Clinical Development

NORFLO® ORO

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Study protocol

Assessment of the anti-inflammatory effects of NORFLO® ORO in acute relapses of HLA-B27 associated autoimmune uveitis: a multicenter randomized, placebo-controlled, double-blind clinical study.

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SPONSOR'S SIGNATURE FOR APPROVAL

Clinical Research Protocol

Assessment of the anti-inflammatory effects of NORFLO® ORO in acute relapses of HLA-B27-associated autoimmune uveitis: a multicenter randomized, placebo-controlled, double-blind clinical study.

Protocol Number:	NORFLO-ORO-16
Version Date:	Version n. 1.6, version date 10-Oct-2019
Investigational Product:	NORFLO® ORO (curcumin-phospholipid 600mg)
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Coordinating Center:	S.S. Uveitis Center, Rapallo Hospital, Genoa- Italy

_____ _____

Giuseppe Campora *Date*
C.E.O.
Eye Pharma S.p.A.

This confidential information about an investigational product is provided for the exclusive use of investigators of this product and is subject to recall at any time. The information in this document may not be disclosed unless law or regulations require such disclosure. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, with the obligation not to further disseminate this information.

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing Eye Pharma SpA with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. I require and I will get written informed consent from each study participant before starting any procedure.

I am aware that my electronic signature or manual, or that of a co-investigator, on a Case Report Form indicates that the data contained on that form has been reviewed and approved by the person who affixes the signature.

Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: NORFLO-ORO-16

Protocol Date: 10-Oct-2019

Protocol Title: Assessment of the anti-inflammatory effects of NORFLO® ORO in acute relapses of HLA-B27-associated autoimmune uveitis: a multicenter randomized, placebo-controlled, double-blind clinical trial.

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Investigator Signature *Date*

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Print Name and Title

Site # _____

Site Name _____

Address _____

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Phone Number

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List of Abbreviations

AE	Adverse event
AAU	Acute anterior uveitis
AC	Anterior chamber
ACE	Angiotensin converting enzyme
AIFA	Italian Medicine Agency
ANA	Antinuclear autoantibodies
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under curve
BCVA	Best corrected visual acuity
COX-2	Cyclooxygenase-2
CRF	Case report form
CRP	C-reactive protein
C3	Complement component 3
C4	Complement component 4
CME	Cystoid macular edema
DMC	Data Monitoring Committee
DSMB	Data and Safety Monitoring Board
ENA	Extractable nuclear antigens
ERUPR	Endoplasmic reticulum unfolded protein response
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
FB	Fibrinogen
GGT	Gamma-Glutamyltransferase
HIPAA	Health Insurance Portability and Accountability Act of 1996
HLA	Human Leukocyte Antigen
HSV	Herpes simplex virus
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
Ig	Immunoglobulins
IL-8	Interleukin -8
iNOS	Inducible nitric oxide synthase
IRB	Institutional Review Board

MCP	Monocyte chemoattractant protein
MHC	Major histocompatibility complex
NKR	Natural killer receptors
OCT	Optical coherence tomography
RF	Rheumatoid factor
PI	Principal investigator
RAU	Recurrent anterior uveitis
SAE	Serious adverse event
SUN	Standardization of Uveitis Nomenclature
TNF-α	Tumor necrosis factor-alpha
UAR	Relapsing autoimmune uveitis
VZV	Varicella-zoster virus

Protocol Synopsis

TITLE	Assessment of the anti-inflammatory effects of NORFLO® ORO in acute relapses of HLA-B27-associated autoimmune uveitis: a multicenter randomized, placebo-controlled, double-blind clinical study.
SPONSOR	Eye Pharma SpA, via Borghero 9, 16148 - Genoa (GE) Italy Telephone: +39 010 513188 – Fax: +39 010 3071430
NUMBER OF SITES	4
RATIONALE	In our previous study, Allegri et al. have shown how the treatment with NorFlo® (curcumin-phospholipid (Meriva® 600mg)) 2 tablets daily in 128 patients in combination with conventional therapy is capable of reducing the relapses in patients with recurrent anterior uveitis (RAU) by 88%. The enrolled subjects suffered from uveitis of different etiologies, among which were found three main different etiological groups: herpetic uveitis, autoimmune inflammatory ocular disease and various origin anterior uveitis. Among these three groups, the most sensitive patients to the treatment were autoimmune RAU (n=56). These extraordinary results lay the groundwork for further investigating the effectiveness of curcumin-phospholipids in autoimmune HLA-B27-associated uveitis, which represents the most common type of uveitis (75% of total uveitis). NORFLO® ORO aims at obtaining an anti-inflammatory effect that is synergistic to conventional therapy to counteract the occurrence of secondary symptoms (as cystoid macular edema) of HLA-B27-associated uveitis.
STUDY DESIGN	This is a multicenter, randomized, double-blind, placebo-controlled study.
PRIMARY OBJECTIVE	To explore the efficacy of NORFLO® ORO in reducing the number and severity of relapses, when compared to placebo. The reduction of the mean number of relapses per patient between the year before study treatment and the study period will also be assessed.

SECONDARY OBJECTIVES	- To evaluate the improvement of side effects due to HLA-B27-associated uveitis such as glaucoma, cystoid macular edema, keratopathy and synechia. - To evaluate the improvement in uveitis-related symptoms. - To evaluate cell damage and inflammation reduction in patients with HLA-B27-associated uveitis. - To evaluate the patients' attitude towards the study treatment. - To evaluate the safety profile of the study product.
NUMBER OF SUBJECTS	60
SUBJECT SELECTION CRITERIA	Inclusion Criteria: 1. Subjects ≥ 18 years of age at baseline Visit. 2. HLA-B27 positive related uveitis (acute alternating non granulomatous uveitis); the uveitis shall not be in acute phase at the time of enrolment and at least 8 weeks must have elapsed after the resolution of the last uveitis attack. 3. Subjects with at least one autoimmune uveitis relapse (UAR) in the last year. 4. Written informed consent obtained from subject or subject's legal representative and ability for the subject to comply with the requirements of the study. Exclusion Criteria: 1. Presence of a condition or abnormality that in the opinion of the investigator would compromise the safety of the patient or the quality of the data collected. 2. Subjects that have received systemic therapy for uveitis with anti-inflammatory, immunosuppressive or biological drugs in the 30 days before study start. 3. Subjects with an anticipated need for systemic anti-inflammatory, immunosuppressive or biological drugs during the 12 months of the study. 4. Subjects who received an intravitreal, peribulbar, sub-tenon, periocular injection in the previous 6 months. 5. Subjects that are receiving long-term treatment with systemic anti-inflammatory, immunosuppressive or biological drugs for other diseases different from uveitis. 6. Women who are taking hormonal contraceptives.

	7. Subjects that have taken supplements and nutraceuticals in the last 30 days prior to baseline visit. Use of supplements and nutraceuticals will not be admitted during the study. 8. Subjects for whom baseline LFM and other evaluations cannot be accurately performed. 9. Women who are pregnant or breast-feeding.
TEST PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	NORFLO® ORO at 2 single foil pouches per day (equal to 3.49 g of product).The product will be administered orally every day for 12 months. The administration will take place each day in two separate doses before meals (lunch and dinner).
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	PLACEBO at 2 single foil pouches per day (equal to 3.49 g of product). The product will be administered orally every day for 12 months. The administration will take place each day in two separate doses before meals (lunch and dinner).
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will participate in the study for up to 12 months. **Treatment duration:** 12 months **Visits:** Baseline Visit (Visit 1 - T_0), Visit 2 (T_1, 6 months), Visit 3 (T_2, 12 months). The screening will be done in the same day of the baseline visit. After the first 3 months of treatment subjects will be contacted by phone by the study staff, to assess the correct study product intake. The enrolment period will be 3 months, therefore the total duration of the study is expected to be about 15 months.

CONCOMITANT MEDICATIONS	**Allowed**: In case of relapse the following treatments will be allowed: - any midriatic topical therapy - any traditional topical therapy recommended for the treatment of relapsing autoimmune uveitis. In the case of relapse with LFM values are > 100 ph/ms despite treatment with topical therapy, or in any case the LFM values result to be > 100 ph/ms, then a systemic therapy is recommended and the subject has to be dropped-out from the study and treated according to the best medical judgement. **Prohibited**: Supplements and nutraceuticals; systemic therapies for uveitis with anti-inflammatory, immunosuppressive, biological drugs; hormonal contraceptives; long-term treatment with systemic anti-inflammatory, immunosuppressive or biological drugs for other diseases different from uveitis. Systemic therapies with anti-inflammatory, immunosuppressive drugs are allowed for reasons different from uveitis and in any case for periods not exceeding 15-30 days.
EFFICACY EVALUATIONS	A clinical assessment and diagnosis will be performed on each patient enrolled in the study.
PRIMARY ENDPOINT	Mean number per patient and severity of relapses reduction in the NORFLO® ORO treatment group when compared to the placebo group. The reduction of the mean number of relapses per patient between the year before treatment and the study period within each treatment group will also be assessed. The two endpoints will be assessed in a hierarchical order. Cell damage and inflammation reduction, as assessed by Laser Flare Meter in the NORFLO® ORO treatment group when compared to the placebo group.

SECONDARY ENDPOINTS	The improvement of side effects due to HLA-B27-associated uveitis, such as intraocular pressure (IOP) by Goldmann applanation tonometry, cystoid macular edema (central foveal thickness – central 1 mm subfield thickness) by optical coherence tomography (OCT) Spectralis® (Heidelberg Egineering, Heidelberg Germany), keratopathy, evaluated by fluorescein staining of the cornea, and synechia assessed by photographic slit lamp (anterior chamber photographs will be retained), in the NORFLO® ORO treatment group when compared to placebo group. The improvement in uveitis-related symptoms (BCVA, ocular pain, photophobia, floaters and blurred vision measured by VAS). Patients' attitude towards NORFLO® ORO treatment compared to placebo, through the Quick Questionnaire.
SAFETY EVALUATIONS	Incidence of adverse events in the NORFLO® ORO treatment group compared to placebo group. Use of concomitant medication. Changes in vital signs.
STATISTICS **Primary Analysis**	Mean and standard deviation will be used to describe the number of relapses per patient. The mean number of relapses per patient will be compared between the treatment groups using Student's t-test. ANOVA will be used to adjust for predictive/confounding variables. In addition, a generalized linear mixed model (GLMM) will be used to assess the effects of the treatment on reducing the number of relapses. The average and the maximum intensity will be compared between treatment groups using Student's t-test. ANOVA will be used to include predictive/confounding variables in the model. The mean number of relapses per patient observed during the study will be compared to the mean number of relapses reported during the previous year within each treatment group using paired t-test or ANOVA, to eventually adjust for predictive/confounding variables. The two endpoints will be assessed in a hierarchical order.
Secondary Analysis	The incidence of side effects associated HLA-B27-associated uveitis, such as IOP, cystoid macular edema, keratopathy and synechia, will be compared between treatment groups using logistic regression. The changes in BCVA and symptoms measured by VAS will be compared between treatment groups using ANCOVA, with the baseline level included in the model.

	The level of cell damage and inflammation will be assessed through Laser Flare Meter. The difference between treatment groups will be compared using ANCOVA, with the baseline level included in the model. Each information collected through the Quick questionnaire will be compared between the two treatment groups using chi-square test.
Safety Analysis	Adverse event will be coded using the last updated version of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary to give a preferred term (PT) and a system/organ class term (SOC) for each. Adverse events will be tabulated by treatment group. Tables will include the number of patients who experienced at least one AE, of study product-related AEs (defined as definitely, probably, possibly, or unrelated), of serious AEs, and the number of patients withdrawn due to AE, summarized by treatment arm. Comparisons between treatment arms will be performed using chi-square test. Concomitant medications will be summarized by treatment using descriptive statistics and they will be listed. Vital signs will be summarized by treatment using descriptive statistics for absolute values and change from baseline. Compliance to the study treatment will be assessed through the patient diary and checked versus the used and unused study product containers given back by the patients.
Rationale for Number of Subjects	With a statistical power of 80%, a significance level (alpha) of 5% and a common SD of 0.7, 46 patients are needed to observe a difference of 0.6 relapses/patients between the two treatment groups (2 relapses/patient in the NORFLO® ORO treatment group vs. 2.6 in the placebo treatment group). To take into account a potential dropout rate of 20% over 1 years, 60 patients will be recruited. A second primary endpoint, i.e. the reduction of mean number of relapses between the year before treatment and the study period, will be examined. These two endpoints will be assessed in a hierarchical order.

1. BACKGROUND

1.1 Overview

The first human leukocyte antigen (HLA) haplotype association with inflammatory diseases was discovered in 1972 and it correlated the HLA-B27 haplotype with severity and susceptibility to ankylosing spondylitis. Ankylosing spondylitis remains one of the strongest known disease associated with HLA-B27. Since then, more than 100 disease associations have been demonstrated, including many ocular diseases and systemic diseases with specific ocular manifestations[1]. These diseases also include reactive arthritis (previously referred to as Reiter's syndrome), inflammatory bowel disease, and psoriatic arthritis.

In ophthalmology, HLA associations are strongest in diseases of the uvea. Of patients with uveitis, 19-88% have the HLA-B27 phenotype, depending upon the study population cited. Acute anterior uveitis (AAU) may occur as a distinct clinical entity or in conjunction with a group of autoimmune rheumatic diseases called seronegative spondyloarthropathies[2]. By definition, patients with these diseases have a negative rheumatoid factor, hence the term seronegative [3-4].

