CLINICAL STUDY PROTOCOL	IRCCS FONDAZIONE G.B. BIETTI

STUDY NAME	**Retinal morpho-functional evaluation of patients affected by inherited retinal dystrophies**

Title	**Retinal morpho-functional evaluation of patients affected by inherited retinal dystrophies**
Acronym/ Study Code	NEU 02-25
Protocol version	V. 1.0
Protocol date	09/09/2025
Type of study	Retrospective observational study
Document status	Final
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- SIGNATURE PAGE

CLINICAL STUDY PROTOCOL	IRCCS FONDAZIONE G.B. BIETTI

STUDY NAME	**Retinal morpho-functional evaluation of patients affected by inherited retinal dystrophies**

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Signature	Date
L. Ziccardi	03/09/2025

PROTOCOL SYNOPSIS

TITLE	**Retinal morpho-functional evaluation of patients affected by inherited retinal dystrophies**
ACRONYM/ STUDY CODE	
STUDY PHASE	Retrospective observational study
STUDY PERIOD	Patients affected by inherited retinal dystrophies (IRD) observed since 2015 up to August 31, 2025
AIM OF THE STUDY	Functional and morphological assessment of inner and outer retinal layers' features of IRD patients
STUDY OBJECTIVES	PRIMARY OBJECTIVE • Evaluation of the retinal morpho-functional features in IRD SECONDARY OBJECTIVES • To study visual acuity of IRD patients • To study the outer retinal function from localized macular areas in IRD eyes through multifocal ERG (mfERG) • To study the inner retinal function from localized macular areas in IRD eyes through multifocal PhNR (mfPhNR) recordings • To study the visual field (VF) of patients affected by IRD • To study the retinal structure of the inner and outer retinal layers in localized macular areas according to ETDRS map of Spectral Domain Optical Coherence Tomography (SD-OCT) • To study the retinal perfusion features of the retinal superficial and deep capillary plexus and the choriocapillaris through OCT-Angiography (OCT-A) in localized macular areas • To study the complications of the dystrophic disease in sub-cohorts of IRD patients
STUDY DESIGN	Retrospective observational single-center study involving patients with IRD
SUBJECT SELECTION CRITERIA	INCLUSION CRITERIA • Patients with inherited retinal dystrophy clinically confirmed • Age between 18 and 90 years • Available recordings of mfERG and mfPhNR, SD-OCT and OCT-A, Visual Acuity and Visual Field • Phakic and pseudophakic eyes

	• Informed consent freely granted and acquired before data collection EXCLUSION CRITERIA • Patients underwent cataract surgery 6 months before data acquisition • Patients with any other ophthalmological diseases affecting cornea, lens, optic nerve and acquired retinal diseases (i.e. central serous chorioretinopathy, retinal vein occlusion, age-related macular degeneration) at the time of data acquisition • Patients with diabetes and\or any other systemic condition affecting the macular function and structure • Patients who underwent to macular laser procedures before data acquisition • Concomitant treatment with any systemic or ocular drug influencing macular structure and function at the time of data acquisition
NUMBER OF SUBJECTS	18
PRIMARY ENDPOINTS	• Central Retinal Thickness (CRT) measured by SD-OCT and R1 response amplitude density (RAD) by mfERG.
SECONDARY ENDPOINTS	• Mean best corrected Visual Acuity, expressed in LogMar • Outer macular function, in terms of response amplitude density, measured in nV/dg^2 and analyzed using the mfERG, assessing the amplitude density in 5 concentric rings (R) centered on the fovea (R1-R5) • Inner macular function, in terms of response amplitude density, measured in nV/dg^2 and analyzed using the mfPhNR, assessing the amplitude density in 5 concentric rings centered on the fovea (R1-R5) • Mean Perimetric Sensitivity at visual field testing • Structural analysis of the inner and outer retinal layers using SD-OCT for localized retinal areas • Analysis of superficial capillary plexus (SCP), deep capillary plexus (DCP) and choriocapillaris (CC) using OCT-angiography in localized retinal regions • IRD-related ocular complications

