mediated uveitis.

These results may suggest that both Th17 and Th1 responses need to be targeted to totally resolve chronic eye inflammation. In other inflammatory diseases, such as Giant Cell Arteritis (GCA) IL-17-producing Th17 cells are sensitive to GC-mediated suppression, whereas IFN- $\gamma$ -producing Th1 responses persist in patients treated with GC, thus triggering the recruitment and activation of macrophages and CD8 T cells [19,20]. Th1 responses could thus be implicated in the occurrence of relapses when GC are tapered. It is therefore necessary to target both Th17 and steroid-resistant Th1 responses to totally resolve chronic eye inflammation.

IL-12 and IL-23 are two key cytokines involved in Th1 and Th17 polarization in uveitis, respectively [21–26]. IL-23-deficient mice are thus resistant to experimental auto-immune uveitis (EAU) [27]. Furthermore, these two cytokines share a common subunit (p40). Ustekinumab, a humanized anti-p40 monoclonal antibody, is able to target both IL-12 and IL-23 pathways, thus disrupting Th1 and Th17 immune responses, whereas secukinumab targeted the Th17 pathway only [18].

Decreasing the dose as well as the duration of treatment with GC is of particular importance in NISU, and ustekinumab, which selectively inhibits Th1 and Th17 pathways in the inflammatory cascade, could provide a perfect additional therapy for NISU to reach this objective. Furthermore, ustekinumab has never been assessed in NISU, which ensures the innovative character of this study.

Therefore, in the present study, we propose to evaluate the efficacy and safety of ustekinumab for the treatment of NISU.

### **1.3. Ustekinumab: data about efficacy and safety**

Several studies have demonstrated the efficacy and safety of this drug in other autoimmune disorders: psoriasis, psoriatic arthritis, Crohn's disease, ankylosing spondylitis, multiple sclerosis, sarcoidosis, systemic lupus erythematosus and atopic dermatitis (reviewed in [28]). Studies with a long follow-up are especially available for psoriasis, psoriatic arthritis and Crohn's disease. Here, we chose to describe the efficacy and safety profiles of ustekinumab in the treatment of psoriasis and psoriatic arthritis as in these studies, ustekinumab was used subcutaneously in association with GC and/or immunosuppressive drugs.

#### **Efficacy**

In uveitis, some case of efficacy of ustekinumab have been reported in psoriatic arthritis [29], Behcet's disease [30]

In psoriatic arthritis, ustekinumab met the primary efficacy and safety endpoints in phase 2 and phase 3 clinical trials.[31–34] As a result, this drug is now used for patients with psoriatic arthritis in whom the response to previous non-biological disease-modifying antirheumatic drugs had been inadequate, or for those in whom anti-TNF- $\alpha$  therapy failed [35]. Of note, the efficacy of ustekinumab is generally observed after 8 weeks of treatment.[32,36]

Furthermore, long-term comparisons of the crude, unadjusted survival curves with the log-rank Mantel–Cox test and the adjusted survival curves (for the statistically significant covariates: sex and previous biological treatment) confirmed that patients receiving ustekinumab had significantly longer survival and a lower rate of side effects than those receiving anti-TNF- $\alpha$  agents [37].

#### **Safety**

The safety profile of ustekinumab is very good. In the phase 3 study performed in psoriatic arthritis, 409 patients received 45 or 90 mg of ustekinumab versus placebo [32,33]. Their mean age was 48 [38.5-55] years and notably, 48.9%, 15.6% and 75.1% of them were simultaneously treated with methotrexate (MTX), glucocorticoids (GC) and non-steroidal anti-inflammatory drugs (NSAIDs), respectively. Safety was very good: serious adverse events occurred in 2.4% in the placebo group, 2.9% in the low-dose ustekinumab group (45 mg) and 1.5% in the high-dose ustekinumab group (90 mg) after 24 weeks of treatment [33]

The most common adverse events in ustekinumab-treated patients were nasopharyngitis (4.6%), upper-respiratory-tract infection (3.4%) and headache (3.4%). No opportunistic infections (including tuberculosis), death, or malignancies were reported by week 52. No serious infections were reported by week 24. After week 24, cholecystitis was noted in two patients (one in the placebo group and one in the 45 mg group), salpingitis in one patient (45 mg group), erysipela in one patient (90 mg group) and a pharyngolaryngeal abscess in one patient (90 mg group).

No major adverse cardiovascular events were noted in any treatment group by week 16. One serious cardiac adverse event (angina pectoris) was reported during the placebo-controlled period in a patient given placebo. Between week 16 and week 24, a non-fatal stroke was reported in a 53-year-old former smoker with pre-existing hypertension and hyperlipidemia who had had a previous cerebrovascular event necessitating internal carotid-artery stenting (this patient was assigned to 45 mg ustekinumab). Between week 24 and week 52, two additional patients (in the placebo group) had myocardial infarctions.

By week 52, 1% of patients receiving 45 mg ustekinumab and 2.1% receiving 90 mg ustekinumab had had an injection-site reaction, compared with 1.6% patients in the placebo group. All injection-site reactions were mild, and none resulted in discontinuation of the study drug [33].

Furthermore, the pattern of adverse events in the placebo crossover and randomized withdrawal phases was similar to that in the placebo-controlled phase [38].

Long-term follow-up of 1247 patients with moderate to severe psoriasis treated for at least 2 years in phase 2 and phase 3 trials revealed an excellent safety profile for ustekinumab (45 or 90 mg) in comparison with placebo. Indeed, rates of overall infections per 100 patient-years were similar in the placebo (121.0) ustekinumab 45 mg (145.7) and ustekinumab 90 mg (131.2) groups. Furthermore, rates of serious infections per 100 patient-years were similar in the placebo (1.70) and ustekinumab 90 mg (1.97) groups and even lower in the ustekinumab 45 mg group (0.45). Notably, rates of malignancies per 100 patient-years during the placebo-controlled periods were very low and comparable among groups: placebo (1.70), 45 mg (0.99) and 90 mg (0.98) [39].

## 1.1 Research hypothesis

Despite increasing evidence that imbalance of Th17 and Treg cells may play a vital role in the pathogenesis of the disease, no trial has been conducted to evaluate the effect of ustekinumab in NISU. Targeting simultaneously the Th17 and Th1 pathways is a promising way to achieve sustained remission in these patients with a very good expected tolerance. At an individual and collective level, thanks to its ability to inhibit both Th1 and Th17 immune responses, we hypothesize that ustekinumab could have a dramatic GC-sparing effect and thus lead to better control of the disease as defined by a high remission rate at W6 and a low relapse risk at W24.

## 1.2 Originality of the project and expected results

Decreasing the dose as well as the duration of treatment with GC is of particular importance in NISU, and ustekinumab, which selectively inhibits Th1 and Th17 pathways in the inflammatory cascade, could provide a perfect additional therapy for NISU to reach this objective. Furthermore, ustekinumab has never been assessed in NISU, which ensures the innovative character of this study.

Therefore, in the present study, we propose to evaluate the efficacy and safety of ustekinumab for the treatment of NISU.

## 2 OBJECTIVES

### 2.1 Primary objective

- To determine the proportion of patients failing to achieve remission within 6 weeks or relapsing from a non-infectious severe uveitis during the 24 weeks of treatment with both corticosteroids, with a mandatory tapering schedule, and ustekinumab, with a loading dose of 90 mg at week 0 and week 4 followed by one maintenance injection of 90 mg at week 16.

### 2.2 Secondary objectives

#### EFFICACY:

- To determine the proportion of patients failing to achieve remission at W6
- To determine the proportion of patients achieving remission at W6 and relapsing between W6 and W24
- To determine the relapse rate at W52
- To determine the time to relapse
- To evaluate the quality of life of patients treated by ustekinumab for NISU

#### SAFETY:

- To assess the safety of ustekinumab in patients with NISU, when combined with corticosteroids

#### IMMUNOMONITORING:

##### To assess the efficacy of ustekinumab on:

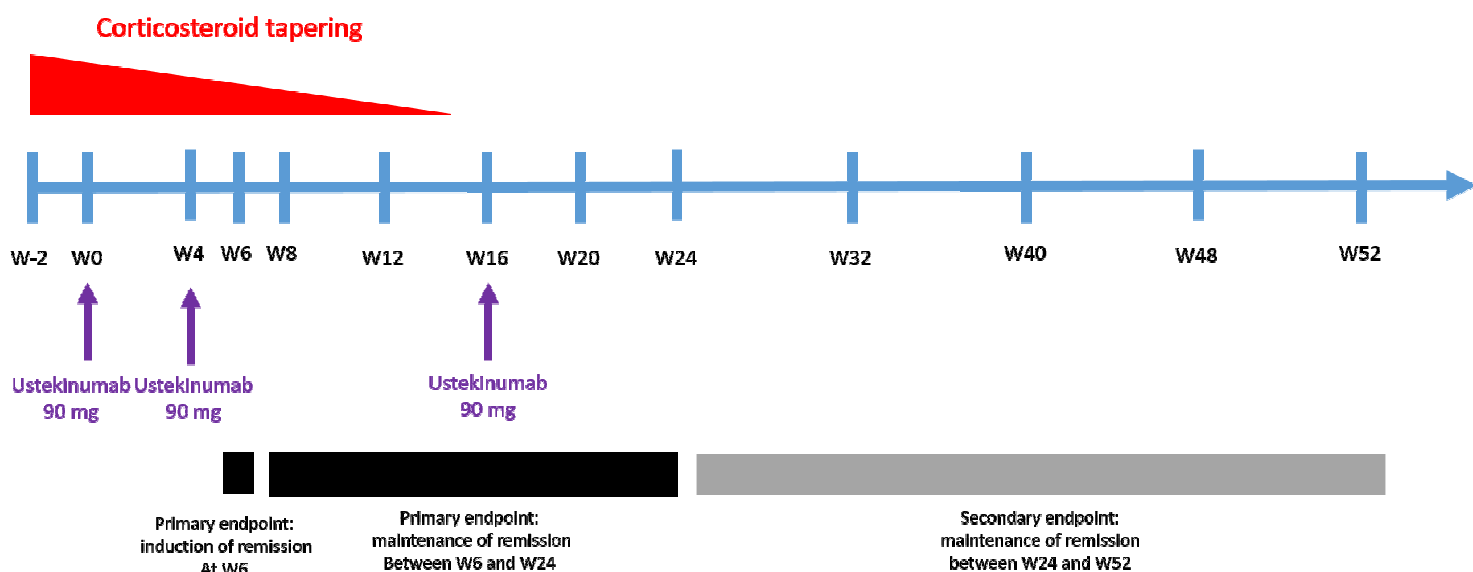
- Th1, Th2, Th17 and Treg polarization
- The concentrations of inflammatory and anti-inflammatory cytokines

## 3 STUDY DESIGN

In this non-randomized, single-arm phase II, proof-of-concept trial, all patients will be given a treatment with ustekinumab (Stelara®) (90mg) at W0, W4 and W16, in addition to corticosteroids with scheduled tapering. The primary endpoint will be evaluated at W6 and W24 and patients will be followed-up for 52 weeks.