An HLA disease association is defined as a statistically increased frequency of the HLA haplotype in individuals with the disease compared to the frequency in individuals without the disease. This is expressed as a relative risk. For example, HLA-B27 appears in 80-90% of patients with ankylosing spondylitis. Expressed as a relative risk, an HLA-B27 positive individual is approximately 87 times more susceptible to developing ankylosing spondylitis compared to the general population.

1.2 Disease Pathophysiology

The HLA system is genetically encoded in humans by the major histocompatibility complex (MHC), which is found on chromosome 6, and plays a determining role in immunity and in self-recognition (autoimmunity) in virtually all cells and tissues, with the exception of erythrocytes[5].

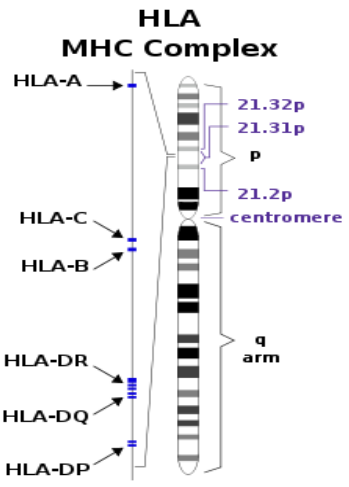

Figure 1- The HLAB gene is located on the short (p) arm of chromosome 6 at the position 21.3

Three classes of gene products are encoded within the small region of the major histocompatibility complex (MHC). Class I MHC molecules include HLA-A, HLA-B, or HLA-C (**Figure 1**) and serve as the antigen-presenting platform for CD8 or cytotoxic T cells. Class I molecules are present on all nucleated cells. Class II MHC molecules, the HLA-D region, serve as the antigen-presenting cells for CD4 or helper T cells. Macrophages and dendritic cells are the important class II antigen-

presenting cells. Class I and class II molecules allow antigen presentation to the specific T-cell receptor via specific structural grooves in their tertiary structure. Autoimmune/inflammatory conditions can occur if mutations in the groove-binding site of class I and II molecules occur, leading to inappropriate binding to self-peptides or certain environmental peptides.

The actual role of HLA-B27 in triggering an inflammatory response causing diseases is still not precisely known. The molecular mimicry is the oldest theory, in which an autoimmune response is mounted initially against a peptide derived from an infectious agent and is subsequently directed against self-peptides due to epitopic similarities resulting in biding affinity to HLA-B27. At least two self-peptides have been identified in patients with ankylosing spondylitis, which supports this hypothesis.

A second theory, referred to as the HLA-B27 misfolding hypothesis, is based on a peculiar biochemical property of the HLA-B27 molecule. Unfolded HLA-B27 proteins accumulate in the endoplasmic reticulum (ER) and trigger a proinflammatory stress response that is called the endoplasmic reticulum unfolded protein response (ERUPR). As a result, interleukin 23 (IL-23) is released, activating a proinflammatory response via interleukin-17-secreting Th17 T lymphocytes.

Another potential pathological mechanism of HLA-B27 is called the HLA-B27 heavy chain homodimer hypothesis. It is suggested that B27 heavy chains dimerize and accumulate in the endoplasmic reticulum. In turn, this initiates the proinflammatory ERUPR. In addition, B27 heavy chains and dimers can bind to other regulatory immune receptors such as the natural killer receptors (NKRs). This in turn recruites proinflammatory leukocytes and triggers the production of proinflammatory mediators.

Alternative theories claim the T-cell antigen as the susceptibility factor or other innate system etiological mechanisms that are unrelated to HLA. Finally, HLA-B27 may simply represent a marker locus, closely linked to the yet unidentified immune response gene that is truly responsible for the inflammatory response[6].

Several hypotheses to explain the association of AAU and HLA-B27 have been tested in animal models. Many cases of uveitis or reactive arthritis follow gram-negative bacillary dysentery or chlamydial infection. These gram-negative organisms include *Shigella, Salmonella, Klebsiella,* and *Yersinia* species. Similarities in the gram-negative cell wall lipopolysaccharide present in these microbes may explain their immunogenicity. Animal experiments with rodents that have been genetically altered to express human HLA-B27 molecules show that bacterial infection of the gut predisposes the animals to arthritis and to a reactive arthritis–like syndrome. In addition, chronic intracellular chlamydial joint or eye infection might stimulate, via the HLA-B27 molecule, a CD8 T cell effector mechanism that was activated to kill the infected cells but that also indirectly injures the eye[7].

Clinical Features

The sequence of HLA-B27 has been known since 1985. The antigen consists of at least 100 subtypes. Some HLA-B27 subtypes are associated with other HLA-B27 inflammatory diseases such as anterior uveitis. The HLA-B27 antigen is present in only 1.4-8% of the general population (higher in certain Native American groups and Scandinavians). Of patients with acute anterior uveitis, up to 50-60% of patients are HLA-B27 positive. Both racial background and country of origin affect the rate of incidence of HLA-B27 associated acute anterior uveitis (AAU). In specific, the frequency of HLA-B27 anterior uveitis is lowest in blacks, intermediate in Asians, and highest in whites[8].

HLA-B27 associated AAU is the most frequent type of endogenous uveitis and it accounts for 18-32% of all anterior uveitis cases in western countries and for 6-13% of all anterior uveitis cases in Asia. The relatively lower frequency of AAU in Asia is related to the lower frequency of HLA-B27 found in this population. As mentioned, there are varying global patterns of HLA-B27 associated AAU that may be attributed to different genetic factors, such as HLA-B27 polymorphisms and non-MHC genes. These geographic variations may also exist because of yet unidentified pathogenic environmental factors.

Studies indicate that HLA-B27 associated uveitis is a distinct clinical entity characterized by a male predominance and frequent association with seronegative arthritic syndromes, such as ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and inflammatory bowel disease[9].

The first episode of HLA-B27 associated AAU most commonly occurs in patients aged 20-40 years, whereas onset of HLA-B27-negative AAU occurs a decade later. Of patients with AAU, at least 50-60% are HLA-B27 positive. The first AAU episode is generally a benign non granulomatous unilateral disease presenting as a classic triad of pain, redness, and photophobia. Corneal manifestations may include fine keratic precipitates and fibrin on the endothelium. Corneal edema may develop due to endothelial decompensation. Band keratopathy, characterized by an accumulation of calcium in the corneal epithelium, may be seen in chronic uveitis. The anterior chamber of the eye shows cells and flare, which appears as a haze upon slit lamp examination, and which reflects protein accumulation in the anterior chamber of the eye due to the breakdown of the blood-aqueous barrier. In severe inflammation, fibrinous exudate in the anterior chamber of the eye may cause apposition of the iris to the lens or anterior vitreous, preventing aqueous from flowing and occluding the pupil, causing iris bombe as depicted in **Figure 2**. The fibrinous exudate may be mistaken for endogenous endophthalmitis, cataract, or hypopyon. In some cases, a hypopyon leukocytic

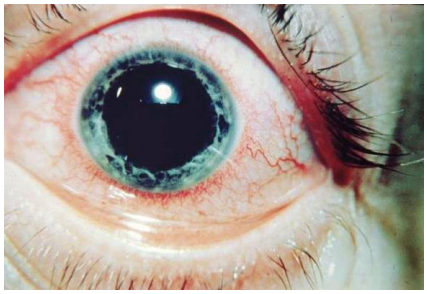

Figure 2 – Clinical signs of acute anterior uveitis (AAU).

exudate may be seen, and, rarely, even a spontaneous hyphema may occurs as a result of severely dilated iris vessels.

Pigment dispersion, pupillary miosis, and iris nodules may be noted, and synechiae, both anterior and posterior, can occur. Posterior segment involvement is relatively rare, but cystoid macular edema, disc edema, pars plana exudates, or choroiditis may be seen. Intraocular pressure often is low, secondary to decreased aqueous production with inflammation of the ciliary body and trabecular meshwork[10]. Intraocular pressure also may be high if inflammatory cells and debris clog the trabecular meshwork, particularly in patients with a preexisting poor aqueous outflow facility.

Uveitis may precede the diagnosis of spondyloarthritis and be the first manifestation. However, there is not trend between uveitis and spondyloarthritis i.e. a joint inflammation is not always associated with an ocular inflammation or viceversa.

Different clinical forms may be present:

- Patient has uveitis and HLA-B27 $^{+}$ but not ankylosing.

- Patient has ankylosing, uveitis and HLA-B27 $^{-}$.

- Patient has ankylosing HLA-B27 $^{+}$ and concomitant exacerbations or not.

Diagnosis

A careful history and physical examination usually helps distinguish between the uveitic entities associated with a systemic disease and with HLA-B27 from those that are not associated with HLA-B27. Disease entities causing AAU are varied and include traumatic iritis, postcataract extraction iritis, juvenile rheumatoid arthritis, herpetic infection (both herpes simplex and herpes zoster), syphilis, sarcoidosis, Fuchs heterochromic iridocyclitis, glaucomatocyclitic crisis, Behcet disease, and low-grade endophthalmitis[11].

The diagnosis of HLA-B27 associated anterior uveitis is clinical. However, blood chemistry and diagnostic tests are necessary for a differential diagnosis:

- HLA-B27 typing. The role of HLA-B27 testing in patients with unilateral AAU is important in the differential diagnosis. The lack of HLA-B27 antigen in unilateral AAU may be a clue for the clinician to search for other specific uveitis entities and other systemic diseases. It also may be useful in determining the prognosis of AAU, as AAU associated with HLA-B27, even in the absence of a systemic disease, is less favorable when compared with that of patients who are HLA-B27 negative.

- Inflammatory markers: ESR, CRP and fibrinogen, C_3 and C_4.

- Radiographs of sacroiliac joints to identify sclerosis and narrowing of the joint space, which is followed by ligamentous ossification, and osteoporosis. Both sacroiliac joints usually are involved, but signs may first appear on one side. Ankylosing spondylitis may first present to an ophthalmologist in the form of AAU. A family history or symptoms of back problems and a positive HLA-B27 are highly suggestive of the diagnosis.
- ACE, total IgG and IgM HSV-1 and VZV, ANA , ENA, anti-DNA.

Treatment

Medical management of AAU includes topical or systemic corticosteroids and topical cycloplegics. Periocular corticosteroid injections are extremely useful in acute, recalcitrant, or noncompliant cases, particularly when posterior segment involvement occurs. Immunosuppressive therapy may be necessary in refractory cases or in those patients with corticosteroid-induced adverse effects. The primary goal of the treatment is to eliminate all cells, thereby minimizing complications including cataracts, cystoid macular edema, hypotony or glaucoma.

Cycloplegics help relieve photophobia, secondary to ciliary spasm, and prevent/break synechiae formation. Corticosteroids are the mainstay of uveitis therapy, but they should be used prudently due to their adverse effects. The treatment goal is to use the minimum amount of corticosteroids necessary to control inflammation and to prevent complications. Aggressive initial therapy may hasten recovery and limit the duration of therapy. Prednisolone acetate 1% given every hour is strongly recommended for acute presentations. Usually, 2-3 weeks treatment at maximal frequency is sufficient to completely eliminate all cells. Always discontinue corticosteroids by tapering the dose is recommended. Corticosteroids may be administered by 4 routes, including topical, periocular, intraocular (intravitreal), and systemic. Topical therapy is used in anterior uveitis. The dosing varies from hourly to once daily. Occasionally, severe inflammation may not respond and may require periocular, intraocular, or systemic corticosteroids treatment, especially if the posterior segment is involved. Periocular corticosteroids are usually given as depot injections in the sub-Tenon space. Intravitreal corticosteroids by injection or by implantation of a sustained released device have been shown to be useful in the treatment of both chronic uveitis and uveitic cystoid macular edema.

Systemic corticosteroids can be administered orally or intravenously. These are especially beneficial when the systemic disease requires therapy as well. More potent immunosuppression may be required in patients with vision-threatening inflammation interfering with activities of daily living, lack of response to corticosteroid treatment, and intolerance of corticosteroids[12].

The role of the rheumatologist in the management of AAU is important in identifying underlying systemic diseases that may be present and in monitoring subsequent immunosuppressive therapy. Current therapies for uveitis remain nonspecific in their mode of action, and there have a number of adverse effects, as already mentioned. Owing to this, future novel therapeutic approaches should target the specific mechanisms underlying the immune response and will include utilization of compounds that target cytokines, chemokines, cell adhesion molecules, and T-cell subsets.

Complications

AAU generally runs a short course of a few days to weeks and up to 3 months, with a tendency to recur in the same eye, especially in individuals who are HLA-B27 positive. Complications of AAU include:

- Posterior subcapsular cataracts
- Open and close angle glaucoma
- Keratopathy (**Figure 5**)
- Posterior synechiae (**Figure 3**)
- Cystoid macular edema and retinal vasculitis (**Figure 4**).

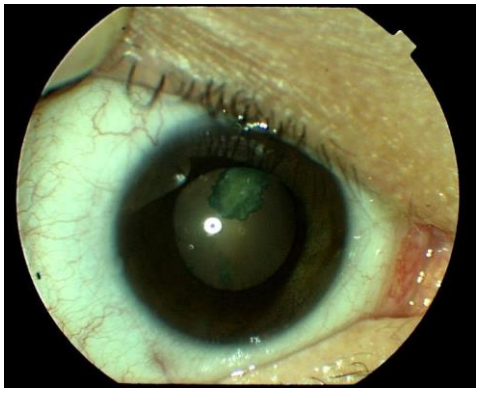

Figure 3 - Posterior subcapsular cataracts

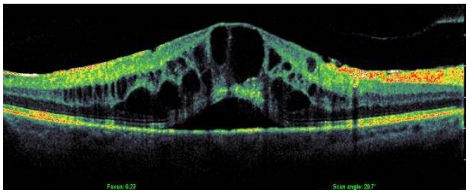

Figure 4 - Cystoid macular edema.