STATISTICS	SAMPLE SIZE ESTIMATE • R1 mfERG and OCT CRT will be considered to assess the number of participants for each group. α and β values are set to 0.05 and 0.20 (power = 80%) respectively. R1 mfERG controls (N=41) (Ziccardi L. et al. Functional Assessment of Outer and Middle Macular Layers in Multiple Sclerosis. J Clin Med. 2020;9:3766) showed mean = 56.14 nV/dg^2, std = 10.77 nV/dg^2 and patients' preliminary data (N=10) mean = 26.08 nV/dg^2, std = 12.04 nV/dg^2 giving us 3 participants for each group. OCT CRT controls (N=15) (Grover S. et al. Normative data for macular thickness by high-definition spectral-domain optical coherence tomography (spectralis). Am J Ophthalmol. 2009; 148:266-71.) showed mean = 227.3 µm std = 23.2 µm and patients' (N=14) preliminary data mean = 202.5 µm, std = 73.83 µm giving us 18 participants for each group. Therefore the number of participants is 18 for each group STATISTICAL ANALYSIS • Normality distributions will be verified using Anderson-Darling test for each parameter. Morphological and functional parameters' descriptive statistics will be evaluated showing: mean values, standard deviations, medians and interquartile range (IQR) (25% - 75%) for each group. Each parameter groups' will be compared using unpaired 2-sample t-test. Relationship between morphological and functional parameters (CRT and R1 mfERG) will be assessed using Pearson for patients' group. • SPSS software (version 25) and Python statistics libraries will be used for the statistical analysis of the data.
CHRONOGRAM OF VISITS AND EVALUATIONS	After signing the informed consent, data from a single visit during which patients underwent the following examinations will be collected: medical history, inclusion/exclusion criteria evaluation, enrolment, collection of demographics, ophthalmological and instrumental data (BCVA, VF examination, mfERG,

	mfPhNR, SD-OCT and OCT-A), assessment of IRD-related complications, whether present.
ETHICS COMMITTEE	Comitato Etico Territoriale Lazio Area 5

LIST OF ABBREVIATIONS

Abbreviation	Description
BCVA	Best Correct Visual Acuity
CRT	Central Retinal Thickness
CA	Competent Authority
CC	Choriocapillaris
CVI	Choroidal vascular index
DCP	Deep capillary plexus
EC	Ethics Committee
ETDRS	Early Treatment for Diabetic Retinopathy Study
ICF	Informed Consent Form
IOP	Intraocular Pressure
IQR	Interquartile range
IRD	Inherited Retinal Dystrophy
mfERG	Multifocal Electroretinogram
mfPhNR	Multifocal Photopic Negative Response
NA	Not Applicable
SD-OCT	Spectral Domain-Optical Coherence Tomography
OCT-A	Optical Coherence Tomography-Angiography
PI	Principal Investigator
R	Ring
RA	Regulatory Authorities
RAD	Response Amplitude Density
RP	Retinitis pigmentosa
SCP	Superficial capillary plexus
SD	Standard deviation
VF	Visual Field

INDEX

1. FLOWCHART 9
2. BACKGROUND 10
3. RATIONALE 11
4. TRIAL OBJECTIVES AND PURPOSE OBJECTIVES 12
   4.1 Primary objective 12
   4.2 Secondary objectives 12
5. ENDPOINTS 13
   5.1 Primary endpoint 13
   5.2 Secondary endpoint 13
6. SELECTIONS CRITERIA 13
   6.1 Inclusion criteria 13
   6.2 Exclusion criteria 13
7. STUDY DESIGN 14
   7.1 Specific study procedures 15
8. STATISTICS 16
   8.1 Sample size determination 16
   8.2 Statistical Methods 17
9. ETHICAL, LEGAL AND FINANCIAL ASPECTS 17
   9.1 AC / EC approval 17
   9.2 Informed consent 18
   9.3 Enrollment procedures 18
   9.4 Processing of personal data 18
   9.5 Financing 19
   9.6 Insurance 19
10. DATA HANDLING AND RECORD KEEPING 20
   10.1 Data collection and management 20
   10.2 Data retention 21
11. CONTROL AND ASSURANCE QUALITY 21
   11.1 Audits 21
   11.2 Inspections 21
12. PUBLICATION POLICY 21
13. BIBLIOGRAPHY 23