All patients will receive 2 weeks of treatment with 60 mg of prednisone before beginning the treatment by ustekinumab (W-2 to W0). After 2 weeks (at W0), a scheduled systemic corticosteroid tapering scheme will be applied. Prednisone has to be decreased to 5mg after 10 weeks (W-2 to W8) and stopped after 15 weeks (W-2 to W13). Patients relapsing during the study will be withdrawn and will no longer receive the study drug.

Subjects who enter the study on topical corticosteroids will undergo a standardized taper schedule beginning at Week 0 until all subjects are off topical corticosteroids by Week 8. Depending on the dose that the subject is on at study entry, the number of drops per day will be decreased every week at predefined increments



Study diagram

Since no efficacy data are available for ustekinumab in this indication, this study first and foremost aims to describe the relapse rate in patients on ustekinumab plus corticosteroids. Moreover, the design will allow us to determine whether the proportion of patients given ustekinumab without relapse significantly exceeds 25% (75% of uveitis patients relapsed under CS alone in a previous trial using the same tapering schedule [12]) with a 5% alpha-risk.

Prednisone will be given according to a standardized protocol (Table1).

**Table 1.** Prednisone tapering schedule.

Week of follow-up	Prednisone (mg/day)
Week -2 to 0	60
Week 0-1	50
Week 1-2	40
Week 2-3	30
Week 3-4	20
Week 4-5	15
Week 5-6	12.5
Week 6-7	10
Week 7-8	7.5
Week 8-9	5
Week 9-10	4
Week 10-11	3
Week 11-12	2
Week 12-13	1
Week 13	Stop prednisone

Week 0 is the day of inclusion/first ustekinumab injection

**4 STUDY TREATMENT AND STRATEGIES**

**4.1 Studied treatment: Ustekinumab (STELARA®) (see Appendix)**

Medicinal product used in the experimental treatment arm: ustekinumab (STELARA®), solution for injection in a pre-filled syringe.

EU/1/08/494/002

Date of first authorization: 16 January 2009

Date of latest renewal: 22 June 2015

ATC code: L04AC05

Description of the investigational medicinal product:

- Active ingredient: Ustekinumab is a fully humanized IgG1k monoclonal antibody that blocks the p40 subunit, which is common to interleukins (IL)-12 and 23. Ustekinumab is produced in a murine myeloma cell line using recombinant DNA technology.
- Administration: Patients in the Ustekinumab group will receive one subcutaneous injection of Ustekinumab (90 mg) at W0, W4 and W16
- Approved pharmaceutical companies responsible for the release of the investigational medicinal product for the European community:  
Janssen-Cilag International NV.  
Turnhoutseweg 30  
2340 Beerse  
Belgium

## 4.2 Supply and handling of products

### 4.2.1 Supply of the products

The coordinating pharmacy will provide the studied treatment mentioned above to the pharmacy of each center. Janssens laboratory has undertaken to provide the study drug (ustekinumab (Stelara®) : 3 injections per patient to each center.

### 4.2.2 Distribution and management of the products

The coordinating pharmacy will provide sufficient packaging of the studied treatment mentioned above to the pharmacy of each center. Ustekinumab will be supplied in its original packaging. Specific labels for the trial will be made in accordance with French regulatory requirements by the sponsor. A pharmacist in each pharmacy will be responsible for product inventory, verification of expiration dates, and storage under the recommended conditions: between 2°C and 8°C and keep away from light

Upon receipt of the prescriptions and as prescribed, authorized pharmacy personnel will dispense a ustekinumab 90 mg/ 1 ml pre-filled syringe for subcutaneous injection on the same day.

### 4.2.3 Return and destruction of unused products

Unused products will be destroyed according to each site's procedure after monitoring and authorization of the promoter. Certificates of destruction will be written by the authorized person.

## 4.3 Allowed and forbidden treatment

Subjects who enter the study on topical corticosteroids (based on the investigator's decision) will undergo a standardized taper schedule beginning at Week 0 until all subjects are off topical corticosteroids by Week 8. Depending on the dose that the subject is on at study entry, the number of drops per day will be decreased every week at predefined increments. The maximum duration of concomitant topical steroid use during the study is 9 weeks.

In accordance with article D5125-45-1 of the Public Health Code, the corticosteroids used in this study will be dispensed by pharmacies, all the conditions specified in the article of law being respected, namely:

- that the persons participating in the research have the same characteristics as those covered by the authorised indication;
- that the design of the research does not require any particular manufacturing or packaging;
- that these medicines, as part of the care, are dispensed in pharmacies;

- that patients would have received these drugs if they had not been included in the clinical trial;
- that the sponsor sets up a monitoring of compliance and tracking.

**Table 2. Topical corticosteroid tapering**

Week	Drops/day
0	12
1	10
2	8
3	6
4	5
5	4
6	3
7	2
8	1

Forbidden treatments during the study are the following:

- anti TNF- $\alpha$ , tocilizumab, abatacept, anakinra
- methotrexate, azathioprine, ciclosporine, cyclophosphamide
- dapsone
- corticosteroid pulses
- prednisone >1 mg/Kg/day
- live vaccines

Beyond these contraindications, we also recommend (not mandatory):

- Prevention of osteoporosis:
  - o Supplementation with vitamin D (880 UI/day) and calcium (1000 mg/day)
  - o Bisphosphonate according to usual recommendations (Haute Autorité de Santé)
- Proton pump inhibitors
- Vaccination against pneumococcus (Pneumo 23®)

#### 4.4 Compliance

Ustekinumab will be administered by a subcutaneous injection at W0, W4 and W16 during a one-day hospitalization. As a consequence, there will be no problem of compliance for ustekinumab. The investigator will prospectively register the administration of the study product in the e-CRF.

#### 4.5 Risk-benefit analysis

Benefit: Individual benefit resulting from the decreased duration and cumulative dose of GC received during NISU treatment.

Risk: Risk related to ustekinumab (see paragraph 8.3).

Due to the low incidence of serious adverse effects related to ustekinumab [32,33,39] and short-term morbidity associated with GC the risk/benefit ratio appears favorable.

## 5 ENDPOINTS

### 5.1 Principal endpoint

Composite end-point comprising:

- Remission at week 6: patients will be considered remitting in the absence of any one of the following criteria in at least one eye:
  - new inflammatory lesions relative to baseline,
  - or anterior chamber cell or vitreous haze grade that did not decrease to 0.5+ or lower
  - or worsening of best-corrected visual acuity by 15 or more letters on the early treatment diabetic retinopathy study chart, relative to the best state previously achieved

- presence of macular edema, same or worse than baseline
- any deviation from the scheduled prednisone tapering because of uveitis activity
- AND patients free of relapse between week 6 and week 24, patients will be considered to have disease relapse if they have:
  - new active, inflammatory lesions relative to baseline
  - or a two-step increase in anterior chamber cell or vitreous haze grade, or a worsening of best-corrected visual acuity by 15 or more letters on the early treatment diabetic retinopathy study chart relative to the best state previously achieved, in at least one eye
  - presence of macular edema at a value greater than the OCT machine-specific, pre-defined upper limit of normal for central retinal thickness
  - any deviation from the scheduled prednisone tapering because of uveitis activity

Summary of treatment failure criteria:

Parameter	Week 6 visit	All other visits after Week 6
Chorioretinal and/or retinal vascular lesion	New lesions relative to baseline	New lesions relative to baseline
OCT evidence of macular edema	Presence of macular edema, same or worse than baseline	Presence of macular edema
Anterior Chamber Cell grade (SUN Criteria) [1]	Inability to achieve $\leq 0.5$	2-step increase relative to best state achieved
Vitreous Haze grade (NEI/SUN criteria) [1,40]	Inability to achieve $\leq 0.5$	2-step increase relative to best state achieved

## 5.2 Secondary endpoint

### EFFICACY:

- Proportion of patients failing to achieve remission at W6: the failure to achieve remission at week 6 is defined by:
  - new inflammatory lesions relative to baseline,
  - Or anterior chamber cell or vitreous haze grade that did not decrease to 0.5+ or lower
  - Or worsening of best-corrected visual acuity by 15 or more letters on the early treatment diabetic retinopathy study chart, relative to the best state previously achieved
- Proportion of patients achieving remission at W6 and relapsing between W6 and W24. Disease relapse between W6 and W24 is defined by:
  - new active, inflammatory lesions relative to baseline
  - or a two-step increase in anterior chamber cell or vitreous haze grade,
  - or a worsening of best-corrected visual acuity by 15 or more letters on the early treatment diabetic retinopathy study chart relative to the best state previously achieved, in at least one eye.
- Relapse rate at W52  
Disease relapse before W52 is defined by:
  - new active, inflammatory lesions relative to baseline
  - or a two-step increase in anterior chamber cell or vitreous haze grade,
  - or a worsening of best-corrected visual acuity by 15 or more letters on the early treatment diabetic retinopathy study chart relative to the best state previously achieved, in at least one eye.
- Time to relapse: time (in days) from corticosteroid initiation to relapse, as defined above. Among patients who fail to achieve remission at the W6 visit, time to relapse will be arbitrarily



set at 42 days (6 weeks) plus the duration of corticosteroid treatment before the first ustekinumab injection