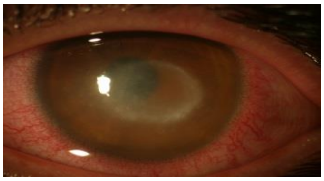

Figure 5 - Keratopathy.

The prognosis of HLA-B27 associated anterior uveitis, either with or without systemic disease, is less favorable when compared with patients who are HLA-B27 negative with idiopathic anterior uveitis. Despite the potential for sequelae, the overall prognosis is good[13]. Classic AAU resolves completely when promptly and aggressively treated. Undertreated or

misdiagnosed cases may progress to chronic iridocyclitis due to permanent damage of the blood-aqueous barrier.

1.3 Overview of NORFLO® ORO

NORFLO® ORO is based on curcumin-phospholipids complex that contributes to the anti-inflammatory and the anti-edema effects.

Curcumin is the yellow pigment of Turmeric (*Curcuma longa L.)*, the most popular spice of the Indian cuisine and a major ingredient of curry powders. In the Western diet, turmeric is mainly used as a food additive to color dairy products. Because of the different use (spice vs. food additive), the dietary intake of curcumin in the Western diet is negligible, but it can reach as much as 150 mg/day in the Indian diet [14].

Turmeric has a long history of medicinal use in India, and because it may be beneficial for many conditions, turmeric is a veritable *panacea*. Modern cellular studies on curcumin have validated most of its indications in traditional medicine, even expanding the potential of curcumin to genetic diseases associated with Caucasians[15]. Curcumin shows strong anti-oxidative and anti-inflammatory effects. In the past two decades, over 8000 articles have demonstrated the molecular basis of curcumin antioxidant, anti-inflammatory, antibacterial, anti-apoptosis and anticancer properties. As a result, curcumin has emerged as a master switch of inflammation, with both a direct and a genomic activity on regulation of proinflammatory enzymes, inflammatory transcription factors and inflammatory cytokines[16]. Over 100 clinical trials have focused on unravelling the role and the benefits of curcumin in various chronic diseases, including diabetes and cancers, as well as autoimmune, cardiovascular, neurological and psychological diseases.

Curcumin modulates the inflammatory response by down-regulating the activity of cyclooxygenase-2 (COX-2), lipoxygenase and inducible nitric oxide synthase (iNOS) enzymes; inhibits the production of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-a), interleukin (IL) -1, -2, -6, -8, and -12, monocyte chemoattractant protein (MCP) and migration inhibitory protein; down-regulates mitogen-activated and Janus kinases[17-18].

Curcumin, just like most dietary phenolics, is sparingly soluble both in water and in organic solvents, but has polar groups (two phenolic hydroxyl and one enolic hydroxyl) that can interact via hydrogen bindings and polar interactions with complementary group, like the polar heads of phospholipids. Phosphatidylcholine has a highly polarized head, the negative charge of a phosphate group and the positive charge of the choline ammonium group. Therefore, the phosphatidylcholine head can complex a variety of poorly soluble phenolics, including curcumin. Phenolic like curcumin show a high affinity for biological membranes. Once formulated with phospholipids, curcumin is embedded into their lipidic matrix that

shields it from hydrolytic degradation. The rapid exchange of phospholipids between biological membranes and extracellular fluids, allows shuttling curcumin from the phospholipid carrier into the biological membranes, increasing curcumin uptake by cells.

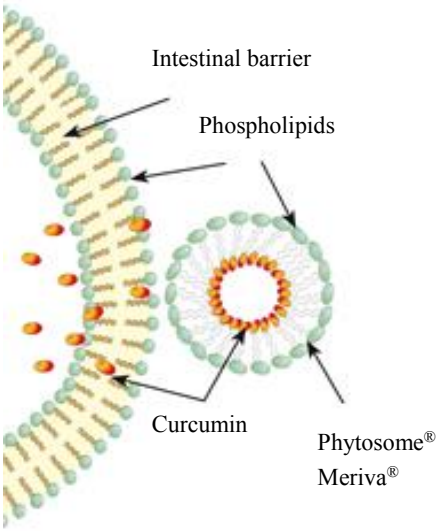

Figure 6 - Schematic of the release mechanism of curcumin phospholipid complexes (Phytosome – Meriva) in the gut.

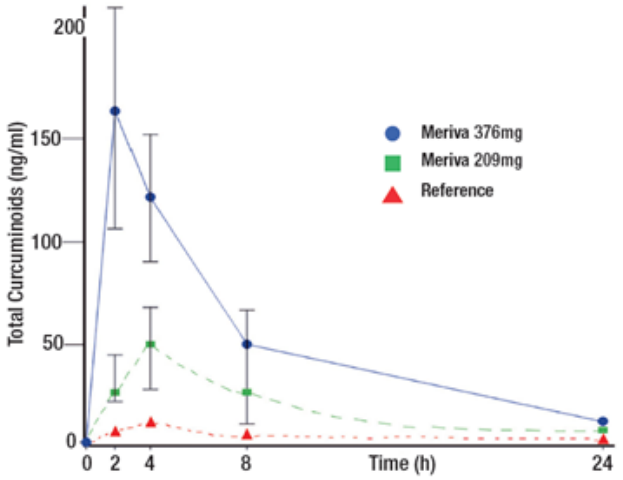

Figure 7 - Human pharmacokinetic study. Meriva has shown a bioavailability of about 30 times higher than standard curcumin (Reference)

NORFLO® ORO contains a patented formulation of curcumin and phosphatidylcholine enriched soy lecithin (Phytosome – Meriva®) [19]. Curcumin and phosphatidylcholine form a non-covalent adduct when mixed in a 1:2 weight ratio. Further, two parts of microcrystalline cellulose are added to improve flowability of the powder. The overall content of curcumin is around 20% and its bioavailability is increased [20-21]. Phytosome® has been shown to increase the hydrolytic stability of curcumin and to increase the oral absorption of curcumin by over 20 folds.

By embedding curcumin into the hydrophobic domains of phospholipids, curcumin is shielded from water-triggered degradation while, at the same time, the rapid exchange of phospholipids between biological membranes and the extracellular fluids can shuttle curcumin into biological membranes, boosting its cellular uptake (**Figure 6**). The improved oral bioavailability of curcumin as Phytosome® has been confirmed by human pharmacokinetic studies. Clinical efficacy of Phytosome® in the treatment of inflammatory conditions has been proven at dosages significantly lower than those of unformulated curcumin [22] confirming its higher bioavailability (**Figure 7**).

1.4 Overview of Non-Clinical Studies

Meriva® has shown an improved bioavailability compared to uncomplexed curcumin in rats. Male Wistar rats received 340 mg/kg of either unformulated curcumin or curcumin formulated with phosphatidylcholine (Meriva®) by oral gavage. Rats were euthanized 15, 30, 60 and 120 minutes post administration of the compounds. Plasma, intestinal mucosa and liver were analyzed for the presence of curcumin and metabolites using HPLC with UV detection. Identity of curcumin and metabolites was verified by negative ion electrospray liquid chromatography/tandem mass spectrometry. Peak plasma levels and area under the plasma concentration time curve (AUC) values for parent curcumin after administration of Meriva® were fivefold higher than the AUC of unformulated curcumin. Similarly, liver levels of curcumin were higher after administration of Meriva® compared to unformulated curcumin. The results suggest that curcumin formulated with phosphatidylcholine provides higher systemic levels of parent agent than unformulated curcumin. The improved bioavailability does not translated into an increased toxicity. Just like curcumin, the acute oral toxicity of Meriva ® in rats is higher than 2 g/Kg[23].

Colorectal tumor-bearing mice with oxaliplatin-resistant cells were treated with Meriva® alone and in combination with oxaliplatin. Oxaliplatin-resistant HCT116 p53wt and p53(-/-) cell lines were generated and the effects of oxaliplatin in combination with curcumin on resistance- and proliferation-associated proteins investigated. Eighty nude mice were implanted with HCT116 p53wt colorectal cancer cells before randomization into the following treatment groups: control, Meriva only, oxaliplatin only, Meriva® + oxaliplatin. Meriva® in combination with oxaliplatin was able to decrease the proliferative capacity of oxaliplatin-resistant p53wt and p53 (-/-) cell lines more effectively than oxaliplatin alone. Meriva® in combination with oxaliplatin also decreased expression of markers associated with cell proliferation. After 21 days of treatment in the xenograft model, the order of treatment efficacy was Meriva® + oxaliplatin > Meriva® > oxaliplatin > control. The decrease in tumor volume when compared to vehicle-treated animals was 53, 35 and 16%, respectively. Meriva® did not adversely affect the DNA-platinating ability of oxaliplatin. On the other hand, curcumin enhanced the cytotoxicity of oxaliplatin in models of oxaliplatin resistance *in vitro*. *In vivo*, Meriva greatly enhanced oxaliplatin efficacy, without affecting the mode of action of oxaliplatin. Therefore, addition of formulated curcumin to oxaliplatin-based chemotherapy regimens has the potential for clinical benefit in colorectal cancer[24].

1.5 Overview of Clinical Studies

The efficacy and tolerability of curcumin-complex was evaluated as an adjunctive therapy to traditional treatment. Curcumin-phosphatidylcholine complex (Meriva®/NorFlo) was administered twice a day in recurrent anterior uveitis of different etiologies. The study group consisted of 106 patients who completed a 12-month follow-up therapeutic period. The patients were divided into three main groups based on the uveitis origin: group 1 (autoimmune uveitis), group 2 (herpetic uveitis), and group 3 (different etiologies of uveitis).

The primary endpoint was the evaluation of relapse frequency in all treated patients, before and after Meriva® treatment, followed by the number of relapses in the three etiological groups. The secondary endpoints were the evaluation of relapse severity and of the overall quality of life. The results showed that Meriva® was well tolerated and could reduce eye discomfort symptoms and signs after a few weeks of treatment in more than 88% of patients. There was also an improvement in symptoms and signs associated with relapses after Meriva® treatment, including improvement in ocular pain, blurring of vision, pericorneal hyperemia and aqueous or vitreous cells, and flare in 42% of patients. In conclusion, this is the first study that reports the potential therapeutic potential of curcumin and its efficacy in eye relapsing diseases, such as anterior uveitis, and points out that curcumin treatment may be beneficial also in other eye inflammatory and degenerative conditions, such as the dry eye, maculopathy, glaucoma, and diabetic retinopathy[25].

The improvement of diabetic microangiopathy and retinopathy was evaluated in 38 diabetic patients treated with Meriva®. Inclusion criteria for the study were established diabetes for at least 5 years and signs of retinal edema and peripheral microangiopathy. Meriva® was administered at the dosage of 2 tablets/day (each tablet containing 500 mg Meriva® corresponding to 100 mg curcumin) for a period of at least 4 weeks in addition to the standard management plan, while the control group (n = 39) followed the standard management plan alone. All subjects (treatment and controls) completed the follow-up period, there were no dropouts and Meriva® showed an optimal tolerability. At 4 weeks after starting the treatment, microcirculatory and clinical evaluations indicated an improvement of microangiopathy. In terms of peripheral microangiopathy, in the Meriva® supplemented group, there was a significant improvement in the venoarteriolar response ($p<0.05$) and a decrease in the score of peripheral edema ($p<0.05$), a sign typically associated with the failure of the venoarteriolar response. At the retinal level, high-resolution duplex scanning, used to measure retinal flow, showed improvements in the Meriva® supplemented patients. The evaluation of retinal edema (Steigerwalt's scale) showed an improvement indicated by improved visual acuity (Snellen scale). There were no clinical or microcirculatory improvements in the control group. These preliminary observations indicate that curcumin administered in a bioavailable form such as Meriva®, is beneficial for the management of diabetic microangiopathy and retinopathy[26].

In addition to its anti-inflammatory activity, Meriva® has been anecdotally reported to decrease acute pain in patients with various chronic diseases. Curcumin can desensitize the transient receptor potential A1 (TRPA1), a nociceptor-specific ion channel, which mediates the analgesic effect of acetaminophen. Further curcumin can inhibit and downregulate the expression of cyclo-oxygenase 2 (COX-2), the selective target of nimesulide, a nonsteroidal anti-inflammatory agent. Building on these effects of curcumin, we carried out a pilot comparative study of the acute pain-relieving properties of curcumin compared to acetaminophen and nimesulide. At a dose of 2 g (corresponding to 400 mg of curcumin), Meriva® showed analgesic properties that were comparable to those of a standard dose (1 g)

of acetaminophen, but lower than a therapeutic (100 mg) dose of nimesulide. The analgesic activity of lower doses (1.5 g) of Meriva® was less satisfactory, displaying longer onset of activity than that of nimesulide for both doses. On the other hand, gastric tolerability of Meriva® was significantly better than that of nimesulide and comparable with that of acetaminophen. Taken together, these results suggest that the analgesic properties of curcumin have clinical relevance, at least at a dose of 2 g when administered in the Meriva® formulation. While this dose is significantly higher than that used to relieve chronic inflammatory conditions (1–1.2 g/day), its pain-relieving activity could benefit from the general downregulation of the inflammatory response induced by curcumin, considering that the TRPA1-mediated mechanisms of analgesia are magnified by attenuation of inflammation. In patients treated with Meriva, this would also translate into better control of acute pain, providing a rationale for the analgesic properties associated with this specific curcumin formulation[27].