1. FLOWCHART

Visit	**V1**
Demographic data	✔
Medical History	✔
Concomitant disease	✔
Concomitant and previous therapies	✔
Inclusion/exclusion criteria	✔
Collection of data of comprehensive ophthalmological examination: BCVA, anterior and posterior biomicroscopy, intraocular pressure measurement, fundus oculi	✔
Collection of SD-OCT	✔
Collection of OCT-angiography	✔
Collection of mfERG	✔
Collection of mfPhNR	✔
Collection of Visual field	✔

2. BACKGROUND

Degenerative diseases of the visual system classified as rare, and particularly those affecting the retina (known as Inherited Retinal Dystrophies, IRD) cause highly severe functional deficits. Their manifestation is in many cases early-onset, with consequent visual impact of extreme severity. They constitute a heterogeneous group from a clinical point of view, and in all of them, the progressive loss of photoreceptors can be variable although causing vision impairment up to complete blindness [1-2]. These degenerative entities can be complicated by the presence of cataract, epiretinal membrane and macular oedema (10-50%) and choroidal/retinal neovascularization [3], resulting in a sudden worsening of central visual acuity [4].

Genetic diseases may target the rod system or the cone system independently; psychophysical and electrophysiologic testing can help determine the relative involvement of these two systems. Specialized retinal function and electrophysiologic testing are becoming more important as we gain a better understanding of the roles of various genes in maintaining structure and the function of the retina. The different components of the ERG allow the separate evaluation of rod and cone functions depending on the dark or light adaptations of the retina, therefore permitting the assessment of the integrity of each system. For example, in cone dystrophy the flicker or photopic ERG in significantly reduced while the dark-adapted ERG may be near-normal. In retinal degeneration involving both systems, scotopic, photopic and flicker ERGs are concomitantly abnormal [5]. On the other hand, the mfERG provides a map of retinal function across the stimulated area, which can be examined into localized retinal regions. Indeed, the mfERG can play an important role in assessing the outer retinal dysfunction from localized retinal areas from 0 up to 25 degrees of eccentricity from the fovea [6]. To examine the same settings but from the innermost retinal layers, the mfPhNR can be a useful tool to localize ganglion cells and fibers abnormalities using two different topographies (Ring or Sectors analyses) [7]. As the responses from mfERG and mfPhNR reflect the function of outer and inner retinal layers, respectively, from small, localized retinal areas, these methods have been of interest in the study of inherited retinal dystrophies correlating functional data with morphological data obtained by OCT and OCT-A. In fact, both functional (mfERG and mfPhNR) and morphological (OCT and OCT-A) methods can examine corresponding and almost overlapping areas to better investigate on whether a

retinal dystrophy can affect the function or the structure of outer and inner layers. In recent years, structural OCT and OCT-angiography have provided further information useful in better understanding IRD pathogenesis. Indeed, these techniques are able to investigate retinal microstructural features non-invasively, providing histologically comparable information on the involvement of each retinal layers and integrity of the retinal vascular network. For example, regarding retinitis pigmentosa (RP), previous OCT-A studies have shown macular vascular density alterations both in the superficial capillary plexus (SCP) and in the deep capillary plexus (DCP). These findings proved a novel choroidal involvement in the progression of degenerative phenomena, previously attributable exclusively to loss of outer retinal cellular elements [8, 9,10].

3. RATIONALE

Recent advances in spectral-domain optical coherence tomography (SD-OCT) have facilitated high-resolution, non-invasive visualization of retinal microarchitecture in IRD [11, 12]. Concomitant electrophysiological and psychophysical assessments have also described the IRD-related functional impairment in the context of the chronic structural degenerative process, with some degree of reversibility following appropriate therapeutic interventions in cases of retinal complications (macular oedema, macular neovascularization). In this view, mfERG records from localized outer retina dysfunction can be a useful tool to identify vulnerable areas in retinal degeneration [13, 14]. Additionally mfPhNR, an innovative electrophysiological tool, is available to study the inner retinal function from localized macular areas [7, 15]. Through these methods, it is possible to assess the role of the outer and inner retinal layers in the context of degenerative diseases that primarily affect the photoreceptors. The correlation between the anatomical data and measurable functional outcomes remains an area of ongoing research, and no consensus has been reached regarding prognostic implications based on the involving either outer and inner retinal layers.