- quality of life of patients treated with ustekinumab for NISU
  - The French version of the VFQ-25 [41] will be completed prior to any study procedure or examination at visit W0, W6, W24 and W52. The questionnaire will be interview administered. The VFQ-25 is a 25-item disease-specific questionnaire about the vision or feelings that patients have about the state of their vision. The VFQ-25 generates the following vision-targeted subscales: global vision rating, difficulty with near vision activities, difficulty with distance vision activities, limitations in social functioning due to vision, role limitations due to vision, dependency on others due to vision, mental health symptoms due to vision, driving difficulties, limitations with peripheral and color vision, and ocular pain. Changes in VFQ-25 scores from the baseline visit will be calculated at each subsequent visit.
  - The generic SF-36 questionnaire will be completed by patients at visits W0, W6 and W24. The SF-36 is a widely used 36 items generic QoL questionnaires that provide population-normed scores with 8 subscales, including: physical functioning; role limitations due to physical health; role limitations due to emotional problems; energy/fatigue; emotional well-being; social functioning; pain;

#### **SAFETY:**

- Frequency and type of side effects (infection, cancer...) related to ustekinumab within 1 year after inclusion

#### **IMMUNOMONITORING:**

- For the immunomonitoring study, blood samples will be taken at W0, W6, W24 (=M6) and W52 (=M12) and sent to Pr. Bonnotte's team, INSERM U1098, Dijon.
- 3) Flow cytometry analysis (for patients included in Dijon only): percentages of Th1, Th2, Th17, and cytotoxic CD8 T cells.
- 4) Serum concentrations of IL-1 $\beta$ , IL-2, IL-6, IL-6Rs, soluble gp130, IL-12p35, IL-12/23p40, IL-17, IL-23p19, IL-17A, TNF- $\alpha$ , IFN- $\gamma$  (all centers)

The immunomonitoring of this phase-II study will provide data with high scientific and medical value. It will validate the concept that ustekinumab triggers a decrease in the Th1 response (unlike to GC alone) and more importantly it will allow us to identify factors able to predict a better or a worse response to ustekinumab before starting a phase-III study. In the future, these data will help clinicians to identify patients who will respond to ustekinumab rather than tocilizumab or GC alone.

### **5.3 Other recorded variables**

These parameters are explained in more detail in paragraph 7.2

- Inflammatory lesions
- Anterior chamber vitreous haze
- Best corrected visual acuity
- Presence of macula edema

## **6 STUDY POPULATION**

### **6.1 Inclusion and non-inclusion criteria**

## 6.1.1 Inclusion criteria

- Patients with newly diagnosed active NISU:
  - o evidence of activity within the 3 months prior to the screening visit as per:
    - VH (visual haze)  $\geq 4$  on the Miami 9-step scale (or VH  $>1+$  according to SUN classification)
    - and/or macular edema on OCT (Central retinal thickness  $\geq 300$  microns)
    - and/or other signs of intraocular inflammation (e.g. perivascular sheathing of retinal vessels or leakage of retinal vessels on fluorescein angiography (FA)).
- Patients judged to be in good health as determined by the Principal Investigator based upon the results of medical history, laboratory profile, physical examination, chest x-ray (CXR), and a 12-lead electrocardiogram (ECG) performed during Screening.
- For men and women of childbearing age, effective contraception must be used by the patient and/or his/her partner throughout the duration of treatment with ustekinumab and until 23 weeks after the end of treatment. Breastfeeding is allowed 23 weeks after the end of treatment. Women considered without risk of pregnancy are those with :
  - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
  - progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
  - intrauterine device (IUD)
  - intrauterine hormone-releasing system ( IUS)
  - bilateral tubal occlusion
  - vasectomised partner
  - sexual abstinence
  - or those surgically sterile (, bilateral oophorectomy or hysterectomy).
  - or at least one year of menopause (amenorrhea for at least 12 months)
- Patients over 18 years of age
- Affiliation to the french social security system
- Patients who have given their consent

## 6.1.2 Non-inclusion criteria

- Subjects considered by the Investigator, for any reason, to be unsuitable candidates for the study.
- Surgery scheduled within 12 months
- Patients with dementia
- Non-compliant patients
- Weight  $<45$  kg or  $> 100$  kg
- Patients under ward of court, tutelage or legal guardianship
- Pregnant or breast-feeding women
- Non-inclusion criteria related to uveitis:
  - Infectious uveitis, masquerade syndromes, or uveitis due to causes other than non-infectious uveitis disease (idiopathic uveitis is permitted)
  - Isolated anterior uveitis
  - Presence of cataract or posterior capsular opacification so severe that an assessment of the posterior segment of either eye is inadequate or impossible
  - Contraindication to mydriasis in either eye or presence of posterior synechiae in the study eye such that mydriasis is inadequate for posterior segment examination
  - Intraocular pressure  $\geq 25$ mmHg by Goldmann tonometry or advanced glaucoma (e.g., cup-to-disc ratio  $> 0.9$ , split fixation on visual field, or need for  $> 3$  intraocular pressure lowering medications to keep IOP  $< 22$  mmHg) in either eye
  - Monocular patient
  - Sarcoidosis-related uveitis
- 
- Non-inclusion criteria related to ustekinumab:

- History of congenital or acquired immunodeficiency (e.g. common variable immunodeficiency disease).
  - History of prior treatment with ustekinumab
  - Hypersensitivity to ustekinumab, one of its excipients or another human or murine monoclonal antibody or latex
  - Evidence of active infection at the time of baseline visit, or other Infectious contraindication to ustekinumab
  - Neoplasia < 5 years, (except for in situ cervical cancer and skin carcinoma with R0 resection)
  - Active tuberculosis or sign of latent tuberculosis (based on a history of untreated contact, a history of opacity of more than 1 cm in diameter on the chest x-ray, or an in vitro test positive[Quantiferon® or T-spot-TB®]). A history of TB disease or latent TB whose treatment was completed is not an exclusion criteria, regardless the Quantiferon® or T-spot-TB® is positive or not.
  - Known positive syphilis serology, HIV antibody, hepatitis B surface antigen or anti-nucleocapsid antibody of hepatitis B virus, and/or hepatitis C antibody.
  - History of multiple sclerosis and/or demyelinating disorder
  - Infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the Baseline Visit or oral anti-infectives within 14 days prior to the Baseline Visit.
  - Screening laboratory and other analyses showing any of the following abnormal results:
    - AST, ALT > 1.75 × upper limit of the reference range;
    - WBC count <  $3.0 \times 10^9/L$ ;
- Other treatments:
- o Corticosteroids
    - History of ≥3 systemic corticosteroid therapies (topical or inhaled treatments allowed) for another disease (e.g. asthma) within the last 6 months before screening visit
    - Subjects who have received IV corticosteroids within 2 weeks prior to the screening Visit
    - Dexamethasone intravitreal implant less than 6 months prior to study
  - o Patients receiving (or having stopped for less than 6 months or 5 elimination half-lives) an immunosuppressive or immunomodulatory drug or biotherapy:
    - anti TNF- $\alpha$ ,
    - tocilizumab,
    - abatacept,
    - anakinra,
    - methotrexate,
    - azathioprine,
    - ciclosporine,
    - cyclophosphamide,
    - dapsone
    - or corticosteroid pulses
  - o Live vaccine administered within 30 days preceding inclusion

## 6.2 Calculation of the number of subjects required

### 6.2.1 Justification

In the VISUAL 1 study, the median time to treatment failure (defined by uveitis relapse) was 24 weeks (plus at least two weeks of corticosteroid prior to the beginning of the study) in the adalimumab group and 13 weeks. An approximate relapse rate of 75% in corticosteroid arm (25% relapse-free patients) and 50% in adalimumab plus corticoid arm (50% relapse-free patients) [12] was observed 24 weeks after the beginning of the treatment.

We calculated the sample size using the following hypothesis:

- More than 25% relapse-free patients at W24 are expected (less than 75% relapse, as observed under corticosteroid alone)

- At least 50% relapse-free patients at W24 are needed to confirm the significant clinical efficacy of Ustekinumab (less than 50% relapse, as observed under adalimumab + corticosteroids)
- An alpha risk of 0.05 and a power of 0.8

Sample size was determined using Fleming's single-stage phase II design.[42,43] We hypothesized that ustekinumab would be considered clinically inactive if more than 75% of patients with NISU experience relapse W24 ( $\leq 25\%$  relapse-free patients), whereas ustekinumab would be considered clinically active if less than 50 % of patients experienced relapse ( $>50\%$  relapse-free patients). Based on these hypotheses, with a one-sided alpha risk of 0.05 and a power of 90%, 26 patients are required. Allowing for 10% of drop-outs, **29 patients will be included in this study**

**If the number of patient responding (relapse-free) is  $\geq 11$ , the hypothesis of a responder rate of less than 25% will be rejected with a power of 0.8**

**If the number of patient responding (relapse-free) is  $\leq 10$ , the hypothesis of a responder rate of more than 50% will be rejected with a power of 0.8**

### 6.2.2 Feasibility

A minimum of 7 sites were selected in France based on their experience in inflammatory eye disease and their participation in a French network for inflammatory eye diseases. A team including both an ophthalmologist and an internist is involved in each selected site, allowing the systematic screening of all eligible patients in each site participating in the study. According to available data from participating centers, 2 to 6 eligible patients are expected per 3 months in each of the 7 sites. 1 to 2 patients are expected to be included in each site every 3 months. A mean of 0.23 patients included per center are needed to complete our recruitment objectives.