In a three-month study, Meriva® was able to decrease joint pain and to improve joint function in 50 patients with osteoarthritis (OA). Since OA is a chronic condition requiring prolonged treatment, the long-term efficacy and safety of Meriva were investigated in a longer (eight months) study involving 100 patients with OA. The clinical end points were complemented by the biochemical evaluation of a series of inflammatory markers (interleukin [IL]-1beta, IL-6, soluble CD40 ligand [sCD40L], soluble vascular cell adhesion molecule (sVCAM)-1, and erythrocyte sedimentation rate [ESR]). Significant improvements of both the clinical end points and biochemical markers were observed for the Meriva treated group compared to the control group. These results, coupled with an excellent tolerability, suggest that Meriva® may be beneficial for the long-term complementary management of OA[28].

2 STUDY RATIONALE

In a previous study, Dr. Allegri's team has shown that treatment of 128 patients with NorFlo® (curcumin-phospholipids (Meriva® 600mg) 2 tablets/day) in combination with conventional therapy was capable of reducing the 88% of relapses in patients with recurrent anterior uveitis (RAU) (**Figure 8**). The enrolled subjects suffered from uveitis of different etiologies. The three main different etiological groups of enrolled subjects were herpetic uveitis, autoimmune inflammatory ocular disease and various origin anterior uveitis. A few months after starting the treatment, a significant improvement in symptoms associated with relapse, like the ciliary pain, blurred vision, hyperemia and the presence of aqueous humor cells was observed in 42% of the treated patients. Only 8% of the patients worsened and required other treatments, such as sub-Tenon space injections. Among the three groups of RAU etiology, the patients that were most sensitive to the treatment with NorFlo® belonged to the autoimmune RAU etiology (n=56) [26].

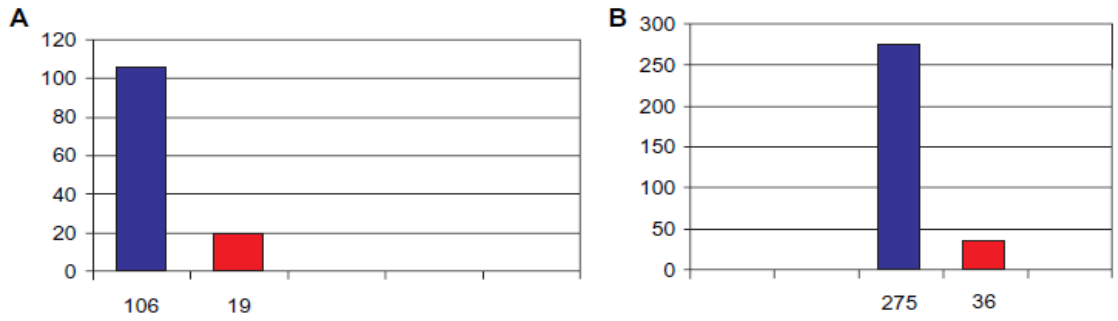

Figure 8 - A) Total number of patients with relapses before (blue) and after (red) Norflo therapy. B) Total relapse number before (blue) and after (red) Norflo therapy.

Relapse of uveitis is defined as an occurrence of anterior chamber cells of grade 1+ or higher according to the Studies of Uveitis Nomenclature criteria. In cases in which view of the anterior chamber is impaired by the loss of corneal clarity, a relapse will be defined as new corneal findings of endothelial inflammatory deposits or edema obscuring the anterior chamber in the absence of other causes of corneal edema and combined with two or more of the following features: conjunctival hyperemia, photophobia, decreased vision, or pain.

These extraordinary results provide the rationale to further study the effectiveness of curcumin-phospholipids in autoimmune HLA-B27-associated uveitis, which represents the most common type of uveitis (75% of total uveitis). NORFLO® ORO will provide a synergistic anti-inflammatory effect and will counteract the occurrence of cystoid macular edema, which is the most serious complications associated with the HLA-B27-associated uveitis. We expect that treatment with NORFLO® ORO will reduce recurrence of anterior uveitis in patients with HLA-B27-associated uveitis by targeting trigger factors such as inflammation, and the side effects related to the pathology (cystoid macular edema, synechia, keratophathy) overall improving the quality of life of the treated patients.

The study will be conducted by inserting a group of control patients and diagnostic ophthalmologic analysis, including analysis with the Kowa Laser Flare Meter instrument (LFM).

The role of intraocular inflammation in the disruption of the blood-aqueous barrier leading to the spreading of proteins and inflammatory cells into the aqueous humor has been well documented. To evaluate and grade this kind of inflammatory leakage (flare) in the anterior chamber (AC) of the eye the Standardization of Uveitis Nomenclature (SUN) is generally used. Grading, which ranges between 0 and 4+, is unreliable and not useful to detect and give a correct measurement of AC inflammation because it relies on the subjectivity of evaluation and the nonlinear grading of flare at the slit-lamp, therefore subjected to high variability.

Currently, the only system that allows to quantitatively, reproducibly and objectively measure intra-ocular inflammation is the Kowa Laser Flare Meter (LFM) instrument. Such instrument includes a photomultiplier that amplifies the intensity of the light scattered by

small molecules (flare) or larger particles (inflammatory cells) in the aqueous humor. The information is then processed by a computer and the result is expressed in photon counts per millisecond (ph/ms).
LFM instruments can quantify back-scattered light both from small molecules and from larger particles such as inflammatory cells.

LFM measurements may be unreliable in eyes with extensive posterior synechiae or mature cataract due to increased background scattering of light. Seven measurements are usually obtained, the highest and lowest values are discarded and the mean and standard deviation of the remaining five readings are automatically calculated. Patients do not experience any pain or discomfort during measurements. Aqueous flare intensity has been found in the range of 2.9–3.9 ph/ms in healthy individuals between 20 and 40 years of age. Flare values have been found to increase slightly with age, reaching 5.0–6.5 ph/ms in subjects between 70 and 80 years of age. Flare values < 10 ph/ms are considered normal.

Effective management of uveitis requires a reproducible and quantitative method to determine and monitor intraocular inflammation. It has become evident that clinically meaningful changes in flare counts could be achieved both in low and high-flare situations because LFM allows measuring flares ranging between 3 and 1000 ph/ms on a linear scale. Gonzales *et al*. reported an inverse relationship between LFM flare and visual acuity in patients with uveitis. While no relationship was found between complications and anterior chamber cell or flare scores at the slit-lamp, a strong relationship was found between LFM flare and complications such as posterior synechia and macular edema, highlighting the importance of utilized LFM as diagnostic tool.

HLA-B27-Associated Acute Anterior Uveitis

The inflammatory pattern of acute HLA-B27-associated anterior uveitis has been evaluated using LFM. In a study on 44 patients presenting an acute episode of anterior uveitis, the mean initial flare was 160 ± 22 ph/ms (range: 11–787 ph/ms). All patients were given standard therapy consisting of hourly instillations of 1% prednisolone drops progressively tapered after 3 days according to the evolution of inflammation. A 50% and 90% flare reduction occurred after 2 and 8 days, respectively, under the standard therapeutic regimen used. In 15 out of the 44 patients enrolled, an additional periocular corticosteroid injection was needed because of insufficient flare decrease (less than 30% of initial flare) or because of flare increase after 48 h. Following periocular injection of 4 mg of betamethasone, a 50% flare reduction occurred between 10h and 24h. The end of an episode of anterior uveitis was defined as a flare level below 8 ph/ms. This study demonstrates that LFM allows meticulous adjustment of therapy in patients with HLA-B27-associated uveitis.

The sensitivity of LFM in monitoring anterior chamber inflammation in HLA-B27-associated uveitis has been further evaluated in a recent study that compared LFM measured

values to slit-lamp grading system of aqueous cells. In this prospective masked trial, the mean time for a 50% reduction was 3.9 days for LFM flare and 14 days for aqueous cells. The mean time for a 90% reduction was 19.6 days for LFM flare and 40 days for aqueous cells. Based on these results, the authors concluded that LFM flare was a more sensitive parameter than the slit-lamp grading of cells in assessing evolution of acute anterior uveitis. Currently, uveitis specialists who use LFM as diagnostic instrument continue treatment until LFM flare returns to normal levels following an episode of HLA-B27-associated acute anterior uveitis [29-35].

3 STUDY OBJECTIVES

3.1 Primary Objective

To explore the efficacy of NORFLO® ORO in RAU, measured as a long-term reduction of the frequency and severity of relapses, in patients with HLA-B27-associated uveitis, under conditions of routine medical practice. The reduction of the mean number of relapses per patient between the year before study treatment and the study period will also be assessed.

3.2 Secondary Objectives

The secondary objectives of this study include:

- the evaluation of the improvement of side effects due to HLA-B27-associated uveitis such as IOP, cystoid macular edema, keratopathy and synechia;
- the evaluation of the improvement in uveitis-related symptoms (BCVA and symptoms measured by VAS like ocular pain, photophobia, floaters and blurred vision).
- the evaluation of cell damage and inflammation reduction in patients with HLA-B27-associated uveitis;
- the evaluation of the patients' attitude towards the study treatment;
- the evaluation of the safety profile of the study product.

4 STUDY DESIGN

4.1 Study Overview

This is a multicenter, double blind, placebo-controlled and randomized study. This study will be conducted in compliance with both European and FDA requirements.

Patients eligible for participation in this study, as part of their routine medical care, will receive NORFLO® ORO or placebo in addition of the conventional therapy. In the study, patients will be followed up to 1 year. This study will include patients with HLA-B27-associated relapsing uveitis. Participating sites will be encouraged to enroll patients in both

cohorts (NORFLO® ORO or placebo), through an e-based randomization system in order to minimize bias in patients' selection.

Sixty subjects with HLA-B27-associated uveitis will be enrolled and they will be divided into 2 groups, 30 will receive the treatment and 30 the placebo, in addition to conventional therapy. In Italy 46 patients will be recruited.

Each subject will receive a single dose of either placebo or NORFLO® ORO two times a day for 1 year. Subjects will be assigned to the treatments in a random order. Evaluations will be taken at baseline (t_0) and during each of the following two visits within the study (t1 6 months, t_2 12 months).

Data from screened patients will be reviewed to determine the subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be enrolled in the study and randomized to treatment.

The following treatment regimens will be applied:

- NORFLO® ORO – 1.7450 gr
- Placebo – 1.7450 gr

Total duration of subject participation will be of about 12 months. Total duration of the study is expected to be about 15 months.

Table 1 – Dosage Regimen

	Dosage regimen/Each center	**Administration**	**Duration**
NORFLO® ORO	3.49 gr total (2 single foil pouches of 1,7450 g) per day	Each single pouch (1,7450 g) at main meal in a glass of water	12 months
PLACEBO	3.49 gr total (2 single foil pouches of 1,7450 mg) per day	Each single pouch (1,7450 g) at main meal in a glass of water	12 months

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be the mean number and intensity of relapses per patient occurred during the study, from baseline to end of treatment, in patients treated with the NORFLO® ORO compared to patients treated with placebo.

The reduction in relapses will be determined by a reduction of the intraocular inflammation through a clinical and diagnostic evaluation that includes Laser measurement of AC flare

with Kowa LFM 600 or LFM 700 (Normal range 2.5-7 ph/ms. Outside normal range > 10 ph/ms).

The reduction of the mean number of relapses per patient between the year before treatment and the study period within each treatment group will also be assessed.

The reduction of cell damage and inflammation will be measured by the Laser Flare Meter, in patients affected by HLA-B27-associated uveitis after treatment with NORFLO® ORO, when compared to placebo.

5.2 Secondary Efficacy Endpoints

The following secondary endpoints will be examined:

- The reduction of the side effects due to HLA-B27-associated uveitis, such as IOP assessed by Goldmann applanation tonometry (APL), cystoid macular edema (central foveal thickness – central 1 mm subfield thickness), assessed by optical coherence tomography (OCT) Spectralis® spectralis, keratopathy, evaluated by fluorescein staining of the cornea (present/absent), and synechiae, assessed by photographic slit lamp (present/absent and if present, involving one or more quadrants; photograpsh shall be retained to document synechia), after treatment with NORFLO® ORO, when compared to placebo.
- The improvement in uveitis-related symptoms (BCVA, symptoms like ocular pain, photophobia, floaters and blurred vision, measured by VAS) after treatment with NORFLO® ORO, when compared to placebo.
- The patients' attitude towards the treatment with NORFLO® ORO, compared to placebo, will be captured by means of a questionnaire (Quick Questionnaire) specifically developed for the study on the basis of previous experiences[4,36-39].

5.3 Safety Evaluations

The safety evaluations will include:

- The incidence and typology of adverse events in the NORFLO® ORO treatment group compared to placebo group.
- The use of concomitant medications.
- The changes in vital signs.

6 SUBJECT SELECTION

6.1 Study Population

Subjects with a diagnosis of HLA-B27-associated uveitis who meet the inclusion and exclusion criteria will be eligible for participation in this study.

6.2 Inclusion Criteria

1. Subjects ≥ 18 years of age at baseline Visit.
2. HLA-B27 positive related uveitis (acute alternating non granulomatous uveitis the uveitis shall not be in acute phase at the time of enrolment and at least 8 weeks must have elapsed after the resolution of the last uveitis attack.
3. Subjects with at least one autoimmune uveitis relapse (UAR) in the last year.
4. Written informed consent obtained from subject or subject's legal representative and ability for the subject to comply with the requirements of the study.

6.3 Exclusion Criteria

1. Presence of a condition or abnormality that in the opinion of the investigator would compromise the safety of the patient or the quality of the data collected.
2. Subjects that have received systemic therapy for uveitis with anti-inflammatory, immunosuppressive or biological drugs in the 30 days before study start.
3. Subjects with an anticipated need for systemic anti-inflammatory, immunosuppressive or biological drugs during the 12 months of the study.
4. Subjects who received an intravitreal, peribulbar, sub-tenon, periocular injection in the previous 6 months.
5. Subjects that are receiving long-term treatment with systemic anti-inflammatory, immunosuppressive or biological drugs for other diseases different from uveitis.
6. Women who are taking hormonal contraceptives.
7. Subjects that have taken supplements and nutraceuticals in the last 30 days prior to baseline visit. Use of supplements and nutraceuticals will not be admitted during the study.
8. Subjects for whom baseline LFM and other ocular evaluations cannot be accurately performed.
9. Women who are pregnant or breast-feeding.