In addition to changes occurring into different retinal layers, several recent investigations have also reported that structural alterations in the choroid—particularly increased choroidal thickness (CT) and reduced choroidal vascular index (CVI)—may reflect compromised outer retinal support and impaired choroidal perfusion [8, 9,10]. These choroidal changes have been associated with worse visual function in IRD (specifically RP) and may also contribute to the pathogenesis of macular complications,

suggesting that both retinal and subretinal factors are implicated in disease expression, progression and complications [9,10]. Hence, the importance of studying choroidal and retinal vascularization and correlating this data with the function of the retinal layers in all IRD.

4. TRIAL OBJECTIVES AND PURPOSE OBJECTIVES

The present study aims to perform a detailed morpho-anatomical and electro-functional characterization of patients affected by IRD, to investigate on the features of specific retinal layers (outer and inner) and to identify the functional involvement of macular elements located in specific areas. Through a systematic approach to anatomical and functional pattern classifications, this study seeks to refine the phenotypic understanding of IRD and to contribute to a deeper comprehension of its pathophysiological underpinnings, for exploring whether subretinal factors are involving in the etiopathogenesis.

4.1 Primary objective

- Evaluation of the retinal morphological and functional features of IRD

4.2 Secondary objectives

- To study visual acuity in patients affected by IRD
- To study the outer retina function from localized macular areas in IRD eyes through multifocal ERG (mfERG)
- To study the inner retina function from localized macular areas in IRD eyes through multifocal PhNR (mfPhNR) recordings
- To study the visual field (VF) of patients affected by IRD
- To study the retinal structure of the inner and outer retinal layers in localized macular areas according to ETDRS map of SD-OCT.
- To study the retinal perfusion features of the retinal superficial and deep capillary plexus and the choriocapillaris through OCT-Angiography (OCT-A) in localized macular areas
- To study the complications of the dystrophic disease in sub-cohorts of IRD patients

5. ENDPOINTS

5.1 Primary endpoint

- Central Retinal Thickness measured by SD-OCT and R1 response amplitude density (RAD) by mfERG

5.2 Secondary endpoint

- Mean best corrected visual acuity, expressed in LogMar,
- Outer macular function, in terms of response amplitude density, measured in nV/dg^2 and analysed using the mfERG, assessing the amplitude density in localized areas within 25 degrees of eccentricity (R1-R5)
- Inner macular function, in terms of response amplitude density, measured in nV/dg^2 and analysed using the mfPhNR, assessing the amplitude density in localized areas within 25 degrees of eccentricity (R1-R5)
- Mean Perimetric Sensitivity at visual field testing
- Structural analysis of the inner and outer retinal layers using SD-OCT for localized retinal areas
- Analysis of superficial capillary plexus (SCP), deep capillary plexus (DCP) and choriocapillaris (CC) using OCT-angiography in localized retinal regions
- IRD-related ocular complications

6. SELECTIONS CRITERIA

6.1 Inclusion criteria

- Patients with clinically confirmed inherited retinal dystrophy
- Age between 18 and 90 years
- Available recordings of mfERG and mfPhNR, SD-OCT and OCT-A, Visual Acuity (BCVA) and Visual Field (VF)
- Phakic and pseudophakic eyes
- Informed consent freely granted and acquired before data collection

6.2 Exclusion criteria

- Patients underwent cataract surgery 6 months before data acquisition

- Patients with any other ophthalmological diseases affecting cornea, lens, optic nerve and acquired retinal diseases (i.e. central serous chorioretinopathy, retinal vein occlusion, age-related macular degeneration) at the time of data acquisition
- Patients with diabetes and\or any other systemic condition affecting the macular function and structure
- Patients who underwent to macular laser procedures before data acquisition
- Concomitant treatment with any systemic or ocular drug influencing macular structure and function at the time of data acquisition

7. STUDY DESIGN

Retrospective observational, single-center study involving consecutive enrolment (see sample size in section "Statistics") of patients with inherited retinal dystrophies clinically confirmed.

