STATISTICAL ANALYSIS PLAN

Protocol Code: NORFLO-ORO-16
EudraCT number: NA

"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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APPROVAL

Protocol code: NORFLO-ORO-16

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

Document: Statistical Analysis Plan

Version No.: 1.0

Date: 20/07/2020

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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 **C4**	Complement component 3 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
VAS	Visual Analogue Scale
VZV	Varicella-zoster virus

1. VERSION HISTORY

1.1 Version history of the SAP

Version Number	Summary/Reason for changes	Date issued
1.0	First version	20/07/2020

1.2 Version history of the Protocol

Version Number	Date	Description
1.3	15/02/2017	First version
1.4	14/09/2017	Hormonal contraceptive use included as a prohibited treatment. Consequently, the exclusion criterion n. 6. (Women who are taking hormonal contraceptives) was added, as well as urine dipstick specific pregnancy test at each visit.
1.5	11/01/2019	More details about how the co-primary efficacy endpoints of the study should be analyzed were added.
1.6	10/10/2019	The definition of relapse of uveitis was added.

1.3 Version history of the CRF

Version Number	Date	Description
1.0	06/04/2018	First version
1.1	08/06/2018	Update BCVA score

2. INTRODUCTION

3. STUDY OBJECTIVES

3.1 Primary Objectives

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 be also assessed.

3.2 Secondary Objectives

The secondary objectives of this study included:

- 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 METHODS

4.1 Study Design

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

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

4.2 Treatment Administration

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

Each subject received a single dose of either placebo or NORFLO® ORO two times a day for 1 year. Subjects were assigned to the treatments in a random order. Evaluations were taken at baseline (t0) and during each of the following two visits within the study (t1 6 months, t2 12 months).

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

The following treatment regimens were applied:

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

4.3 Randomization and Blinding

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

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

- Access to the randomization code was strictly controlled.

Packaging and labeling of test and control treatments were 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.

5. STUDY ENDPOINTS

5.1 Primary Endpoints

The primary efficacy endpoint is 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 was 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 were measured by the Laser Flare Meter, in patients affected by HLA-B27-associated uveitis after treatment with NORFLO® ORO, when compared to placebo.

The number and intensity of relapses and LFM data, used in primary efficacy endpoints, were reported in the first unscheduled visit.

Only patients with relapses will be analyzed in primary efficacy endpoints.

5.2 Secondary 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; photographs 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, was captured by means of a questionnaire (Quick Questionnaire) specifically developed for the study on the basis of previous experiences.

These data were reported at visit 1 (baseline), at visit 2 (after 6 months) and at visit 3 (after 12 months). In case of relapse near visit 3, the data collected during the visit 3 will be replaced with the data collected during the first unscheduled visit.

5.3 Safety Endpoints

The safety endpoints 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. PLANNED ANALYSIS

6.1 Interim Analysis

No interim analysis was planned.

6.2 Final Analysis

Final analysis will be performed according to the protocol and to this Statistical Analysis Plan, after data cleaning operations and DB Lock is performed.

7. SAMPLE SIZE AND STATISTICAL POWER CONSIDERATION

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 were 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. No formal sample size estimate was 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 was needed.

8. ANALYSIS POPULATIONS

8.1 Intent-to-Treat Population (ITT)

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 will be included in the efficacy analysis. Primary endpoints will be also analyzed in a modified Intention-to-Treat Population, where the patients with the protocol violations mentioned in the session 10.2 (Protocol Deviations) will be excluded.

8.2 Per-Protocol (PP) Population

No per-protocol analysis was planned.

8.3 Safety Population

All eligible patients who are randomized into the study and receive at least one dose of the study product will be included in the safety analysis.

9. GENERAL ISSUES FOR STATISTICAL ANALYSIS

9.1 Definitions, Derived Variables and Datasets

Definitions of indicators and methods to derive variables are described in the relevant sections of this document. Datasets will be derived from the database used to record the information gathered through the e-CRF.

9.1.1 Baseline Values

The values assessed at Visit 1, before the first product administration, will be considered as baseline values.

9.1.2 Duration of Exposure

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

9.1.3 Treatment Compliance

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

9.1.4 Methods for Withdrawals and Missing Data

A subject could be discontinued from the study treatment at any time if either the subject, and/or the investigator, and/or Eye Pharma feel 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.

All subjects who discontinued the study treatment should come back 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 were free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

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

No missing data will be replaced.

9.2 Multicenter Studies Considerations

Analysis will be adjusted for the clinical site. Analyses specific for each clinical site will be considered, based on the number of subjects enrolled in each clinical site.