The study will be considered completed once the last clinical site will be closed. Participation in this study has no impact on the type of medical care that the patient will receive during the study as well as post-study participation.

7 CONCURRENT MEDICATIONS

All subjects should be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies.

7.1 Allowed Medications and Treatments

All topical drugs (any topical midriatic treatment and any traditional topical therapy for uveitis) will be admitted for the treatment of the signs and symptoms associated with HLA-B27-associated chronic relapsing uveitis.

In the case of relapse with LFM values are > 100 ph/ms despite treatment with topical therapy, or in any case the LFM values result to be > 100 ph/ms, then a systemic therapy is recommended and the subject has to be dropped-out from the study and treated according to the best medical judgement.

7.2 Prohibited Medications and Treatments

The following medications are prohibited during the study and the administration will be considered a protocol violation: supplements and nutraceuticals, systemic therapies for uveitis (anti-inflammatory, immunosuppressive, biologicals), hormonal contraceptives, long-term treatment with systemic anti-inflammatory, immunosuppressive or biological drugs for other diseases different from uveitis. Systemic therapies with anti-inflammatory, immunosuppressive drugs are allowed for reasons different from uveitis and in any case for periods not exceeding 15-30 days.

8 ENROLLMENT, TREATMENT ASSIGNMENT AND BLINDING

8.1 Method of Assigning Subjects to Treatment Groups

Up to 60 eligible patients will be randomly assigned to NORFLO® ORO or placebo treatment groups in a 1:1 ratio using a stratified randomization blocks scheme. The patient randomization list will be generated by Latis S.r.l., using the procedure PROC PLAN of SAS 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

8.2 Blinding

Due to the objectives of the study, the investigators, research staff, or patients will not know the treatment identity (test or control). The following study procedures will be in place to ensure double-blind administration of study treatments:

- Access to the randomization code will be strictly controlled.

Packaging and labeling of test and control treatments will be identical to maintain the blind.

The study blind will be broken on completion of the clinical study and after the study database has been locked.

During the study, the blind may be broken **only** in emergencies when knowledge of the patient's treatment group is necessary for further patient management.

The Principal investigator will receive a study treatment identification key in the form of sealed envelopes containing the kit number and the corresponding treatment.

The envelope can be opened only in case of an emergency presenting the need to disclose the identification of the study treatment assigned to the patient, for the purpose of establishing the appropriate therapy. Once the code is broken for a patient, this patient shall be withdrawn from the study, with the completion of the final study evaluation, indicating the specific reason of the patient withdrawal.

The Study Monitor must be notified immediately by the investigator of any emergency unblinding; the date and time, along with the reason for the unblinding, will be noted. Treatment codes will not be freely available to the investigator or personnel monitoring the study until after the study completion and database lock.

8.3 Formulation of Test and Control Products

8.3.1 Formulation of Test Product

NORFLO® ORO is a new formulation of Eye Pharma S.p.A., for oral administration. NORFLO® ORO is a yellow-colored solution that requires no reconstitution. See **Table 2** for the formulation of NORFLO® ORO.

Table 2 - Formulation and Measured pH of NORFLO® ORO and Placebo

	NORFLO® ORO	**g/ST**	**Placebo**	**g/Kg**
Active Ingredient, mg/mL	Turmeric lecithin	0.500 g		
	Turmeric - phosphatidylserine	0.100 g		
Other ingredient, mg/mL	Erythritol	0.2891 g	Erythritol	165.67 g
	Silicon Dioxide	0.0175 g	Silicon Dioxide	4.53 g
	Polysorbate 20 (Tween 20)	0.0174 g	Polysorbate 20 (Tween 20)	9.99 g
	Isomalt	0.192 g	Isomalt	533.30 g

	Guar Gum	0.300 g	Guar Gum	171.92 g
	Orange flavor	0.100 g	Orange flavor	57.31 g
	Stevia	0.050 g	Stevia	8.60 g
	Lemon flavor	0.100 g	Lemon flavor	28.65 g
	Citric acid	0.008 g	Citric acid	4.58 g
	Sucro ester E473	0.006 g	Sucro ester E473	0.006 g
			Sunset yellow (E110)	12 g

8.3.2 Formulation of Control Product

A placebo will be provided by Eye Pharma in a pack containing 30 single foil pouches ready for administration. The placebo composition is reported in Table 2.

8.3.3 Packaging and Labeling

Packaging: study product and placebo will be supplied in cartons containing 30 single foil pouches that are enough for a month-long treatment.

The study products will be delivered to the subjects based on the interval period between visits as indicated below:

Visit 1 (baseline, t_0)): each patient receives 13 kits containing 30 single foil pouches

Visit 2 (t_1, 6 months): each patient receives 18 kits containing 30 single foil pouches.

Labeling: Each carton (kit) of study products will be labeled with the protocol number, a treatment number, production lot, expiration date, the name of the sponsor, and directions for patient use and storage.

8.4 Supply of Study Products at the Site

Eye Pharma (or designee) will ship the Study Products to the investigational sites after sites activation (i.e. all required regulatory documentation has been received by Eye Pharma and a contract has been executed).

8.4.1 Dosage/Dosage Regimen

Study products will be administered as follows.

Two single foil pouches per day, each with main meals, with an estimated interval of about 8 hours between doses. A minimum interval of 4 hours between doses should be maintained.

The treatment will last for a period of 12 months.

Table 3 - Dosage Regimen

	Dosage regimen/ Each center	Administration	Minimum interval between doses	Duration
NORFLO® ORO	3.49 gr (2 single foil pouches of 1.7450 g) per day	Each single pouch (1.7450 g) at main meal in a glass of water	4 hr	12 months
PLACEBO	3.49 gr (2 single foil pouches of 1.7450 g) per day	Each single pouch (1.7450 g) at main meal in a glass of water	4 hr	12 months

8.4.2 Dispensing

Investigator (or designee) delivers the study product to the patient at each visit.

8.5 Supply of Study Product at the Site

8.5.1 Storage

Study products should be stored by the study site at controlled room temperature, 15 to 30ºC (59 to 86ºF). If the temperature of the study drug storage in the clinic/pharmacy exceeds or falls below this range, this should be reported to Eye Pharma (or designee) and captured as a deviation. Subjects will be instructed to store the medication in original packaging (foil pouch and protected from light) at room temperature.

8.6 Study Product Accountability

An accurate and current accounting of the dispensing and return of study product for each subject will be maintained on an ongoing basis by a member of the study site staff. The number of study product foil pouches dispensed and returned by the subject will be recorded on the appropriate form. The study monitor will verify these documents throughout the course of the study.

8.7 Measures of Treatment Compliance

Subjects will be asked to keep a patient diary noting the day and date they take the study product and any adverse events they experience. Subjects will be asked to bring their patient diary to each study visit along with all used and unused study product containers.

Due to non-compliance with study procedures, the investigator can withdraw subjects from study participation. The investigator will communicate promptly to Eye Pharma the patient withdrawal from the study.

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in APPENDIX 1. Data sheets on diagnostic ophthalmologic exams to be carried out during the study are shown in APPENDIX 2.

Prior to conducting any study-related activities, written informed consent must be signed and dated by the subject or subject's legal representative.

9.1 Clinical Assessments

9.1.1 Demographics

Patient demographic and baseline characteristic data to be collected on all patients includes: date and place of birth, place of living, sex, race, and ethnicity (where legally possible), work typology.

9.1.2 Concomitant Medications

All concomitant medications will be registered at baseline visit and their changes, if any, will be documented at each following visit. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.3 Medical History

Relevant medical history, including history of current disease and information regarding underlying diseases, with special attention to ocular diseases and uveitis, will be recorded at baseline visit (t_0).

9.1.4 Physical Examination

A physical examination will be performed by the investigator at baseline visit (t_0). Qualified staff may complete the abbreviated physical exam at all other visits. New abnormal physical exam findings during the study must be documented as adverse event and will be followed by a physician or other qualified staff at the next scheduled visit.

A rheumatologic evaluation will be done at screening in order to assess if the whether the disease also has a systemic involvement (ankylosing spondylitis) or not.

9.1.5 Urine dipstick specific pregnancy test

Urine dipstick specific pregnancy test will be performed at the site at baseline and at each following visit. The study products cannot be administered if the pregnancy test results positive or doubtful.

9.1.6 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study product will be recorded on the case report form (CRF).

9.1.7 Vital Signs

Systolic and diastolic blood pressure and heart rate will be measured at baseline and at each following visit.

9.2 Ophthalmological exams guide

Both eyes will be evaluated at each visit.

9.2.1 BCVA

One goal of a complete eye examination is to determine the best corrected visual acuity (BCVA). Normal visual acuity is generally accepted as 20/20, although many people can see 20/15, and a few can see 20/10. If the eye cannot see 20/20 with a glasses or contact lens correction, then a refraction is required to determine the BCVA.

The visual acuity testing protocols recommended are:

• Distance acuity with correction (CC) if the patient needs glasses or contact lenses for the best distance vision. The exception is visual acuity testing after cataract or refractive surgery, as these procedures will likely change the refractive status of the eye.

• Distance acuity without correction (SC) if the patient wears no glasses or contact lenses (default test).

BCVA will be measured at baseline and at each following visit.

9.2.2 Laser Flare Photometry

Anterior Chamber Flare Assessment and Measurement Kowa LFM 600 and 700

The role of intra-ocular inflammation in driving disruption of blood-aqueous barrier and leading to the spreading of proteins and inflammatory cells into the aqueous humor has been previously established. The Standardization of Uveitis Nomenclature (SUV) system to evaluate and grade this kind of inflammatory leakage (flare) in the anterior chamber (AC) of the eye, ranging from 0 to 4+, is not useful or unreliable to detect and quantify AC

inflammation because the SUV test depends on the subjectivity of the evaluation and on the nonlinear grading of flare at the slit-lamp.

Currently, the only available system to quantitatively and objectively measure (with reproducibility) intra-ocular inflammation is the Kowa Laser Flare Meter (LFM) instrument. Such instrument includes a photomultiplier that amplifies the intensity of the light scattered by small molecules (flare) or larger particles (inflammatory cells) in the aqueous humor. The information is then processed by a computer and the result is expressed in photon counts per millisecond (ph/ms).

LFM instruments quantify back-scattered light both from small molecules and from larger particles such as inflammatory cells. Therefore, LFM measurements may be unreliable in eyes with extensive posterior synechiae or mature cataract due to increased background scattering of light. Seven measurements shall be obtained with LFM. The highest and the lowest LFM values are discarded and the mean and standard deviation of the remaining five LFM readings are automatically calculated. Patients do not experience any pain or discomfort during measurements. Aqueous flare intensity in the range of 2.9–3.9 ph/ms corresponds to healthy individuals between 20 and 40 years of age and they increase slightly with age, reaching 5.0–6.5 ph/ms for patients between 70 and 80 years of age.

Effective management of uveitis requires a reproducible and quantitative method to determine and monitor intraocular inflammation. Clinically meaningful changes in flare counts can be detected both in low and high-flare values because LFM allows measuring flare values that range between 3 and 1000 ph/ms on a linear scale. Gonzales *et al*. reported an inverse relationship between LFM flare and visual acuity in patients with uveitis. While no relationship was found between complications and anterior chamber cell or flare scores at the slit-lamp, a strong relationship was found between LFM flare and complications such as posterior synechia and macular edema.Intra-ocular inflammation evaluation by the Kowa Laser Flare Meter examination will be done at baseline and at each following visit.

9.2.3 OCT

Optical coherence tomography (OCT) Spectralis® (Heidelberg Egineering, Heidelberg Germany) is a non-invasive imaging test that uses light waves to take cross-section pictures of your retina, the light-sensitive tissue lining the back of the eye.

Cross-sectional visualization is an extremely powerful tool in the identification and assessment of retina abnormalities. The high resolving power (10µm - Time Domain, 5µm – Spectral Domain) provides excellent detail for evaluating the vitreo-retinal interface, neurosensory retinal morphology, and the RPE-choroid complex. The ability to perform volumetric and retinal thickness analysis also provides a quantitative and repeatable method to evaluate surgical and pharmacological interventions. Individual high resolution line scans are a simple way to identify overt as well as very subtle retinal interface pathologies, such as a persistently adherent posterior hyaloid, fine epiretinal membranes, and vitreomacular

traction. In a procedure that is easily tolerated by most patients, well-placed line scans can differentiate between pseudo holes, lamellar holes and full thickness macular holes with a high degree of confidence. Line scans can also confirm the presence of retinal edema from various causes. When combined with serial thickness map or volume analysis, these different data sets provide a detailed picture of disease progression or therapeutic response.

OCT Spectralis® examination will be done at baseline and at each following visit.

9.2.4 Slit lamp

Slit-lamp biomicrography encompasses a wide spectrum of challenging photographic techniques for imaging structures and diseases of the anterior segment. Most photographic slit-lamps are equipped with two lighting sources, variable flash intensity, changeable magnifications, and changeable angles of illumination. Patients present a wide variety of disease entities that have specific textures, colors, transparency, size and depth. The slit lamp is a binocular microscope that provides the examiner with a stereoscopic (i.e. three-dimensional) view of the eye. The slit lamp allows examining the eye with a beam or "slit" of light (versus diffuse light) whose height and width can be adjusted. The slit of light, when directed at an angle, accentuates the anatomic structures of the eye, allowing close inspection. The slit lamp provides greater magnification (10 to 25 times) and illumination than most handheld devices (i.e. the Wood's lamp), which is necessary to diagnose a number of traumatic and non-traumatic disorders.