Each patient referred to the Outpatient Clinical and Research Center of Neuro-ophthalmology and Genetic and Rare Diseases with IRD and will be duly informed about the outcomes of this study. After verification of the criteria for inclusion and exclusion in the study and after being informed and signing of the consent form, the physicians of the Clinical and Research Center of Neuro-ophthalmology and Genetic and Rare Diseases and Medical Retina will collect recruitable patient data.

For all patients we will collect:

- Medical History
- Ophthalmological examination comprehensive of BCVA, anterior and posterior biomicroscopy, intraocular pressure measurement
- SD-OCT central retina thickness (CRT) and of localized macular areas
- OCT-angiography vessel density of superficial and deep plexus and choriocapillaris
- mfERG Response amplitude density (RAD) derived to macular localized areas into 25 degrees centered to the fovea.
- mfPhNR Response amplitude density (RAD) derived to macular localized areas into 25 degrees centered to the fovea.
- Mean sensitivity of visual field

7.1 Specific study procedures

Collection of patient data relative to:

1. Overall examination of the eye, including measurement of BCVA expressed in LogMar, applanation tonometry (Goldman), anterior segment biomicroscopy, fundus oculi (in mydriasis).
2. Multifocal electroretinogram (VERIS Clinic TM 4.9 Electro-Diagnostic Imaging, San Mateo, CA USA, CSO RETIMAX Advanced Plus, CSO, Firenze, Italy and Diagnosys UK, Ltd.; Histon, Cambridge, Regno Unito), for detailed ring analyses of the response of the various outer retina components of the macula in particular the photoreceptors (cones and rods) and bipolar cells.
3. Multifocal photopic Negative Response (Diagnosys UK, Ltd.; Histon, Cambridge, Regno Unito) for detailed ring analyses of the response of the various inner retina components of the macula particularly the retinal ganglion cells.
4. Visual Field test (perimetric measurements of Goldmann Visual Field - Goldmann perimeter Haag-Streit 940, Kőniz, Switzerland - or Humphrey Visual Field - Humphrey Field Analyzer (HFA) 740; Zeiss, San Leandro, CA, USA) of central and peripheral areas of vision and of physiological blind spots. The test involves fixing the gaze on a central point while the patient press a button each time sees a flash of light in the central and peripheral vision. It is a painless test, often used to diagnose or monitor the peripheral visual field restriction or central scotoma typical of IRD.
5. Optical coherence tomography (Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany, Topcon DRI Triton), which is a non-invasive technique based on a low coherence interferometry system that allows high-resolution images of the retina and retinal pigment epithelium complex. The analysis of the mathematical reflectivity algorithms allows a quantitative assessment of the central retinal thickness and of the thickness of segmented different layers of the retina.
6. OCT angiography (Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany), a non-invasive examination that allows the study of retinal microvascular

features, particularly of the superficial and deep plexus and choriocapillaris in the absence of contrast medium.

7. Biomicroscopic evaluation of the anterior segment, evaluation of the fundus oculi and instrumental examinations allow for the identification of possible complications in a sub-cohort of IRD patients.

8. STATISTICS

8.1 Sample size determination

The exact incidence of retinal dystrophies is unknown, but the most common form, retinitis pigmentosa, affects about 1 in 5000 individuals worldwide, while other dystrophies such as achromatopsia are rarer, with an incidence of 1:30000.

Recent literature on single-center studies focusing on IRDs and their subtypes — including Retinitis Pigmentosa (RP), Usher Syndrome, and Occult Macular Dystrophy — indicates that sample size is closely linked to the incidence of these conditions within the Italian population [13, 16–18]. In particular, population-based studies typically include no more than 50 patients even for the most common IRDs (e.g., RP), while reports on ultra-rare IRDs often consist of only a few cases [18, 19]. Based on this evidence and the known incidence of IRDs, a sample size of approximately 18 patients—based on assessments conducted since 2015—is considered appropriate for the statistical analyses proposed in this study.