The coordination of the study will be under the responsibility of CIC INSERM 1432 team, which has proven expertise in conducting early phase trials.

Study investigators are skilled physicians involved in the clinical management of uveitis. Internist investigators belong to the "Club Medecine interne et Oeil" (CMIO), a French research network that has conducted several national clinical studies about inflammatory eye diseases funded by national "PHRC" (UVEXATE study in 2007, ULISSE study in 2009, RUBI study in 2016). All investigators of the participating centers are used to participating in studies dealing with uveitis.

Severe uveitis, as defined in our protocol, corresponds to patients presenting with intermediate uveitis, posterior uveitis and pan-uveitis referred to university hospitals to ophthalmologists and/or internists, with less than 25% being related to an infectious etiology [44].

### 6.3 Total duration of the study

<b>Duration of inclusion period</b>	18 months
<b>Duration of participation of each patient</b>	12 months
<b>Total duration of the study</b>	30 months

#### Conditions of temporary or permanent cessation of the study

In case of inclusion of less than 20% of the total number of patients required to carry out the study at the mid-point of the study, the opinion of the steering committee will be asked about:

- Methods to optimize recruitment
- The possible termination of the project

The study could also be stopped following a decision of the data safety and monitoring board, particularly if there are a significant number of serious adverse events. Along this line, a safety monitoring board will be created (see §10).

Administrative delays can also lead to temporary cessation of the research (e.g. review of inclusion criteria, pending review of CPP on protocol amendments...)

#### **6.4 Duration of participation for a patient: 12 months**

Patients participating in this study should not simultaneously participate in another clinical trial until the end of the study (i.e. 12 months after inclusion).

For the men and women of childbearing age, effective contraception must be used for the patient or his/her partner throughout the duration of treatment with ustekinumab and until 23 weeks after the end of treatment. Women considered with no risk of pregnancy are those with menopause for at least one year or those surgically sterile (tubal ligation, bilateral oophorectomy or hysterectomy).

#### **6.5 Permanent or temporary cessation of participation for the patient**

Participants are free to withdraw their consent at any time. They will be managed according to their health state. If consent is withdrawn, data collected up to the moment of withdrawal will be deleted or analyzed depending on the patient's wishes.

In the case of serious adverse events, patients could be temporarily or permanently excluded from the research. In this case, safety data and efficacy data will be collected until the end of the follow-up planned for the study (1 year), as these patients will be included in the intention-to-treat analysis.

In cases of emergency surgery (patients for whom surgery is scheduled during the study will be excluded), ustekinumab will be stopped and the patient will be temporarily or permanently excluded from the research. In this case, safety data and efficacy data will be collected until the end of the follow-up planned for the study (1 years), as these patients will be included in the intention-to-treat analysis.

Pregnancy is an exclusion criterion in this trial. However, if a pregnancy is discovered after inclusion, the patient must be excluded from the trial, but will be followed to the end of the pregnancy.

## **7 STUDY PROCEDURE**

### **7.1 Course of the study**

#### **7.1.1 Pre-screening of patients**

Identification of patients for screening:

Each investigator will screen all eligible patients during a routine visit. In all participating centers, the investigator will investigate the uveitis etiology before beginning a treatment, according to national and international guidelines. If the diagnosis of NISU is finally retained and if the decision to begin a CS treatment is made, the patient will be checked for eligibility.

#### **7.1.2 Screening visit (W-2)**

- During this visit, information on the implementation of the study and the objectives of the research will be given to the subject (the information sheet will be read and then given to the subject.)
- The patient will have time to think about joining the study before giving his/her consent
- The informed consent form must be signed by the participant before the participant can be included in the study. Any subjects/patients participating in the study must have a prior medical examination that is appropriate for the research.

Checklist for screening visit:

- Information is provided to the patient: set-up and objectives of the study, answer patients' questions regarding the objectives, the nature, the constraints, the likely risks and the potential benefits of the study

- Written consent
- Checking for inclusion and non-inclusion criteria
- Medical history, physical examination, vital signs
- Routine lab tests: hematology (FBC), blood chemistry, C-reactive protein, fibrinogen, ESR
- Ophthalmologic examination (see 7.2): best corrected visual acuity (BCVA) testing, Slit Lamp Exam, tonometry, dilated indirect ophthalmoscopy, optical coherence tomography (OCT)

In case of eligibility:

- A pre-therapeutic appraisal will be performed:
  - o ECG
  - o Chest X Ray
  - o Quantiferon test®
  - o urine analysis
  - o SGOT, SGPT
  - o alkaline phosphatase, gamma GT
  - o Serology for HIV, B and C hepatitis
  - o Serum protein electrophoresis
  - o Pregnancy test
- Prednisone will be started at 60 mg/day 2 weeks before inclusion
- If topical corticosteroids are necessary, based on the investigator's opinion. Tapering is scheduled according to table 2
- Vaccination against pneumococcus (Pneumo23®) can be proposed
- **Pré-Inclusion** will be performed online by the investigator using the secure CleanWeb platform, after identification through a personal password and after a final check of the eligibility criteria. In case of difficulties, the investigator may contact the coordinating center, INSERM CIC1432.

#### 7.1.3 Inclusion visit (W0)

- This inclusion visit takes place 2 Weeks after the screening visit if all the criteria are gathered, on the occasion of a subsequent hospitalization (1 day hospitalization).
- Eligible patients will definitively be included after a **final check of inclusion and non-inclusion criteria** (particularly results of Quantiferon® and ophthalmologic examination).
- **Medical history, physical examination, vital signs, and collection of clinical and biological data**
- **Ophthalmologic examination (see 7.2):** BCVA testing, Slit Lamp Exam, tonometry, dilated indirect ophthalmoscopy, OCT
- **Self-administered questionnaires: VFQ-25, SF-36**
- 
- **Blood samples:**
  - o **Routine lab tests:** hematology (FBC), blood chemistry, serum creatinine, C-reactive protein, fibrinogen, ESR, SGOT, SGPT, gamma GT, Pregnancy test
  - o **Research samples:**
    - **Centers of Dijon:** total blood (8 heparin tubes of 6 mL) to isolate peripheral blood mononuclear cells (PBMC), to be sent within 24 hours to Pr. Bonnotte's team, INSERM U1098, Dijon
    - **All centers:** serum (1 dry tube of 5 mL) and DNA storage (1 EDTA tube of 6 mL) These samples will be stored at -20°C in each center and sent later to Pr. Bonnotte's team, INSERM U1098, Dijon.
- **Inclusion** will be performed online by the investigator using the secure CleanWeb platform, after identification through a personal password and after a final check of the eligibility criteria. In case of difficulties, the investigator may contact the coordinating center, INSERM CIC1432.
- **Delivery of a diary for patients**

The study summary, visit calendar, prednisone doses and all instructions related to the study will be written in the patient's diary in order to guide the patient and to enable other healthcare professionals (e.g. general practitioner) to have the necessary information for any other follow-up of the patient. The phone number of the investigator and coordinating center will also be written so that the patient may contact them in case of questions or problems.

This diary will also be used to collect data concerning possible undercurrent diseases and medical consultations with other health care professionals. The patient will be asked to bring his/her diary for each follow-up visit.

- **Prescription of corticosteroid therapy (Cortancyl®, non-substitutable) and of associated measures detailed in the protocol.** The dose of prednisone will be recorded in the e-CRF (total dose and equivalent in mg/kg/day).
- **If applicable, tapering of topical corticosteroid** according to table 2
- **Subcutaneous administration of 90 mg of ustekinumab**

#### 7.1.4 Follow-up visits (W4, W6, W8, W12, W16, W20, W24, W32, W40, W48)

Follow-up visits will be scheduled in the center where the patient was included during a one-day hospitalization. At Follow-up visits at W4 and W16, a subcutaneous injection of ustekinumab will be administered.

#### Checklist for Follow-up visits:

- **Medical history, physical examination, vital signs, and collection of clinical and biological data**
- **Ophthalmologic examination** (see 7.2): BCVA testing, Slit Lamp Exam, tonometry, dilated indirect ophthalmoscopy, OCT
- **inflammatory activity of uveitis:** achievement of remission (W6), occurrence of relapse (W8 to W24 for the primary objective, and from W12 to W52 for the secondary objective)
- **Monitoring of occurrence of skin tumors : skin examination in order to detect potential onset of skin cancer**
- **Self-administered questionnaires:** VFQ-25 and SF-36 (W6, W24 and W52 only)
- **Blood samples:**
  - **Routine lab tests:**
  - Hematology (FBC), blood chemistry, C-reactive protein, fibrinogen, ESR
  - SGOT, SGPT (until W24), Pregnancy test
  - **Research samples (W6 and W24 only)**
  - Dijon center: total blood for PBMC isolation (8 heparin tubes 6 mL): to be sent within 24 hours to Pr. Bonnotte's team, INSERM U1098, Dijon
  - All centers: serum storage (1 dry tube of 5 mL). Serum will be stored at -20°C in each center and then sent to Pr. Bonnotte's team, INSERM U1098, Dijon.
- Tapering of prednisone according to the protocol (Table 1).
- **If applicable, tapering of topical corticosteroid** according to table 2
- **Completion of the patient's diary** (date of visits, prednisone and topical corticosteroid doses)

Subcutaneous injection of ustekinumab (90 mg) will be administered at W4 and W16. If it is impossible to give the ustekinumab injection (typically because of an interfering infection) the ustekinumab injection will be scheduled for 2 weeks later. If the injection of ustekinumab is still impossible after this delay, ustekinumab will be stopped. In this case, tapering of prednisone will be continued according to the standardized protocols. Safety data and efficacy data will also be collected until the end of the follow-up planned for the study (1 year), as these patients will be included in the intention-to-treat analysis.