Slit lamp examination will be done at baseline and at each following visit.

9.2.5 Goldmann tonometry

Tonometry is the procedure to determine the intraocular pressure (IOP), the fluid pressure inside the eye. IOP is an important test in the evaluation of patients at risk from glaucoma. [1] Most tonometers are calibrated to measure pressure in millimeters of mercury (mmHg). Goldmann tonometry is considered to be the gold standard and most widely accepted method IOP test. A special disinfected prism is mounted on the tonometer head and then placed against the cornea. The examiner then uses a cobalt blue filter to view two green semi circles. The force applied to the tonometer head is then adjusted using a dial connected to a variable tension spring until the inner edges of the green semicircles in the viewfinder meet. When an area of 3.06 mm (0.120 in) has been flattened, the opposing forces of corneal rigidity and the tear film are roughly approximate and cancel each other out allowing the pressure in the eye to be determined from the force applied.

Intraocular pressure will be evaluated at baseline and at each following visit.

10 EVALUATIONS BY VISIT

10.1 Visit 1 (t_0)

1. Review the study with the subject (subject's legal representative) and obtain written informed consent
2. Assign a unique screening number to the subject
3. Record subject's demographics data
4. Record subject's medical history, including a history of uveitis, diagnosis date and prior uveitis treatments and the number of relapses during the previous year
5. Record subject's concomitant medications
6. Perform a physical examination of the subject
7. Vital signs collection
8. • Urine dipstick specific pregnancy test
9. Perform a rheumatologic evaluation of the subject
10. Perform subject's ophthalmic evaluation (BCVA, Slip lamp, OCT Spectralis®, LFM, Goldman tonometry).
11. Evaluation of uveitis symptoms by VAS (ocular pain, blurry vision, floaters, photophobia)
12. Evaluation of the patient's attitude towards the study treatment, through the Quick Questionnaire
13. Evaluate inclusion/exclusion criteria adherence
14. Randomize subject and dispense study product
15. Initiate subject diary.

After about 3 months of treatment the study staff will contact the patient by phone to verify that the study product is correctly taken.

10.2 Visit 2 (t_1, 6 Months ± 10 days)

1. Perform subject's ophthalmic evaluation (BCVA, Slip lamp, OCT Spectralis®, LFM, Goldman tonometry)
2. Evaluation of uveitis symptoms by VAS (ocular pain, blurry vision, floaters, photophobia)
3. Perform a physical examination of the subject
4. Vital signs collection
5. Urine dipstick specific pregnancy test

6. Record any Adverse Event
7. Review subject's diary for Adverse Events and for dosing compliance
8. Study product collection and accountability
9. New diary and study product delivery
10. Concomitant medications review
11. Evaluation of the patient's attitude towards the study treatment, through the Quick Questionnaire

10.3 Visit 3 – End of Study (t_2, 12 Months ± 10 days)

1. Perform subject's ophthalmic evaluation (BCVA, Slip lamp, OCT Spectralis®, LFM, Goldman tonometry)
2. Evaluation of uveitis symptoms by VAS (ocular pain, blurry vision, floaters, photophobia)
3. Perform a physical examination of the subject
4. Vital signs collection
5. Urine dipstick specific pregnancy test
6. Record any Adverse Event
7. Review subject's diary for Adverse Events and for dosing compliance
8. Study product collection and accountability
9. Concomitant medications review
10. Evaluation of the patient's attitude towards the study treatment, through the Quick Questionnaire

10.4 Additional Unscheduled Visits in Case of Relapse

Should a relapse occur, an unscheduled visit will be performed including a complete ophthalmic evaluation. The number of cells in the AC will be determined by slit lamp, too.

Topical or systemic treatment will be prescribed to the subject according to the severity of the relapse and according to the best medical judgement.

Two following visits will be scheduled 2 and 6 weeks thereafter. During these visits a complete ophthalmic evaluation will be done.

If the subject is prescribed a systemic treatment for the relapse, he/she will be withdrawn from the study, and treated according to the best medical judgement.

If only topical treatments are prescribed, the subject will be allowed to continue the study. Depending on the onset time of the relapse it could be necessary to delay Visit 2 or Visit 3 around 2 months after the topical treatment conclusion.

Should Visit 2 be delayed, the delay will be recovered by keeping the date of Visit 3 at 12 months.

Should Visit 3 be delayed, the delay will not be recovered.

10.5 Early Withdrawal Visit

In the case of early withdrawal from the study, activities planned at Visit 3 will be performed, as far as possible.

11 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

11.1 Early Discontinuation of Study Drug

A subject may be discontinued from the study treatment at any time if either the subject, and/or the investigator, and/or Eye Pharma feels that it is not in the subject's best interest to continue the study treatment. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent
- Subject is not compliant with study procedures
- Need for the subject to start a systemic anti-inflammatory, immunosuppressive, biologicals therapy for uveitis or for other pathologies
- Adverse event that indicated in the opinion of the investigator that it would be in the best interest of the subject to discontinue study treatment
- Pregnancy
- Protocol violation requiring discontinuation of study treatment
- Missed follow-up
- Eye Pharma requests early study termination

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue the study treatment should come in for an early discontinuation visit as soon as possible and then they should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to obtain a reason for subject's withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

11.2 Replacement of Subjects

Only subjects dropping out the study because they are beginning systemic therapy with anti-inflammatory, immunosuppressive, biologic drugs will be replaced.

12 PROTOCOL VIOLATIONS

A protocol violation occurs when either the subject, and/or the investigator, and/or Eye Pharma fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Compliance with study product regimen under 90%.

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. Eye Pharma will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be immediately reported by written (via e-mail) to and discussed with the Sponsor. The Sponsor's evaluation results and, request of corrective actions will be reported to the investigator by written (via e-mail).

13 ADVERSE EVENTS REPORTING AND DOCUMENTATION

13.1 Overview

An Adverse Event (AE) is "Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including for example an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product".

This definition includes intercurrent illnesses or injuries, exacerbation of pre-existing conditions, and adverse events occurring as a result of drug withdrawal, abuse, misuse or

overdose. Adverse events observed during all periods of the study are to be recorded, including adverse events occurring during a period without study product intake. This also includes adverse events which are reported within in the screening phase (since the patient has signed Informed Consent Form).

Signs and symptoms considered as lack of efficacy and occurring during the study will not be recorded on the AEs Section of the CRF except on the condition that, in the investigator's opinion, they are caused by any reason different from lack of efficacy of study product or meet the definition of serious AE.

Clinically significant findings at screening (e.g., laboratory findings) are not considered an AE/SAE.

If a clinical significant finding recorded at screening worsens (in terms of severity or frequency) during the study, it must be recorded as an AE/SAE.

Unexpected Adverse Event

An Unexpected Adverse Event is any experience not previously reported (in nature, severity or incidence) in the current package insert for the study product.

13.2 AE Severity

The international common terminology criteria for Adverse Events should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 4 - AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

13.3 Abnormal test findings

An abnormal test finding will be classified as an *adverse effect* if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug or other therapy (Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse effect.)
- The test finding leads to a change in study dosing or exposure or discontinuation of subject participation in the clinical study
- The test finding is considered an adverse effect by the investigator and /or Eye Pharma

13.4 Events to be reported

13.4.1 All adverse Events

All observed adverse events (serious or non-serious) and abnormal test findings, regardless of the treatment group, or any suspected causal relationship of adverse event to the investigational products will be recorded in the subjects' case histories. For all adverse events, sufficient information will be pursued and/or obtained so as to permit (1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a serious adverse event) and (2) an assessment of the casual relationship between the adverse event and the investigational treatment . Adverse events or abnormal test findings suspected to be associated with the investigational product will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the sponsor-investigator.

13.4.2 Adverse Events requiring immediate Notification

Serious Adverse Events (SAE)

A serious adverse event (SAE) is any event that suggests a significant hazard, contraindication, side effect, or precaution, whether or not it is considered to be associated with the study product. A SAE is an AE that meets any of the following criteria:

- **Results in death**. This includes any death that occurs during the conduct of a clinical trial, including deaths that appear to be completely unrelated to the study products (e.g., car accident).

- **Is life-threatening**. This includes any AE during which the patient is, in the view of the investigator, at immediate risk of death from the event as it occurs. This definition does not include events that may have caused death if they had occurred in a more severe form.
- **Requires inpatient hospitalization** or prolongation of existing hospitalization.
- **Results in persistent or significant disability or incapacity**.
- **Is a congenital anomaly or birth defect**.
- **Other medical events** that based upon appropriate medical judgment are thought to jeopardize the patient and/or require medical or surgical intervention to prevent one of the outcomes defining a SAE.

Planned hospitalizations scheduled prior to the informed consent but performed during the study should not be considered (serious) AEs.

Serious Adverse Event Reporting

Study sites will document all SAEs that occur (whether or not related to the study product). The collection period for all SAEs will begin after the informed consent is obtained and will finish 2 weeks after the patient has withdrawn study participation (defined as time passed from the last visit). All SAE occurred in that time range must be reported to Eye Pharma within 24 hours of learning about its occurrence:

Contact person for USA:

Alice Tomei – Eye Pharma US

Phone: 001 3052433469
e-mail: alice.tomei@eyepharma.com

Contact person for Italy:

Lucia Degrassi – Eye Pharma S.p.A.

Phone: +39 010 513188
Fax: +39 010 3071430

e-mail: lucia.degrassi@eyepharma.com

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

The sponsor will be responsible for reporting to Competent Authorities, according to local laws and regulations.

13.5 Investigator Responsibilities

The Eye Pharma-investigator will promptly review documented adverse events and abnormal test findings to determine (1) if the abnormal test finding should be classified as an adverse event; (2) if there is a reasonable possibility that the adverse event was caused by the investigational product and (3) if the adverse event meets the criteria for a serious adverse event.

If the Eye Pharma-investigator's final determination of causality is "unknown and of questionable relationship to the investigational product" the adverse event will be classified as associated with the use of the investigational product, for reporting purposes.

13.6 Evaluation of Causality

AE Relationship to Study Product

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 5.

Table 5 - AE Relationship to Study Product

Relationship to Product	Comment
Definitely	Previously known toxicity of the agent; or an event that follows a reasonable temporal sequence from administration of the product; that follows a known or expected response pattern to the suspected product; that is confirmed by stopping or reducing the dosage of the product; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the product; that follows a known or expected response pattern to the suspected product; that is confirmed by stopping or reducing the dosage of the product; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the product; that follows a known or expected response pattern to that suspected product; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study product.

14 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be issued, describing all analyses that will be performed. The SAP will contain any

modifications to the analysis plan described below. SAS 9.4 for windows (SAS Institute Inc., Cary, NC, USA) will be used for statistical analysis. A level of statistical significance (alpha) of 5% will be used to evaluate statistically significant differences between the two treatment groups, placebo and active treatment.

14.1 Data Sets Analyzed

All eligible patients who are randomized into the study and receive at least one dose of the study product (the Safety Population) will be included in the safety analysis. All eligible patients who are randomized into the study, receive at least one dose of the study product and have at least a post-randomization endpoint estimate (the Intention-to-Treat Population) will be included in the efficacy analysis.

14.2 Demographic and Baseline Characteristics

The following demographic variables collected at screening will be summarized by treatment group: race, gender, age, height and weight.

14.3 Analysis of Primary Endpoint

The number and intensity of relapses will be assessed through instrumental analysis and physical examination. These endpoints will be assessed from baseline to end of treatment.

Mean and standard deviation will be used to describe the number of relapses per patient. The mean number of relapses per patient will be compared between the treatment groups using Student's t-test. ANOVA will be used to include predictive/confounding variables in the model.

In addition, a generalized linear mixed model (GLMM) with Poisson statistical distribution and with the number of relapses as dependent variable will be used to assess the effects of the treatment on reducing the number of relapses, also including in the model other potentially predicting/confounding variables.

The intensity of relapses will be scored as mild (either trace to 1+ cell OR flare $\leq$ 20), moderate (2+ to 3+ cell OR Flare > 20 and < 100) and severe (4+ cell OR Hypopyon OR flare $\geq$ 100). For each patient, the average intensity will be estimated as the mean of the intensity observed during each relapse. The average and the maximum intensity will be compared between treatment groups using Student's t-test. ANOVA will be used to include predictive/confounding variables in the model.

The mean number of relapses per patient observed during the study will be compared to the mean number of relapses reported the previous year within each treatment group using paired t-test or ANOVA, to eventually adjust for predictive/confounding variables. As group means can be somewhat deceptive with small number of events, the patients will be classified based on the number of relapses before treatment and then on the number of relapses after treatment. The number of patients that change class before and after treatment (for example, from a high number of relapses to a low number) will be described and compared between treatment groups.

The primary efficacy endpoints will be analyzed in the following hierarchical order: first, "the mean number and intensity of relapses during the study between treatment groups" and then "the reduction of mean number of relapses between the year before treatment and the study period".

The level of cell damage and inflammation will be assessed through Laser Flare Meter. The difference between treatment groups will be compared using ANCOVA, with the baseline level included in the model.

An analysis of the number of relapses per eye will be also considered, if appropriate.

14.4 Analysis of Secondary Endpoints

The incidence of side effects associated HLA-B27-associated uveitis, such as cystoid macular edema (central 1 mm subfield thickness), keratopathy and synechia, will be compared between treatment groups using logistic regression. In addition, the changes in IOP, in central 1 mm subfield thickness will be compared between treatment groups using ANCOVA, with the baseline level included in the model. The presence of keratopathy and synechiae will be compared between treatment groups using logistic regression. The number of quadrants involved by synechiae, when present, will be described.