For sample size estimate to assess the number of participants for each group, the variables, taken into consideration based on the outcomes, are:

R1 mfERG and OCT CRT. In details, α and β values are set to 0.05 and 0.20 (power = 80%) respectively.

For Control and Patient Groups:

-since R1 mfERG observed in a similar population of Controls (N=41), where we applied the same procedures but in a different population [20], showed mean = 56.14 nV/dg2, std = 10.77 nV/dg2 and patients' preliminary data from our database on IRDs (N=10) mean = 26.08 nV/dg2, std = 12.04 nV/dg2 , for R1 mfERG the calculation gives us 3 participants for each group

-since OCT CRT observed in Controls (N=15) from a similar population of subjects where the same procedure was applied [21] showed mean = 227.3 μm std = 23.2 μm and patients' preliminary data (N=14) from our database on IRDs mean = 202.5 μm, std = 73.83 μm, for OCT CRT the calculation gives us 18 participants for each group.

Therefore the number of participants expected is 18 for each group.

8.2 Statistical Methods

SPSS software (version 25) and Python statistics libraries will be used for the statistical analysis of the data.

First of all, the normality of the distribution of the variables under study will be checked by means of the Anderson-Darling and Kolmogorov-Smirnov (Shapiro-wilk) tests. Morphological and functional parameters' descriptive statistics will be used. Gaussian variables will be summarized by means of mean, standard deviation and range; for variables that do not conform to the Gaussian distribution, the median and interquartile range (25% - 75%) will be used. Categorical variables will be summarized by counts and percentages.

Each parameter groups' will be compared using unpaired 2-sample t-test.

The comparison of the medians of the non-normal continuous variables will be carried out by means of the Mann-Whitney test in the case of two independent samples.

Relationship between morphological and functional parameters (CRT and R1 mfERG) will be assessed using Pearson for patients' group.

9. ETHICAL, LEGAL AND FINANCIAL ASPECTS

9.1 AC / EC approval

A copy of the patient's informed consent must be submitted to the CA and EC together with the protocol for written approval. Written approval of the protocol and informed consent must be obtained before starting the recruitment of patients in the study.

The approval of the Competent Authority (AC) / and the favorable opinion of the local Ethics Committee (EC) must be obtained before the start of the experimentation.

The researcher must inform the CA and the CE of any amendments to the protocol, which must be approved by both.

9.2 Informed consent

The subject is considered included in the study when he voluntarily provides written informed consent. No collection of clinical data will be initiated before the Informed Consent has been signed. Before acquiring informed consent, the investigator explains to the subject what the study consists of, what are the objectives it aims to achieve. The explanation must take place in a manner and in a language understandable to the subject and dedicating the time necessary for the subject to fully understand the study and to ask any questions. Once this interview phase is over, the investigator delivers the informed Consent form to the subject who can decide to sign at that moment or to take home, calmly evaluate and deliver later.

9.3 Enrollment procedures

- Identification of IRD patients in a consecutive manner
- Signing of informed consent and enrolment
- Verification of inclusion/exclusion criteria
- One-time data collection of ophthalmological examination comprehensive of BCVA, anterior and posterior biomicroscopy and intraocular pressure measurement.
- SD-OCT thickness
- OCT-angiography superficial, deep and choriocapillary plexus vessel density
- mfERG RAD
- mfPhNR RAD
- Mean sensitivity of visual field

9.4 Processing of personal data

The personal data object of the study must be processed in compliance with the Regulation EU 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (GDPR), the Legislative

Decree 196/2003 and subsequent amendments and additions, and any other Italian law applicable to the protection of personal data (henceforth referred to as the "applicable data protection law").
About personal data made available to the Promoter in pseudo anonymized form, the Institute and Promoter (GBB) is considered controller independent of the personal data and will act in compliance with the applicable data protection law.
In addition, the Institute and the Promoter will cooperate to take the necessary measures to comply with the applicable data protection law and will also have to implement appropriate technical and organizational measures to guarantee the compliance with the requirements established under the applicable data protection law.
The Institute is responsible for providing its Principal Investigators and Research Staff with all the necessary information relating to the methods by which the Promoter will eventually collect and manage their personal data before such information is provided.
The Promoter ensures the correctness of the processing of personal data as required by the GDPR.
If one of the parties involved becomes aware of a data breach regarding the personal data processed, the other must be notified of this event, and in any case no later than 24 hours from the knowledge of the event. In this case, the Institute and the Promotor must fully cooperate with each other to remedy the data breach, fulfilling the mandatory notification within the set times and managing any damage caused.
The data breach of personal data is defined by art. 33 and 34 of the GDPR.
The roles and responsibilities related to the project will be explained in a further and separate act between the Promoter and the Institute.