## 7.1.5 End of visit (W52)

The study will end at W52:

- **Medical history, physical examination, vital signs and collection of clinical and biological data**
- **Ophthalmologic examination (see 7.2): BCVA testing, Slit Lamp Exam, tonometry, dilated indirect ophthalmoscopy, OCT Completion of the patient's diary (date of visits, prednisone doses)**
- **inflammatory activity of uveitis: occurrence of relapse**
- **Monitoring of occurrence of skin tumors**
- **Self-administered questionnaires: VFQ-25, SF-36**
- **Routine lab tests: Hematology (FBC), blood chemistry, C-reactive protein, fibrinogen, ESR**
- **Research samples**
  - Dijon center: total blood for PBMC isolation (8 heparin tubes 6 mL): to be sent within 24 hours to Pr. Bonnotte's team, INSERM U1098, Dijon
  - All centers: serum storage (1 dry tube of 5 mL). Serum will be stored at -20°C in each center and then sent to Pr. Bonnotte's team, INSERM U1098, Dijon.

## 7.1.6 Description of the rules for ending or interrupting the study

Any person included in the study will be followed to the end of the study apart from those who have withdrawn their consent.

The Research may be terminated if the Competent Authority suspends or prohibits the conduct of the Research and/or by decision of the promoter for safety reasons

## 7.1.7 Period of exclusion-exclusivity and National Files

<b>Period of exclusivity</b> If yes, the patient cannot take part in another study simultaneously The patient cannot take a part in another study simultaneously if this study modifies the treatment of NISU or introduces an exclusion criterion	<input checked="" type="checkbox"/> yes <input type="checkbox"/> no
<b>Period of exclusion</b> If yes, the patient cannot take part in another study at the end of this one for a specified duration	<input type="checkbox"/> yes Duration: .... <input checked="" type="checkbox"/> no
<b>Amount of compensation received by a patient</b>	None
<b>Registration in the National File</b>	<input type="checkbox"/> yes <input type="checkbox"/> no

Definition of the National File:

In accordance with article L. 1121-16 of the Public Health Code, persons who should be registered in this file are those who take part in biomedical research bearing on products mentioned in article L. 5311-1 and are

- either healthy persons
- or patients whose disease is not concerned by the product being studied.

In addition, on a case by case basis, the Ethics Committee could require, given the risks and constraints induced by the protocol, that persons involved in other categories of research, whether or not they are included among the products mentioned in article L. 5311-1 of the Public Health Code, be registered.

The investigators are the only persons authorized to register volunteers in this file.

## 7.1.8 Reimbursement



During the study, there are 3 more visits than the usual follow-up for this condition. The sponsor therefore plans to reimburse patient travel expenses for these 3 visits as follows:

10€ for a place of residence located in the agglomeration of the investigator site

30€ for a place of residence located in the department of the investigator site

75€ for a place of residence located in the region of the investigator site

## 7.2 Ophtalmologic procedures

### **Best Corrected Visual Acuity Testing**

Refraction and assessment of best corrected visual acuity (BCVA) will be assessed at every visit. At each visit, subjects should undergo refraction testing and the result of the refraction test for each eye will be recorded on the eCRF. Using the appropriate corrective lenses based on the subject's refraction at that visit, the subject's best corrected visual acuity (BCVA) will be measured using a standard ETDRS chart. Subjects will stand 4 meters away from the chart. The test lighting level will be 85cd/m<sup>2</sup>. Testing for BCVA will be done for individual eyes, starting with the right eye, with the contralateral eye covered. BCVA results will be recorded as the number of letters read from the ETDRS chart.

### **Slit Lamp Exam**

The slit lamp exam will be completed to measure the following findings: Anterior chamber cell count and Age-Related Eye Disease Study (AREDS) [45] lens opacity grading. The slit lamp examination will be performed prior to the application of mydriatic eyedrops to dilate the subject's pupils for further assessments.

The number of anterior chamber (AC) cells observed within a 1 mm × 1 mm slit beam will be recorded for each eye. The reported number will be used to determine the grade according to the SUN criteria [1]

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

Lens opacity will be graded using the AREDS [45] standard photographs as reference.

### **Tonometry**

Tonometry will be performed at every visit to measure the intraocular pressure for both eyes. Applanation tonometry is preferred but non-contact tonometry can also be used if the site does not have the equipment to perform applanation tonometry. However, the same technique should be used for all visits for an individual patient.

### **Dilated Indirect Ophthalmoscopy**

Subject's pupils will be dilated in preparation for indirect ophthalmoscopy. Dilated indirect ophthalmoscopy is performed to determine both the vitreous haze grading and the absence/presence of active chorioretinal and/or retinal vascular lesions. Grading of vitreous haze will be based on the publication from the National Eye Institute (NEI) which has also been adapted by the SUN working group. [1,40] Sites will use the standard photographs given to them by the sponsor and the description as follows when determining the grade for vitreous haze.

Grade	Description
0	No evident vitreal haze
0.5+	Slight blurring of the optic disc margin because of the haze; normal striations and reflex of the nerve fiber layer cannot be visualized
1+	Permits a better definition of both the optic nerve head and the retinal vessels (compared to higher grades)
2+	Permits better visualization of the retinal vessels (compared to higher grades)
3+	Permits the observer to see the optic nerve head, but the borders are quite blurry
4+	Optic nerve head is obscured

The presence of chorioretinal or retinal vascular lesions will also be determined via dilated indirect ophthalmoscopy at Screening and Baseline visits. At all subsequent visits, dilated indirect

ophthalmoscopy will be performed to determine the presence of new lesions based on the Investigators' clinical judgment.

### **Fundus Photography**

Fundus photography will be performed at Screening, Baseline, at the time of Treatment Failure or completion of study (final visit) to obtain documented evidence of the presence or absence of active chorioretinal and/or retinal vascular lesions.

### **Optical Coherence Tomography**

Each subject will undergo OCT measurements of the central retinal thickness (1 mm subfield) to evaluate macular edema at every visit using the same machine in one given center throughout the study. The definition of normal central retinal thickness in this clinical study is based on machine-specific cut-offs in each center. Any measurement above these machine-specific cut-offs will indicate an increase in central retinal thickness, a surrogate for macular edema.

At the Week 6 visit or beyond, the presence of macular edema will be deemed Treatment Failure.

### **Fluorescein angiography and indocyanin green**

All patients will receive a fluorescein and indocyanin green angiogram (FA/ICG) at W0, W6 and W24; to evaluate retinal vasculitis, (e.g., perivascular sheathing of retinal vessels or leakage of retinal vessels) and /or choroidal lesions.

Products will be used according to their respective marketing authorization and angiogram made following local usual procedure.

## **7.3 Immunomonitoring analyses**

DNA and serum will be stored in each center (4 samples at -80°C or -20°C) at W0 (DNA and serum) and W6, W24 and W52 (serum only) and sent to Pr. Bonnotte's team, INSERM U1098, Dijon at the end of the study. Serum cytokine measurements including IL-1 $\beta$ , IL-2, IL-6, IL-6Rs, soluble gp130, IL-12p35, IL-12/23p40, IL-17, IL-23p19, IL-17A, TNF- $\alpha$ , IFN- $\gamma$  will be performed later on by multiplex technology (duplicate analyses).

PBMCs will be collected at 4 visits (W0, W6, W24 and W52) in Dijon patients only, in order to perform cytometry analyses to measure the percentages of:

- Th1 (CD3<sup>+</sup>CD4<sup>+</sup>IFN $\gamma$ <sup>+</sup>), Th2 (CD3<sup>+</sup>CD4<sup>+</sup>IL-4<sup>+</sup>), Th17 (CD3<sup>+</sup>CD4<sup>+</sup>IL-17<sup>+</sup>)
- Treg (CD4<sup>+</sup>CD25<sup>high</sup>FoxP3<sup>+</sup>) and their phenotype (expression of HELIOS, CD39 and CD45RA)

Unused PBMCs will be frozen in RPMI+DMSO 10% in liquid nitrogen. Considering the small number of centers that will send PBMCs, we expect to obtain around 100 samples (25 patients with 4 samples for each one).

Supernatants will also be collected at W0, W6, W24, W52 in all the centers and measure of the concentrations of IL-1 $\beta$ , IL-2, IL-6, IL-6Rs, soluble gp130, IL-12p35, IL-12/23p40, IL-17, IL-23p19, IL-17A, TNF- $\alpha$ , IFN- $\gamma$  will be performed by ELISA and Luminex® later on.

These experiments are routinely performed in Pr. B. Bonnotte's team, INSERM U1098, Dijon. For this study, experiments will essentially be performed by Marion Ciudad (research technician) under the supervision of Pr. B Bonnotte.

This immunomonitoring study is performed in order:

- to validate the concept that ustekinumab, unlike GC alone, triggers a decrease in the Th1 response
- to identify factors able to predict a better or a worse response to ustekinumab before starting a phase-III study

In the future, these data will help clinicians to identify patients who will respond to ustekinumab rather than tocilizumab or GC alone.

## **7.4 Collection of biological samples**

After the use of serum, DNA and PBMC for the above-mentioned experiments, a biobank will be created with the remaining samples. Serum and DNA will be stored at -80°C and PBMCs in liquid nitrogen (-196°C) in CR INSERM U1098, Pr. BONNOTTE's Team, bâtiment B3, CHU de Dijon, rue Angélique Ducoudray, 21000 Dijon. Samples will be kept until biological material is exhausted.

Patients will be informed that a collection of biological samples will be created during this study. They will be informed about the place of storage and the purpose of the secondary use that may be made of them.