The changes in BCVA and symptoms (ocular pain, blurred vision, floaters and photophobia), measured by VAS, will be compared between treatment groups using ANCOVA, with the baseline level included in the model.

Each information collected through the Quick questionnaire will be compared between the two treatment groups using chi-square test.

14.5 Safety Evaluations

Safety and tolerability data will be summarized by treatment group.

Clinical evaluations for safety and tolerability assessments will include monitoring AEs, vital signs, concomitant medications and compliance.

Adverse event will be coded using the last updated version of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary to give a preferred term (PT) and a system/organ class term (SOC) for each. Adverse events will be tabulated by treatment group. Tables will include the number of patients who experienced at least one AE, of study product-related AEs (defined as definitely, probably, possibly, or unrelated), of serious AEs, and the number of patients withdrawn due to AE, summarized by treatment arm. Comparisons between treatment arms will be performed using chi-square test.

Concomitant medications will be summarized by treatment using descriptive statistics and they will be listed.

Vital signs will be summarized by treatment using descriptive statistics for absolute values and change from baseline.
Compliance to the study treatment will be assessed through the patient diary and checked versus the used and unused study product containers given back by the patients.

14.6 Interim Analysis

No interim analysis planned.

14.7 Sample Size

In a previous study[25], 275 relapses on 106 patients were observed, corresponding to a mean number of relapses per patient of 2.6 (Standard deviation, SD: 0.7) while in the post-treatment group 36 relapses were registered corresponding to a mean number of relapses per patient of 0.34 relapses/patient. With a statistical power of 80% and a significance level (alpha) of 5% and a common SD of 0.7, 46 patients are needed to observe a difference of 0.6 relapses/patients between the two treatment groups (i.e., 2 relapses/patient in the NORFLO® ORO treatment group vs. 2.6 in the placebo treatment group). To take into account a potential dropout rate of 20% over 12 months, 60 patients will be recruited. Subjects dropping out the study because they are beginning systemic therapy with anti-inflammatory, immunosuppressive, biologic drugs will be replaced.
A second primary endpoint, i.e. the reduction of mean number of relapses between the year before treatment and the study period, will be examined. No formal sample size estimate is feasible on this endpoint, as it was not tested previously and no reasonable scenario can be drawn.
As the two endpoints will be assessed in a hierarchical order (first, "the mean number and intensity of relapses during the study between treatment groups" and then "the reduction of mean number of relapses between the year before treatment and the study period"), according to the "Points to consider on multiplicity issues in clinical trials", issued by the Committee for Proprietary Medicinal Products (CPMP - 2002), no sample size adjustment for multiplicity is needed.

15 DATA COLLECTION, RETENTION AND MONITORING

15.1 Data Collection Instruments

During each patient's study visit, the study investigator or designee will collect and report study data in the relevant patient's chart (source documents), documenting all significant observations.
The investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available.

Source Data include the clinical findings and observations, the laboratory and test data, and other information contained in Source Documents. Source Documents are the original records (and certified copies of original records); including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, etc. When applicable, information recorded on the CRF shall match the Source Data recorded on the Source Documents.

Subjects will not be identified by name in the study database or in any study documents to be collected by Eye Pharma (or designee), but will be identified by a site number and subject number.

The e-CRF used for this study will compliant with 21 CFR part 11 requirements.

The investigator will maintain a list of all persons authorized to make entries and/or corrections on the CRFs. Each authorized person will be provided with a user-specific ID protected by a renewable password. Data entries and corrections will be made only by the authorized persons. The e-CRF system will record date and time of any entry and /or correction and the user ID of the person making the entry/correction. The system will keep track of all old and new values (audit trial). It is the responsibility of the investigator to ensure that the CRFs are properly and completely filled in. The CRFs must be completed for all patients who have been included in the trial. The investigator will review all CRFs and electronically sign and date them for each patient, verifying that the information is complete, true and correct. All fields on the CRF must be completed as applicable.

Patients will be provided with paper questionnaires and diaries. Such documents will be filled by the patient during the study, to record data concerning symptoms, evaluation of the patient's attitude towards the study treatment, through the Quick Questionnaire, study treatment assumption.

It is responsibility of the investigators to instruct the study participants on how to fill in the questionnaires and diaries in a clear way and preferably in black ball-point pen. The questionnaires and diaries are anonymous, the subject is identified through the study code assigned. At the end of the study a copy of all questionnaires and diaries will be stored in the Trial Center File. It is responsibility of the investigators to correctly enter the data collected on the questionnaires and diaries in the relevant sections of the e-CRF. The questionnaires and diaries will be considered source data.

Checks to assist during the data entry and to assess the appropriateness and consistence of data will be developed on the e-CRF system. After e-CRF pages will be approved and electronically signed by the investigator, they can be reviewed both on site by the monitor

and remotely, by the data management staff of the sponsor or its designee. Data Clarification Forms (DCF) will be generated through the e-CRF system, both automatically, through edit checks, and manually, by CRAs and/or data managers, and the investigator will have to check and close them. Occasionally, paper DCF can be sent to trial sites for resolution. The investigator is responsible for the review and approval of all query resolutions.

15.2 Availability and Retention of Investigational Records

The investigator must make study data accessible to the monitor, other authorized representatives of Eye Pharma, IRB/IEC, and Regulatory Agency inspectors upon request. The investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of minimum 5 years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which Eye Pharma is required to maintain study records and, therefore, the Eye Pharma should be contacted prior to removing study records for any reason.

The physician must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, and the results of any other tests or assessments.
All information entered in the CRF must be traceable to these source documents in the patient's file. The physician must also keep the original informed consent form signed by the patient (a signed copy is given to the patient). The physician must give Eye Pharma (or designee) access to all relevant source documents to confirm their consistency with the CRF entries.

15.3 Monitoring

Depending on country regulations, formal site monitoring may or may not be performed in this study. However, Eye Pharma (or designee) may perform informal monitoring or auditing occasionally and may request additional information on patients from participating physicians. The Eye Pharma data management or designated CRO will assure compliance monitoring. Monitoring activity will include reviews of the progress of the study and compliance with protocol, SOPs and GPP guidelines.

15.4 Record maintenance and retention

The sponsor-investigator will maintain records to include:

- IEC/IRB correspondence (including approval notifications) related to the clinical protocol; including copies of adverse event reports and annual or interim reports

- Current and past versions of the IEC/IRB-approved clinical protocol and corresponding IEC/IRB-approved consent form(s) and, if applicable, subject recruitment advertisements
- Curriculum vitae (sponsor-investigator and clinical protocol sub-investigators)
- Certificates of required training (e.g., human subject protections, Good Clinical Practice, etc.) for sponsor-investigator and listed sub-investigators
- Normal value(s)/range(s) for medical/laboratory/technical procedures or tests included in the clinical protocol
- Diagnostic Ophthalmic exams
- Laboratory certification information, if applicable
- Master randomization list
- Signed informed consent forms (only the investigator)
- Completed Case Report Forms, signed and dated by the investigator
- Source Documents or certified copies of Source Documents (only the investigator)
- Monitoring visit reports
- Subject identification code list
- Interim data analysis report(s), if applicable
- Final clinical study report.

16 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

16.1 Subject Confidentiality

In order to maintain subject confidentiality, only a site number and subject number will identify all study subjects on the e-CRFs and other documentation submitted to the sponsor. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

16.2 Institutional Review Boards (IRB) and Independent Ethics Committees (IEC)

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse events will be reported to the IRB/IEC in accordance with local regulations, with the standard operating procedures and policies of the IRB/IEC. The investigator will keep the IRB/IEC informed as to the progress of the study. The investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the investigator before the study is initiated

16.3 Study Conduct

This clinical study will be conducted in accordance with the principles contained in the Declaration of Helsinki and in compliance with all international laws and regulations and national laws and regulations of the country in which the study is performed, as well as any applicable guidelines.

16.4 Participant Information and Informed Consent

Informed consent will be obtained in accordance with the Declaration of Helsinki and local regulations.

Eye Pharma will provide to treating physicians a proposed informed consent form that complies with the ICH GCP guideline and local regulatory requirements and is considered appropriate for this study in a separate document. Any changes to the proposed consent form suggested by the investigator must be agreed to by Eye Pharma before submission to the IRB/IEC, and a copy of the approved version must be provided to the Eye Pharma monitor after IRB/IEC approval.

Any amendment to the protocol will be written by Eye Pharma. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRB/IEC are notified within five working days.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the study. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. A copy of the signed consent form will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

16.5 Modification of the Information and Consent Form

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse events occurring during the study in accordance with the standard operating procedures and policies of the IRB/IEC; new information that may affect adversely the safety of the patients of the conduct of the study; and when the study has been completed.

17 OWNER OF THE RESULTS – PUBLICATION POLICY

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study sponsor and participating institutions.

17.1 Investigator Responsibilities

By signing the Agreement of investigator form, the investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study.
3. Ensure that the requirements relating to obtaining informed consent.
4. Report to the sponsor or designee any AEs that occur in the course of the study.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records and to make those records available for inspection with the sponsor (or designee).
7. Promptly report to the IRB/IEC and the sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others).
8. Seek IRB/IEC approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.

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APPENDIX 1- RECOMMENDED DATA COLLECTION SCHEDULE

	VISIT 1 (T_0) BASELINE	VISIT 2 (T_1) 6 MONTHS (± 10 DAYS)	VISIT 3 (T_2) 12 MONTHS (± 10 DAYS)
Informed Consent	**X**		
Demographic data	**X**		
Evaluation of inclusion or exclusion criteria	**X**		
Medical History	**X**		
Physical examination and vital signs	**X**	**X**	**X**
Urine Dipstick specific pregnancy	**X**	**X**	**X**
Rheumatologic evaluation	**X**		
Randomization	**X**		
Evaluation of uveitis symptoms (by VAS)	**X**	**X**	**X**
Diagnostic ophthalmologic examination:			
Measuring visual acuity (BCVA)	**X**	**X**	**X**
Slit lamp exam	**X**	**X**	**X**
OCT Spectralis®	**X**	**X**	**X**
LFM	**X**	**X**	**X**
IOP	**X**	**X**	**X**
Quick Questionnaire	**X**	**X**	**X**
Dispensing of Study Product	**X**	**X**	
Counting of Returned Study Product		**X**	**X**
Subject Diary Initiate and Delivery	**X**	**X**	
Subject Diary Review and Collection		**X**	**X**
Concomitant Medication Review	**X**	**X**	**X**
Adverse Events		**X**	**X**

A phone call will be set about 3 months after treatment start, to the purpose of evaluating that the study product is correctly taken by the subject.

APPENDIX 2 - OPHTALMOLOGICAL EXAMS GUIDE

APPENDIX 2.1 **Best correct visual acuity (BCVA)**
APPENDIX 2.2 **Slit Lamp Biomicroscopy**
APPENDIX 2.3 **Goldman Tonometry**
APPENDIX 2.4 **Optical Coherent Tomography (OCT) Spectralis®**
APPENDIX 2.5 **Kowa Laser Flare-cell Meter (LFM)**

Before dilatation of pupil

2.1 Best correct visual acuity (BCVA)

BCVA assessment by the Early Treatment Diabetic Retinopathy Study **(ETDRS) Method**

- ✓ **Retro illumination Box**
- ✓ **Sets of 3 ETDRS charts (refraction, right eye, left eye)**

Chart R - Refraction

Chart 2- Left Eye (OS)

Chart 1 - Right Eye (OD)

Description

Best correct visual acuity (BCVA) will be assessed and graded using the ETDRS method (Ferris et al 1982).

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

EDTRS equipment (charts, light box, initial primary and spare light tube).

Other equipment:

- 1 meter stick (non flexible)
- Trial lens set (+ and – spheres, + or – cylinder, trial frame)
- 0,37 spherical lens
- Jackson Cross cylinder (0,25, 0,50, 1,00, diopter)

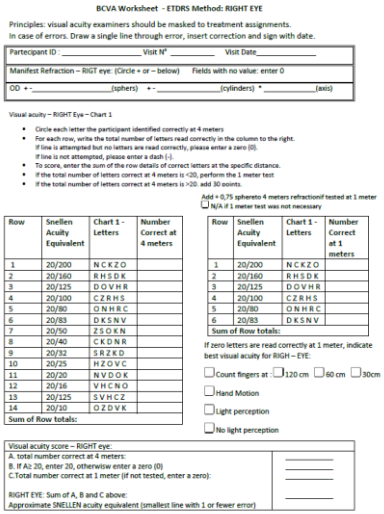
Certification:

EDTRS site certification e-mail (from Latis) listing certified BCVA examiners (either during site visit or grandfathering process by Latis) and examination lane (certified by Latis or trained CRA)

Documentation:

BCVA worksheet (left + right eye) – ETDRS

Example for right eye:



BCVA Worksheet - ETDRS Method: RIGHT EYE

Principles: visual acuity examiners should be masked to treatment assignments.
In case of errors. Draw a single line through error, insert correction and sign with date.

Partecipant ID : _____ Visit N° _____ Visit Date_____

Manifest Refraction – RIGT eye: (Circle + or – below) Fields with no value: enter 0

OD + - _____(sphers) + - _____(cylinders) * _____(axis)

Visual acuity – RIGHT Eye – Chart 1

- Circle each letter the participant identified correctly at 4 meters
- For each row, write the total number of letters read correctly in the column to the right.
  If line is attempted but no letters are read correctly, please enter a zero (0).
  If line is not attempted, please enter a dash (-).
- To score, enter the sum of the row details of correct letters at the specific distance.
- If the total number of letters correct at 4 meters is <20, perform the 1 meter test
- If the total number of letters correct at 4 meters is >20, add 30 points.