9.3 Multiple Comparisons and Multiplicity

No adjustment for multiple comparisons will be done. Even if multiple primary endpoints will be analyzed, no adjustment for multiplicity will be done, as 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".

9.4 Data Safety Monitoring Board (DSMB)

Not applicable.

10. STUDY SUBJECTS

10.1 Disposition of Subjects

The disposition of subjects at each visit was assessed through information reported in the CRF. The number and percentage of dropouts at each visit will be reported, together with the reason for dropout.

10.2 Protocol Deviations

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 is also a protocol violation.

Protocol deviations are minor deviations from the protocol (e.g., missing a visit window because the subject is traveling). Protocol deviations and violations will be summarized, separately for each treatment group and each study phase.

11. EFFICACY ANALYSIS

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. Parametric tests will be used as the first-choice test. When the dependent variables are not normally distributed, also the non-parametric alternative will be used.

11.1 Analysis datasets

All eligible patients who were randomized into the study and received at least one dose of the study product (the Safety Population) will be included in the safety analysis. All eligible patients who were randomized into the study, received at least one dose of the study product and had at least a post-randomization endpoint estimate (the Intention-to-Treat Population) will be included in the efficacy analysis. Primary endpoints will be also analyzed in a modified Intention-to-Treat Population, where the patients with the protocol violations mentioned in the session 10.2 (Protocol Deviations) will be excluded.

11.2 Demographics and Baseline Characteristics

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

11.3 Measurements of Treatment Compliance

Compliance to the study treatment was assessed through the patient diary and checked versus the used and unused study product containers given back by the patients.

Treatment compliance will be estimated as the ratio between the number of the administered doses and the number of planned doses.

11.4 Efficacy Analysis

11.4.1 Primary Efficacy Endpoints

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

When a relapse occurs, the data reported in the first unscheduled visit concerning the intensity of the relapse and data from LFM will be used as they are taken before the administration of both systemic and topical cortisone.

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 each relapse will be scored as mild (either trace to 1+ cell OR flare ≤ 20), moderate (2+ to 3+ cell OR Flare > 20 and < 100) and severe (4+ cell OR Hypopyon OR flare ≥ 100). For each patient, the average intensity will be estimated as the mean of the intensity of relapses observed during the study. 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. As this variable could likely be not normally distributed, Wilcoxon Mann-Whitney will be also used.

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. The patients will be classified based on the number of relapses before treatment, using the median number per subjects as a cut-off to separate subjects with a high number of relapses form those with a low number of relapses. The subjects will be classified on the number of relapses after treatment using the same cut-off. The patients that before and after treatment will change from the high number of relapses category to the low number category, will be considered as responders, while the others will be considered as non-responders. The proportion of responders will be compared between treatment groups using chi-square test.

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.

11.4.2 Secondary Efficacy Endpoints

The incidence of side effects associated HLA-B27-associated uveitis will be compared between treatment groups. The changes in IOP, in central 1 mm subfield thickness, and the changes in OCT 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 chi-square test.

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.

11.5 Summary of Efficacy Analyses

Endpoint	Analysis	Populations
The mean number and intensity of relapses (primary endpoint)	Student's t-test, ANOVA, generalized linear mixed model	*ITT*
The reduction of mean number of relapses (primary endpoint)	Student's t-test, ANOVA	*ITT*
The difference of the level of cell damage and inflammation (primary endpoint)	ANCOVA	*ITT*
The changes in IOP (secondary endpoint)	ANCOVA	*ITT*
The changes in OCT (secondary endpoint)	ANCOVA	*ITT*
The changes in BCVA (secondary endpoint)	ANCOVA	*ITT*
The presence of keratopathy (secondary endpoint)	Chi-square test	*ITT*
The presence of synechiae (secondary endpoint)	Chi-square test	*ITT*
Information collected through the Quick questionnaire (secondary endpoint)	Chi-square test	*ITT*

12. SAFETY EVALUATION

Safety and tolerability data will be summarized by treatment group.

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

12.1 Extent of Exposure

The extent of exposure will be estimated on the treatment duration.

12.2 Adverse Events

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 be included 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.

12.3 Other safety endpoints

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.

13. DEVIATIONS FROM THE PROTOCOL SPECIFIED ANALYSIS

The analysis of the number of relapses per eye will not be performed.

Nonparametric test will be used when the variables are not normally distributed.

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16. APPENDICES

16.1 Study information

Appendices will be attached to the clinical study report.

16.2 List of Subject Data Listings

Appendices will be attached to the clinical study report.