The patient has the right to oppose the subsequent use of his/her biological samples. He/she can exercise this right by contacting the doctor-investigator who proposed the study, and who had the person sign the informed consent form corresponding to the research and the consent form corresponding to the preservation and use of samples.

At any moment, the patient can withdraw his/her consent and demand the destruction of the samples by contacting the organization or the department that is storing the samples.

### 7.5 Study schedule

	Screening	W0	W4	W6	W8	W12	W16	W20	W24	W32	W40	W48	W52
	W-2												
Written Informed Consent	X												
Medical history	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	
Side effects		X	X	X	X	X	X	X	X	X	X	X	
Compilation of eCRF	X	X	X	X	X	X	X	X	X	X	X	X	
ECG	X												
Chest X-rays	X												
Pneumo 23® injection (optional)	X												
Search for any acute contraindications to ustekinumab (infection ...)		X	X				X						
Ustekinumab (90 mg) subcutaneous injection		X	X				X						
<b>Ophthalmologic examination</b>													
BCVA	X	X	X	X	X	X	X	X	X	X	X	X	X
Slip Lamp Exam	X	X	X	X	X	X	X	X	X	X	X	X	X
Tonometry	X	X	X	X	X	X	X	X	X	X	X	X	X
Dilated indirect ophthalmoscopy	X	X	X	X	X	X	X	X	X	X	X	X	X
Fundus photography	X	X		X					X				
Optical Coherence Tomography	X	X	X	X	X	X	X	X	X	X	X	X	X
Fluorescein angiography		X		X					X				
Indocyanin green angiography		X		X					X				
<b>Questionnaires for patients</b>													
VFQ-25		X		X					X				X
SF-36		X		X					X				X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X
Administration of treatment		X											
<b>Routine labs tests</b>													
FBC	X	X	X	X	X	X	X	X	X	X	X	X	X
Quantiferon test	X												
Blood Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X
SGOT, SGPT	X	X	X	X	X	X	X	X	X				
Alkaline phosphatase, Gamma GT	X	X											
C-reactive protein	X	X	X	X	X	X	X	X	X	X	X	X	X
Fibrinogen	X	X	X	X	X	X	X	X	X	X	X	X	X
ESR	X	X	X	X	X	X	X	X	X	X	X	X	X
Serology (HIV, B and C hepatitis)	X												
Serum protein electrophoresis	X												
β HCG	X	X	X	X	X	X	X	X	X	X	X	X	X
<b>Research samples</b>													
Serum storage (5 mL)		X		X					X				X
PBMC (8x6 mL, heparin) *		X		X					X				X
DNA storage (6 mL, EDTA)		X											

\*PBMCs will be sampled in Dijon patients and sent within 24 hours to Pr. Bonnotte's team, INSERM U1098, Dijon.

## 8 EVALUATION OF SAFETY

Injections will be given during day-hospitalization and patients will be monitored for 2 hours after the injection. In cases of hypersensitivity, ustekinumab will be definitively stopped. The safety of ustekinumab will be evaluated at each visit and at any time in case of safety concern.

If it is impossible to give the ustekinumab injection (typically because of an interfering infection) the ustekinumab injection will be scheduled for 2 weeks later. If the injection of ustekinumab is still impossible after this delay, ustekinumab will be stopped. In this case, tapering of prednisone will be continued according to the standardized protocols. Safety data and efficacy data will also be collected until the end of the follow-up planned for the study (1 year), as these patients will be included in the intention-to-treat analysis.

### 8.1 Description of safety parameters evaluated and declaration

Safety will be assessed by evaluating the general, clinical and biological status of patients at the consultations planned for in the protocol and by recording events occurring between these consultations.

### 8.2 Adverse events/side effects, definitions

#### 8.2.1 Definitions:

- **Adverse event** any harmful symptom occurring in a person taking part in biomedical research whether or not this manifestation is linked to the research or the product used.
- **Adverse effect:**
  - *In the context of a trial bearing on a drug*  
**Adverse effect of an experimental drug /preparation for cell therapy:** any unwanted harmful reaction related to a drug/preparation for cell therapy whatever the dose administered.
- **Severity criteria:** an event / an effect is considered serious if it meets at least one of the severity criteria below:
  - leads to death
  - threatens the life of the person taking part in the research
  - requires hospitalization or prolongation of the hospitalization,
  - causes severe or lasting disability or handicap
  - leads to a congenital anomaly or fetal malformation or a termination of pregnancy.
  - is considered medically significant

Any clinical event or laboratory result considered serious by the investigator, but does not meet the severity criteria defined above is considered medically significant. The may present a risk to the patient and require a medical intervention to preclude an outcome that corresponds to one of the severity criteria mentioned above.

The following may be considered medically significant: second cancers, overdoses, events leading to sick leave, events requiring the interruption of a treatment that is essential for the patient, errors in medication, uses of drugs not planned for in the protocol (incorrect use, abuse,...)

Pregnancy is an exclusion criterion in this trial. However, if a pregnancy is discovered after inclusion, the patient must be excluded from the trial. The sponsor must be informed immediately via the declaration form for serious adverse events (in such cases, none of the severity criteria will be ticked). The patient in question must be followed to the end of the pregnancy and the outcome of the pregnancy, whatever it is, must be reported to the sponsor. Congenital anomaly or fetal malformation due to a paternal exposure must also be reported to the sponsor. The child won't be followed after his birth and no information will be collected on the patient's partner.

- **Expected or unexpected SAE:** distinction must be made between expected and unexpected severe adverse effects. The expected nature of an adverse effect is determined by the sponsor in the reference safety information. (RSI)

In any case, any effect for which the nature, severity, frequency or outcome does not match with the RSI will be considered as an unexpected serious adverse effect.

The RSI is given in the summary of product characteristics if the drug has been authorized or in the investigator's brochure if it has not.

N.B. The RSI may change during a clinical trial. The version of the RSI to be applied is that in force at the time of the onset of unexpected severe adverse effects.

- **New fact:** Any new information that could lead to a re-evaluation of the benefit/risk ratio of the research or of the product studied in the research, to modifications in the use of the product, in the conduct of the research, or the documents relative to the research, or to the suspension, or interruption or modification of the research protocol or similar research
- Product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product

### 8.2.2 Events occurring in the context of the research

In the context of this protocol:

- The following will be considered SAE:
  - any event that leads to the death or threatens the life of the person taking part in the research
  - any event that requires hospitalization or prolongation of the hospitalization,
  - any event that causes severe or lasting disability or handicap
  - any event that leads to a congenital anomaly or fetal malformation or a termination of pregnancy in the descendants of patients who received the trial treatments,
  - any event that is considered medically significant, such as those defined above
- The following will NOT be considered SAE:
  - an event leading to an outpatient visit or consultation at a hospital, or outpatient unit or a day-care hospital,
  - hospitalizations (more than one night) or prolonged hospitalization for the following reasons:
    - scheduled hospitalization for routine interventions or treatments that are part of a surveillance or therapy program defined beforehand,
    - hospitalization or intervention required by the protocol,
    - hospitalization for exploration purposes not related to a modification in the patient's condition
    - hospitalization of convenience for social reasons (e.g.: hospitalization of an elderly person dependent on a spouse recently admitted to hospital)
    - elective hospitalization not related to an aggravation of the clinical status and not linked to the objective of the clinical study, but taking place during the clinical study (e.g.: plastic surgery),

### 8.3 Description of expected adverse events

**Expected side effects related to ustekinumab are those listed in the Summary of Medicinal Product of STELARA® 90mg (ustekinumab) Appendix):**

**For information, the side effects are:**

- **infections:**
  - 1 to 10%: nasopharyngitis, upper-respiratory-tract infection, tooth infection
  - 0.1 to 1%: cellulitis, zona, viral upper-respiratory-tract infection
- **immunological disorders:**
  - 0.1 to 1%: hypersensitivity (rash, urticaria)
  - 0.01 to 0.1%: severe hypersensitivity (angioedema, collapses)
- **psychiatric disorders:**
  - 0.1 to 1%: depression
- **neurological disorders:**
  - 1 to 10%: headaches, dizziness
  - 0.1 to 1%: facial paralysis
- **Ear Nose and Throat (ENT) and pulmonary disorders:**
  - 1 to 10%: sore throat

- 0.1 to 1%: nasal obstruction
- **digestive disorders:**
  - 1 to 10%: diarrhea, nausea
- **skin disorders:**
  - 1 to 10%: pruritis
  - 0.1 to 1%: psoriasis
  - 0.01 to 0.1%: erythroderma
- **rheumatologic disorders:**
  - 1 to 10%: backache, myalgia, arthralgia
- **general symptoms:**
  - 1 to 10%: fatigue, rash/pain at the injection site
  - 0.1 to 1%: reaction at the injection site (hemorrhage, hematoma, pruritis, edema)

**Expected side effects related to NISU are:** headache, vision loss

**Expected side effects related to CORTANCYL® (prednisone) are those listed in the Summary of Medicinal Product of CORTANCYL® 20mg appendix:**

- increased risk of infections
- increased appetite, which can potentially lead to weight gain
- diabetes (or worsening of existing diabetes)
- hypertension
- edema
- a combination of fatty deposits that develop in the face, stretch marks across the body and acne, known as Cushing's syndrome
- acne
- thin skin that bruises easily
- muscle weakness
- delayed wound healing
- osteoporosis
- glaucoma and cataracts
- stomach ulcers
- rapid mood swings and mood changes: aggressiveness, irritability
- mental health problems, such as depression, suicidal thoughts, anxiety, confusion and hallucinations
- reduced growth in children

## 8.4 Conduct in such events

### 8.4.1 Role of the investigator

#### Initial declaration of a serious adverse event

The principal investigator informs the sponsor by telephone, fax or mail of the onset of **any serious adverse event** (that is to say whether or not the event is linked to the product being studied or to the research), whether it is expected or unexpected. Adverse events that are not serious will be recorded in the case report forms.