Add + 0,75 sphereto 4 meters refractionif tested at 1 meter
☐ N/A if 1 meter test was not necessary

Row	Snellen Acuity Equivalent	Chart 1 - Letters	Number Correct at 4 meters
1	20/200	N C K Z O	
2	20/160	R H S D K	
3	20/125	D O V H R	
4	20/100	C Z R H S	
5	20/80	O N H R C	
6	20/83	D K S N V	
7	20/50	Z S O K N	
8	20/40	C K D N R	
9	20/32	S R Z K D	
10	20/25	H Z O V C	
11	20/20	N V D O K	
12	20/16	V H C N O	
13	20/125	S V H C Z	
14	20/10	O Z D V K	
Sum of Row totals:			

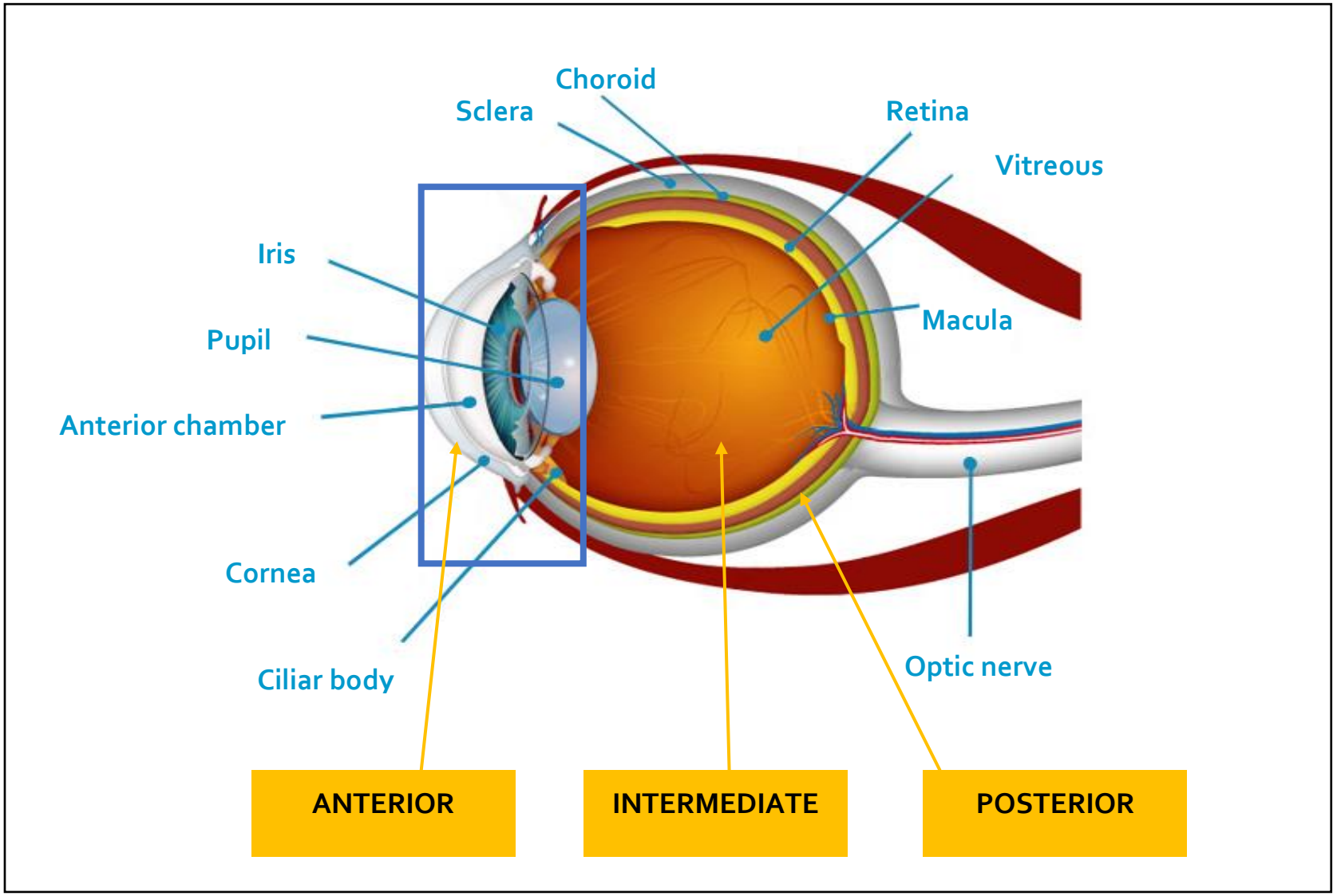
Row	Snellen Acuity Equivalent	Chart 1 - Letters	Number Correct at 1 meters
1	20/200	N C K Z O	
2	20/160	R H S D K	
3	20/125	D O V H R	
4	20/100	C Z R H S	
5	20/80	O N H R C	
6	20/83	D K S N V	
Sum of Row totals:			

If zero letters are read correctly at 1 meter, indicate best visual acuity for RIGH – EYE:

☐ Count fingers at : ☐ 120 cm ☐ 60 cm ☐ 30cm
☐ Hand Motion
☐ Light perception
☐ No light perception

Visual acuity score – RIGHT eye:
A. total number correct at 4 meters: _____
B. If A≥ 20, enter 20, otherwise enter a zero (0) _____
C.Total number correct at 1 meter (if not tested, enter a zero): _____
RIGHT EYE: Sum of A, B and C above: _____
Approximate SNELLEN acuity equivalent (smallest line with 1 or fewer error)

OPHTALMOLOGICAL EXAMS GUIDE



OPHTALMOLOGICAL EXAM GUIDE

2.2 Slit Lamp Biomicroscopy

Assessment of anterior cells and flares.

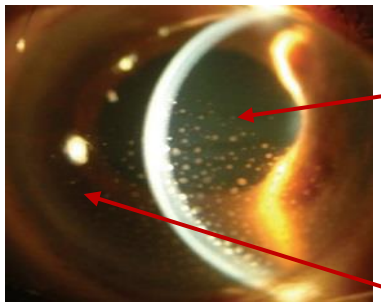
An individual subject **grading** should be performed **by the same investigator with the same slit lamp**

Description

Anterior chamber cells and flare will be assessed with slit-lamp Biomicroscopy and scored using the SUN working group grading scheme. For the determination of anterior chamber cell and flare, the field consists of 1x1 mm beam.

Grading should be performed in a darkened room with the brightest possible slit lamp illumination, a high slit lamp magnification and a beam angle of 45°.

Anterior chamber cells and flares

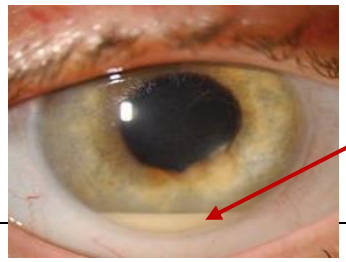


Inflammatory cells in the anterior chamber (Tyndall Phenomenon)

Flare: exudation of proteins in the anterior chamber, which limits the visibility of the iris.

Hypopyon

(identified by slit lamp or visual examination)



Collection of fibrin and dense cellular infiltrate in the lower part of the anterior chamber.

Certification: NA

Documentation:

The SUN grading worksheet

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

Flare gives evidence of only previous inflammation or breakdown of blood aqueous barrier.

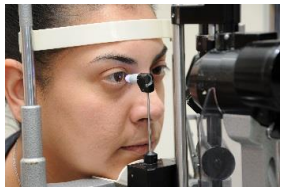
Flare	Description
0	Complete absence
1+	Faint flare (barely detectable)
2+	Moderate flare (iris and lens details clear)
3+	Marked flare (iris and lens details hazy)
4+	Intense flare (fixed coagulated aqueous humor with considerable fibrin)

*Standardization of uveitis nomenclature (SUN)

Documentation:

Medical file

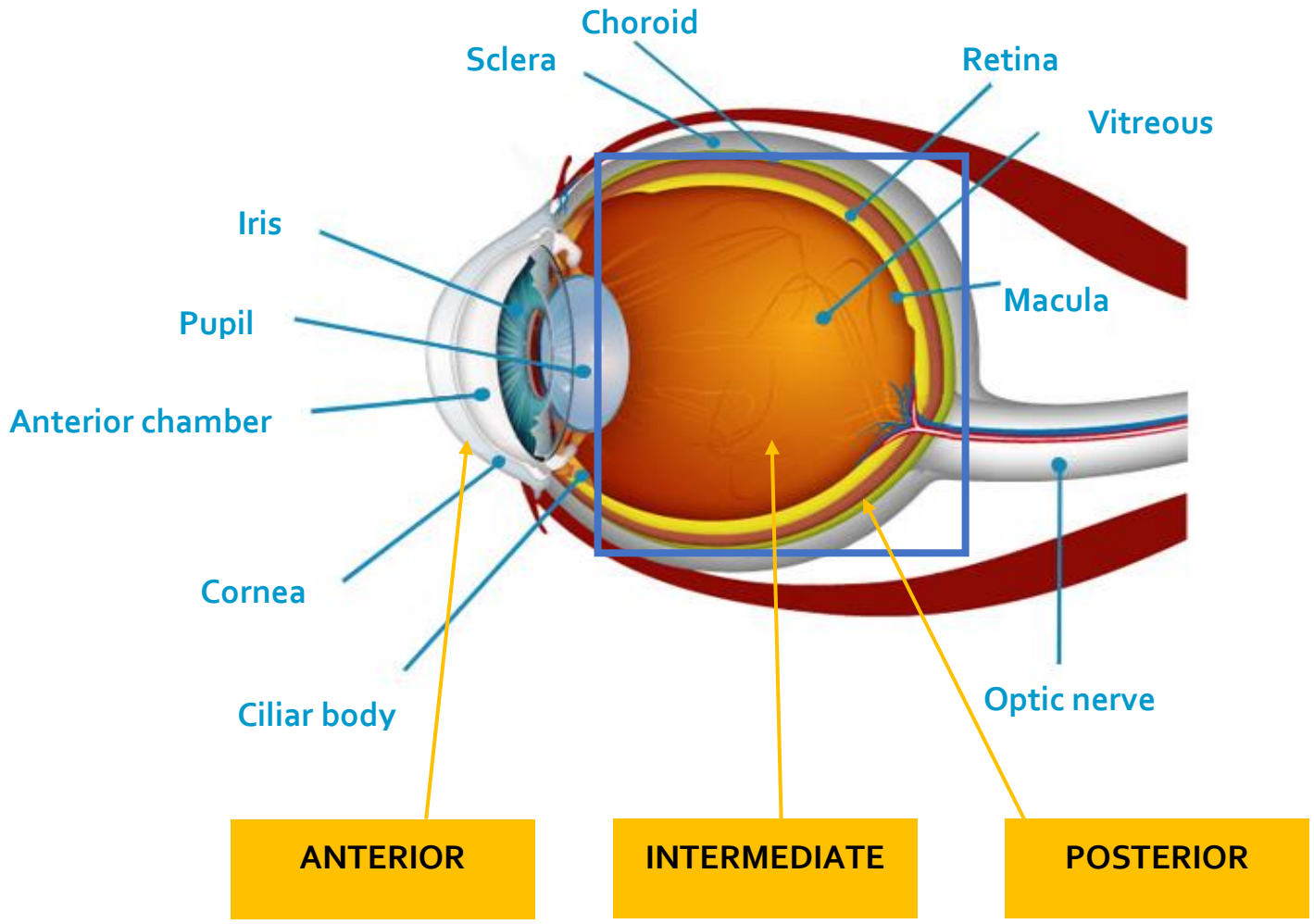
OPHTALMOLOGICAL EXAM GUIDE

2.3 Goldmann tonometry		
Intraocular pressure   	**Description** Goldman tonometry will be used to measure intraocular pressure. Intraocular pressure should be measured after the assessment of anterior chamber flare but prior to the installation of any dilating drops in addition to cycloplegics that a patient may already be taking.	**Certification: NA** **Documentation**: Medical file (expressed in mmHg)

OPHTALMOLOGICAL EXAM GUIDE

AFTER dilatation of pupil

Fundus and Posterior Pole Assessment

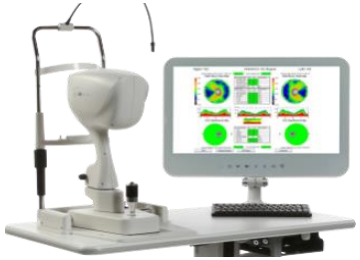


OPHTALMOLOGICAL EXAM GUIDE

2.4 Optical Coherence Tomography (OCT)

Central macular thickness

Topscan 3D SD -



Spectralis SD-OCT

Cirrus HD-OCT

Stratus OCT instrument

Optovue RTvue SD-OCT

Description

Measurement of the central macular thickness

OCT is an optical signal acquisition and processing method. It captures micrometer-resolution, three-dimensional images from within optical scattering media. It is an interferometric technique, typically employing near-infrared light, which allows it to penetrate into the scattering medium.

Certification:

Documentation:

OCT report to be kept as source document in Patient File.

OPHTALMOLOGICAL EXAM GUIDE

2.5 Laser Flare-cell Meter (LFM)		
Assessment of intraocular inflammation  **kowa Flare Meter Laser FML 500-700**	**Description** The laser flare-cell meter has made possible to determine the flare and number of cells in the aqueous humor quantitatively. LFM is a unique, precise, non-invasive, objective, quantitative tool to measure intraocular inflammation.	**Certification:** LFM kowa 700 **Documentation**: LFM report to be kept as source document in Patient File.