9.5 Financing

No financial support.

9.6 Insurance

Due to the nature of the study: retrospective observational study, the insurance provided by IRCCS Fondazione Bietti, Rome, Italy is sufficient for the study period.

10. DATA HANDLING AND RECORD KEEPING

10.1 Data collection and management

The study will be conducted in compliance with the dictates of the Helsinki declaration and in accordance with the rules of good clinical practice (Ministerial Decree of 15/07/1997 and subsequent amendments) as well as with the applicable regulatory provisions.

The participating center will maintain the medical records and research data of this study in an appropriate manner, in accordance with section 4.9 of the ICH-GCP E6, with the provisions of the regulatory bodies and the institution to which it belongs to ensure the protection of the confidentiality of the patients. As a participant in a clinical study, the center will allow staff authorized by the sponsor and regulatory agencies to review (and when permitted by law, to copy) medical records to check the quality of the data, for audits and for evaluations of the study safety and progress.

Source documents are all the information, original records of clinical findings, observations, or other activities of a clinical study necessary for the reconstruction and evaluation of the study itself. Examples of these original documents and records include, but are not limited to, medical records, clinical charts, laboratory notebooks, memos, patient diaries or evaluation lists, drug dispensing records, data recorded by automated tools, copies or transcripts certified after verification that these are accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, plates obtained with x-rays, subject cards and records kept in pharmacies, laboratories, and in the technical-medical departments involved in the clinical study.

Data collection is the responsibility of the staff at the center involved in the clinical study under the supervision of the center's Principal Investigator.

The researcher / institution should maintain the study documents as specified in Essential documents for conducting a clinical study (ICH-GCP E6, section 8) and as required by regulatory bodies and / or guidelines. The researcher / institution should take measures to prevent accidental or premature destruction of the documentation.

Essential documents (written and electronic) should be kept for a period not less than seven (7) years from the completion of the study, unless the Promoter provides a written document that

allows for the disposal and / or conservation of data for an additional period of time if permitted by law, regulatory bodies and / or guidelines.

10.2 Data retention

The IRCCS Fondazione G.B. Bietti is responsible for keeping the patient record of each patient even after the study has been interrupted or terminated up to the maximum time stipulated by law. Patients' clinical records and documents containing the original data will be retained in accordance with the relevant regulations.

11. CONTROL AND ASSURANCE QUALITY

The clinical monitoring activities of the study will be entrusted to the Centre for Neuro-ophthalmology, Genetic and Rare Diseases, Fondazione Bietti-IRCCS. The monitoring activities will be conducted in accordance with the European Union Guidelines for Good Clinical Practice implemented by Ministerial Decree of 15 July 1997.

11.1 Audits

The investigator/institution must allow audits as an integral part of the quality assurance system. The audit is a check, independent and separate from monitoring, of the activities and documents of the trial to verify whether the activities relevant to the trial have been conducted and the data have been recorded, analysed and submitted in accordance with the protocol, GCP, SOPs and applicable regulatory requirements.

11.2 Inspections

The investigator/institution must allow national and foreign Regulatory Authorities to carry out Inspections.

Inspection, by one or more Regulatory Authorities, consists of the official review of documents, facilities, records and any other resources considered by those authorities to be related to the clinical trial.

12. PUBLICATION POLICY

At the end of the research, within 6 months after the end of the study, a Final Clinical Report of the study containing clinical comments based on the data generated by the statistical processing will be prepared by the Investigator and/or delegated person. This report will be structured as an "integrated statistical clinical report" containing the clinical comments based on the data generated by the statistical report.

13. BIBLIOGRAPHY

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