This information must be passed on with 24 working hours following discovery of the serious adverse event, and then by mail within the 48 working hours, by sending the declaration form for serious adverse events (*c.f. annex...*) completed:

**CHU Dijon Bourgogne – Délégation à la Recherche Clinique et à l'Innovation**

**14 Rue Gaffarel**

**21079 Dijon cedex**

**Fax: 03.80.29.36.90**

Additional information may be requested (by telephone, fax, email or during a visit) by the clinical research assistant and/or the sponsor.

The investigator must document the event as precisely as possible in the declaration. For this, he/she must provide as early as possible a copy of the hospital report as well as any documents necessary for the analysis of the case after making sure that the documents have been rendered anonymous: for example, copies of imaging reports, copies of biological analysis results,...

If an adverse event comprises several signs or symptoms that could be represented by a single syndrome or diagnosis, it is preferable to indicate the syndrome or diagnosis in the declaration.

#### Modalities and duration of follow-up of study participants following the onset of an adverse event

The investigator is responsible for the appropriate medical follow-up of patients until resolution or stabilization of the event or until the death of the patient. In certain cases, this may mean that the follow-up continues after the patient has left the study.

The investigator must communicate the complementary information and the follow-up to the serious adverse event to the sponsor within 24 hours of receiving them. For this, the investigator will use the declaration form for serious adverse events, indicating that it is a follow-up report (box to tick). The investigator will also send to the sponsor the last follow-up report following resolution or stabilization of the SAE or the death of the patient.

In case of congenital anomaly or fetal malformation due to a paternal exposure, the investigator must inform the sponsor immediately via the declaration form for serious adverse events. The child won't be followed after his birth and no information will be collected on the patient's partner.

All initial Product quality complaints (PQC) must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

#### 8.4.2 Role of the sponsor

In accordance with law n°2012-300 of 5 March 2012 on research involving humans, as amended by Order n° 2016-800 of 16 June 2016 and its application decrees and the decision of 24 March 2017 amending the decision of 26 December 2016 laying down the form, content and procedures for adverse reaction reports and new facts in the context of research mentioned in 1° of article L.1121-1 of the CSP concerning a medicinal product for human use, the sponsor records any serious adverse events and reports any suspected unexpected serious adverse reactions (SUSAR) during the research within the time allowed by the law to the competent authority (ANSM for France), and to the EMA via the Eudravigilance declaration portal.

For this, the sponsor must determine the causality link between the serious adverse event and the study product/ or the research, and will establish whether the adverse effect is expected or unexpected according to the definitions above.

The official declaration must be made within:

- in case of death or life-threatening event, the sponsor must declare the SUSAR without delay to the ANSM, from the day the sponsor is aware of the event and within 7 calendar days to the EMA
- 15 calendar days for all other unexpected serious adverse effects.
- 8 days for the declaration of complementary information whatever the severity of the event

The sponsor will also report any new information concerning safety to the ANSM and the CPP, and send them an annual safety report.

#### 8.4.3 Modalities for the follow-up of persons at the onset of an SAE

Any SAE must be declared, if it occurs:

- after the participant has signed the consent form for the clinical trial, whether or not the drug or the medical device concerned by the trial has been given/used
- throughout the duration of the follow-up specified in the study protocol
- with no time limit when it is likely to be due to an experimental product (e.g.: cancer, congenital malformations, etc.....).

## 9 STUDY COORDINATION

### 9.1 Data safety monitoring board



The data safety monitoring board will be composed of a statistician experienced in clinical trials, a clinician specialized in internal medicine, and a pharmacologist, all of whom will be independent of the investigators and sponsor.

The aim of this board is to ensure patient safety and compliance with the protocol. Its members will oversee the study (AE, SAE, recruitment, etc...).

The first meeting will be held immediately before the start of the study, to define the frequency and the rules of meetings.

## 9.2 Steering Committee

The scientific committee comprises the coordinating investigators (Dr. Bielefeld – Pr. Bodaghi), two or three principal investigators of center, one person representing the promoter, one person representing the safety and members of the coordinating center.

The steering committee will make decisions concerning the study, including administrative and financial aspects and study promotion.

The first meeting will be held immediately before starting of the study, then regularly until the end of the study by conference call.

## 9.3 Independent adjudication Committee

An independent adjudication and surveillance committee, composed of three specialists of NISU, who do not participate directly to the study, will review all patients' files for identify relapse occurrence. Information reviewed will include laboratory data, clinical data and all other relevant data. The first meeting will be held immediately before starting of the study, then every 6 months. The rhythm of these meetings may be adapted according to the number of inclusions each month.

## 9.4 Final report

The final report of the study will be written in collaboration with the study methodologists. It will be signed by the study coordinator and the promoter and then sent to each principal investigator.

The results of the study, whatever they are, will be submitted for publication.

# 10 DATA MANAGEMENT

## 10.1 Organization of data circuit

- Ethics

Only the patient's anonymous code is reported in the CRF. This is comprised of the patient's initials (first letter of the family name and the first name), the number of the center and the number corresponding to the position in the list of inclusions. For the extraction of data, only the number in the list will be kept.

The Promoter of the study alone will own and be able to use the data of the study.

- Clinical data

Data will be collected by the investigator helped by a clinical research technician, at each of the following times: screening visit and inclusion visit (verification of all inclusion and exclusion criteria, biological and histological data and paraclinical examination results), and follow-up visits and at the end of the study (Clinical data (in particular the uveitis status) and biological data).

The coding and the correspondence of these variables will be available in a document held by the manager of the database. This document will be drafted before the construction of the database.

The data will be entered directly by the investigator helped by a Clinical Research Technician (CRT) into an e-CRF specifically developed for this study using a Clinical Data Management System (CMDS- CleanWeb). All required information will be entered as and when it is obtained (at screening, baseline, at each follow-up visit, and at 12 months). Automatic checks for missing or inconsistent data will be integrated. These checks will follow the data management plan jointly defined by the coordinating center in collaboration with the coordinating investigator. In case of missing or inconsistent data identification, correction requests will be sent to participating centers via the CMDS. If corrections are necessary, they will be made by the CRT or by the investigator directly using CleanWeb.

The electronic system will ensure the traceability of every change made on the e-CRF.

A blind review of data will be performed at the end of the study and may result in additional queries. All queries should be resolved before the final database lock.

The process of data lock/unlock will be performed according to the procedure set up in the coordinating center (raw data lock in CSV format and as an SAS table).

- Data collection

The data will be gathered in an electronic CRF (e-CRF) created using CleanWeb software by a data manager. Data will be entered directly on line at the following address after identification by a Login and a password:

<https://chu-dijon.tentelemed.com/Ctms-chud/portal/login>

- Quality and Security Manager

The security, quality and access to study data will be ensured by the data-manager of the coordinating center (CIC-EC 1432)

Data entry will be validated directly by dynamic coherence checks implemented during the construction of the database.

A series of requests will be made periodically during the project by a data manager, in accordance with monitoring visits, with the aim to validate the coherence of all of the data. These requests will be repeated iteratively until the database contains no errors.

- Storage and archiving

Data storage via CleanWEB software will be ensured by the company Telemedicine Technologies via its secure Internet data storage platform.

A copy of the extract file with a « .csv » format of the blocked database will also be kept in a server of Dijon Burgundy CHU, secured by a pass word by the data manager.

## 10.2 Monitoring

A clinical research assistant, delegated by the sponsor (CRA sponsor), will regularly visit every centre involved in the study during the implementation of the trial, one or several times during the trial according to a predetermined frequency depending on the level of risk attributed to the research.

The aim of these visits is to:

- make sure the protocol is followed,
- check that informed consent has been given,
- check the reporting of serious adverse events,
- follow the traceability of study drugs (visits to the pharmacy, storage of and records for drugs),
- ensure quality control: compare data in the CRF with those in the source

## 11 STATISTICAL ANALYSES

### 11.2 Demographic and baseline characteristics

Patients' characteristics at baseline will be described in terms of frequencies for categorical variables, and in terms of means (+/-SD) or medians (IQR) for continuous variables depending on their distribution.

### 11.3 Primary efficacy analysis

The main analysis will be conducted on an intention-to-treat (ITT) basis.

If both eyes are affected, remission must at W6 occur in both eyes, and failure is defined by the occurrence of a relapse in at least one eye.

If 11 or more patients out of the total of 29 patients treated with ustekinumab are relapse-free with no deviation from the scheduled prednisone tapering because of NISU activity at W24, it will be concluded that the clinical activity of ustekinumab warrants further investigation.

If 10 or fewer patients out of the total of 29 patients treated with ustekinumab are relapse-free with no deviation from the scheduled prednisone tapering because of NISU activity at W24, ustekinumab will be deemed not worthy of any further investigation in this patient population, unless clinical considerations suggest otherwise.

The 95% confidence interval for the proportion of patients who experienced relapse or any deviation from the scheduled prednisone tapering at W24 will be calculated on the basis of an exact binomial probability.

This ITT analysis will be completed with a PP analysis. The conclusion of the trial will only rely on the ITT analysis.

#### **11.4 Secondary analyses**

- **SAFETY**

Safety and tolerance will be described for each adverse event (AE). This analysis will be performed on patients that will take at least one dose of the study drug

- **EFFICACY**

The frequency of all the component of the primary endpoint will be described at each visit

Time to relapse or deviation from the scheduled prednisone tapering within the first 24 and 12 months of follow-up will be described in each group using the Kaplan Meier method.

The frequency of relapse at W52, as well as the frequency of sustained (without prednisone) and partial remission (<5mg/day) at W52 will be described with their 95% confidence intervals.

Cumulative corticosteroid doses, VFQ-25 and SF-36 scores will be described at W0, W6, W24 and W52 with mean ( $\pm$  standard deviation) or median [interquartile range] depending on the distribution.

The SF-36 scoring algorithms will be used to compute scores for the eight scales and the two summary measurements

The evolution of percentages of circulating Th1, Th17 and Treg lymphocytes will be described between W0 and W52.

#### **11.5 Significance level**

The level of significance is set at 0.05 for all analyses.

#### **11.6 Statistical software**

All statistical analysis will be performed using SAS version 9.4 (Cary, NC, USA)

#### **11.7 Person responsible for analyses and place of analyses**

The statistical analysis will be conducted by CIC-EC 1432 biostatistician, under the responsibility of Pr Christine Binquet

## 12 ETHICAL AND REGULATORY ASPECTS

### 12.1 Ethical code of conduct for the study

The planning and running of this study are governed by French and European law (law n°2012-300 of 5 March 2012 on research involving the human person, as amended by Order n° 2016-800 of 16 June 2016 and its application decrees). This research cannot start until all of the legal requirements relative to the implementation of research have been met. The study will be conducted in accordance with the ethical principles of the declaration of Helsinki and the recommendations for good clinical practice. In accordance with article L.1121-1 of the Public Health Code, this study constitutes research involving the human person of category 1 as it constitutes an interventional research involving an intervention on the person not justified by his or her usual management.

### 12.2 Legal and regulatory aspects

#### 12.2.1 Responsibilities of the sponsor

DIJON CHU is the sponsor of this study.

**In accordance with law n°2012-300 of 5 March 2012 on research involving the human person, as amended by Order n° 2016-800 of 16 June 2016 and its application decrees, the sponsor undertakes to carry out all of the operations under its responsibility:**

- **Registering the study:** at the European level (the EUDRACT number)
- **To inform or request authorisation from the French National Agency for Medicines and Health Products Safety (Agence Nationale de Sécurité du Médicament et des produits de santé - ANSM)**
- **To submit the study to the Ethics Committee (Comité de Protection des Personnes - CPP)**
- **To declare or request authorization from the National Commission for Data Protection and Liberties (Commission Nationale Informatique et Libertés - CNIL)**
- **Underwriting Insurance:** for interventional research defined in 1° and 2° of the article L1121-1 of the Public Health Code,
- **Substantial modification:**

After the start of the study, any substantial modification of the protocol requested by the investigator will be submitted to the sponsor; before such modifications can be implemented the sponsor must obtain approval from the CPP and/or the authorization of the competent authority.

#### 12.2.2 Responsibilities of the investigator

- The investigator will ensure that this study is carried out in accordance with the law n°2012-300 of 5 March 2012 relating to research involving the human person, modified by the order n°2016-800 of 16 June 2016 and their implementing decrees, the Declaration of Helsinki and the Good Clinical Practice. All data, documents and reports may be subject to audits and regulatory inspections without the possibility of medical confidentiality being invoked.
- The investigator will inform the volunteers about the objectives and constraints of the study, their right to refuse to take part in the study and to leave the study at any time. Once the information has been given and the investigator will ensure that the volunteers have clearly understood the implications of their participation in the study; the volunteers' written consent will be collected by one of the investigators in duplicate. One copy of the signed informed consent form will be given to the volunteer; the original copy of the consent form will be kept by the investigator.

The informed consent process will be documented in the medical file.

- All of the information collected is confidential and cannot be disclosed. The investigator will ensure that the anonymity of every volunteer taking part in the study is guaranteed. No information making it possible to identify those taking part in the study will be communicated to third parties except to representatives of the sponsor and the Ministry of Health, who are legally authorized to hold such information (and who are subject to professional secrecy).

### 12.2.3 Authorization, study sites and persons responsible

Authorization for the site of the research is necessary for research conducted outside the place of treatment or in hospital departments where such research requires medical procedures other than those usually performed in the context of their usual activity.

The person responsible for the research is the principal investigator in every center

### 12.2.4 Ethics committee (Comité de Protection des Personnes - CPP) and Competent Authority

The trial cannot begin until the authorization of both the CPP and the Competent Authority (ANSM) has been obtained.

The protocol will be submitted to the CPP and the Agence Nationale de Sécurité des Médicaments et des Produits de Santé for authorization

The authorization of the Competent Authority becomes null and void if within 6 months following the authorization the research has not started (meaning no-one has been included in the protocol).

**The authorization of the CPP becomes null and void if within one year** following approval the research has not started (meaning no-one has been included in the protocol).

Neither the investigator, nor the sponsor can modify this protocol without the prior written agreement of the other party. If substantial modifications have to be made, they must be made via an amendment to the protocol.

This amendment will be applied once it has been authorized by both the CPP and the Competent Authority.

### 12.2.5 Protection of personal data

The computer file used to carry out this research will be the subject of an undertaking of conformity with the C.N.I.L. in application of the law "informatique et liberté", law n°2018-493 of 20 June 2018 relating to the protection of personal data and the General Regulation on the Protection of Personal Data (RGPD), adopted for Europe, and which came into effect on 25 May 2018.

#### 12.2.5.1 CNIL

The data collected during this study will be processed in accordance with the MR001 reference methodology. Declaration n°2049146 v 0 of March 29, 2017.

#### 12.2.5.2 Confidentiality

In accordance with the provisions of article R. 5121-13 of the Public Health Code, the investigator and any person involved in the trial will be bound by professional secrecy, in particular with regard to the nature of the products being studied, the trials, the persons taking part and the results obtained subject to the provisions set out in article L. 1123-9 (new numbering system) of the Public Health Code.

Unless they have the agreement of the sponsor (DIJON CHU), they can only provide information on the study to the Health Authorities, including inspectors as mentioned in article L.209-13 (old numbering system) of the Public Health Code.

No comments about the trial, either verbally or in writing, will be made without the authorization of both the coordinating investigator and the sponsor (Dijon CHU).

Patients' medical data undergoing data processing will only be communicated to the sponsor, and, if needs be, to the Health Authorities, in conditions that ensure their confidentiality. Patients can exercise their right to have access to and to rectify their data by contacting the investigator.

### 12.2.6 Information to the management bodies and pharmacies of the participating centres

The sponsor will ensure that the head of the establishment and the pharmacist of the trial centre have been informed about the trial before it starts and that an agreement has been made with every healthcare establishment taking part in the protocol.

#### 12.2.7 Insurance/ Compensation for prejudices suffered by patients

The sponsor has taken out insurance to cover its civil liability in case of any prejudice occurring during this research.

In accordance with the legislation in force (article L. 1121-10 of the Public Health Code) every patient is insured for any deterioration in his/her health that may have resulted from his/her participation in the study.

The name of the insurance company for Dijon CHU is Société Hospitalière d'Assurances Mutuelles (SHAM) Police n° 129.234.

The investigator must immediately report any claim made by a patient and likely to be related to the study to the Direction de la Recherche Clinique du CHU de Dijon. The Director of Clinical Research will forward this claim to the legal department.

#### 12.2.8 Authorization, study sites and persons responsible

Authorization for the site of the research is necessary for research mentioned in 1° of article L.1121-1 of the Public Health Code, conducted outside the place of treatment or in hospital departments where such research requires medical procedures other than those usually performed in the context of their usual activity or when the research is carried out on persons with a clinical condition that is different from that for which the service is specialized.

The person responsible for the research is the principal investigator in every centre

#### 12.2.9 Information to participants on the overall results of the research

At the end of the study, if the volunteer so wishes, he/she can be informed about the overall results of the research (Article L1122-1, last paragraph). Participants cannot be informed about the results of the study that concern them, but they can obtain their medical data.

The patient must apply in writing to the investigating doctor to obtain the above information.

#### 12.2.10 Audit and inspection

The investigators accept to meet the requirements of the sponsor and the Competent Authority concerning study audits or inspections.

Audits can take place at any stage of the study, from the development of the protocol to publication of the results and archiving of the data used or produced in the context of the study.

#### 12.2.11 Archiving

At the end of the study, all of the documents related to the study (including copies of the CRF) will be archived on the site of the study or in a central archive. Particular attention must be paid to the list that makes it possible to identify patients included in the trial and to the consent forms. This list and the consent forms are the most important documents in the files and must be archived by the investigator.

All of the documents related to the study must be kept for 25 years after the end of the study. At the end of this period, the Sponsor will inform the investigators that the period of archiving is over.

### 13 FUNDING FOR THE STUDY

This study is funded by the PHRC-N 2017 for a cost equivalent to 190 194€ and by Janssen laboratory for a cost equivalent to 171 512.50€

Janssen laboratory is committed to providing all pharmaceutical products (STELARA) (see Appendix).

The budget will be managed by the Délégation à la Recherche Clinique et à l'Innovation in agreement with the coordinating investigator of the study.

#### 14 RULES FOR PUBLICATION

The study will be declared to a register that meets the required specifications for the publication of its results in reputed international medical journals, in accordance with the recommendations of the ICMJE (*International Committee of Medical Journal Editors*).

All of the data collected during this study are the property of the study Promoter and cannot under any circumstances be communicated to a third party without the written authorization of the study investigator/coordinator.

The co-investigators will be gathered under the name of the specific study group, so that the publications will be effective and validated by all.

Any publication or communication (oral or written) will be decided by consensus between the investigators and will comply with the international recommendations of the ICMJE: Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. International Committee of Medical Journal Editors; Updated December 2016

[www.icmje.org/icmje-recommendations.pdf](http://www.icmje.org/icmje-recommendations.pdf).

For every publication, the investigator must mention:

- the CHU of Dijon Burgundy
- the source of funding for the study (PHRC, Janssens)
- INSERM CIC 1432 of Dijon

In cases of publications produced jointly with the University of Burgundy Franche Comté or any other research organization, the rules for addresses on publications will comply with the terms of the agreement. That is to say:

- University of Burgundy Franche-Comté, F-21000 Dijon, France
- CHU Dijon Burgundy, F-21000 Dijon, France
- INSERM U1098, Dijon, France

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