STUDY REPORT

A non-randomised, open-label, multicenter phase 4 pilot study on the effect and safety of Iluvien® in chronic diabetic macular edema patients considered insufficiently responsive to available therapies with or without intravitreal corticosteroid therapy. (RESPOND)

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Study Report

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1 Synopsis

Sponsor-Investigator: Prof. Dr. José Cunha-Vaz, AIBILI	
Title of Study: A non-randomised, open-label, multicenter phase 4 pilot study on the effect and safety of Iluvien® in chronic diabetic macular edema patients considered insufficiently responsive to available therapies with or without intravitreal corticosteroid therapy. (RESPOND)	
Investigators: João Figueira, Miguel Amaro, José Henriques, Vítor Rosas	
Study centre(s): AIBILI Clinical Trial Centre (AIBILI-CEC), Hospital V. Franca de Xira (HVFX), Instituto Retina de Lisboa (IRL) and Hospital S. João (HSJ)	
Publication (reference): Not applicable	
Studied period (years): one year **First enrolment:** 29 Oct. 2014 **Last completed:** 09 Mar. 2016	**Phase of development:** Phase 4
Objectives: To assess the effect and safety of ILUVIEN in patients with chronic DME insufficiently responsive to prior available therapies with or without prior history of intraocular corticosteroid therapy.	
Methodology: This was a prospective, non-randomized, multicentre, open-label phase 4 pilot study to assess the effect and safety of ILUVIEN in chronic DME patients considered insufficiently responsive to available therapies with or without intravitreal corticosteroid therapy.	
Number of patients (planned and analysed): Planned 12 patients. Included 12 patients in 4 clinical centres (AIBILI-CEC, HVFX, IRL and HSJ). Analysed 12 patients.	
Diagnosis and main criteria for inclusion: Patients ≥18 years of age, of either sex that have signed informed consent. Chronic DME, defined as a history of macular edema with duration > 1 year having already received other treatment, based on investigator's clinical evaluation and demonstrated using fundoscopic photography and SD-OCT. Patients considered as insufficiently responsive as defined as having underwent other previous treatments, including at least 3 anti-VEGF injections in the last 6 months, and the following: •Mean central foveal thickness (central subfield thickness) ≥ 290 µm in women and ≥ 305 µm in men in Zeiss Cirrus OR ≥ 305 µm in women and ≥ 320 µm in men in Heidelberg Spectralis, in the study eye as measured using SD-OCT; •Vision impairment (20/50 to 20/400 using Snellen visual acuity equivalent) related to DME; •If in the Investigator's opinion a further improvement is possible.	
Test product, dose and mode of administration, batch number: All patients received ILUVIEN 190 micrograms intravitreal implant in applicator with an initial release rate of 0.2 microgram per day. The implant was administered by injection according to the method of administration defined in the SmPC. Only one eye of each patient was treated with ILUVIEN. The other (non-study) eye received ocular treatment at the discretion of the investigator.	
Duration of treatment/follow-up: One year (12 months)	

Criteria for evaluation: All patients included in the study were used for the Intent to Treat (ITT) population analysis.

Efficacy: BCVA and retinal thickness parameters assessed using SD-OCT (i.e., central subfield thickness and macular volume)

Safety: Ocular safety was assessed by evaluating ocular AE, BCVA, IOP, Hemoglobin A1c, slit lamp exams, ophthalmoscopy, and concomitant ocular medications and therapies.

Systemic safety was assessed by evaluating non-ocular AE and concomitant non-ocular medications and therapies.

Statistical methods: Tables of summary statistics for variables related with medical/ophthalmic history, hemoglobin A1c, vital signs, demographic, diabetes history, ophthalmic examination, BCVA, IOP, SD-OCT, fundus photography, concomitant medications and non-drug therapies and AEs are presented.

Continuous variables are summarized using the following statistics: mean, median, standard deviation, interquartile range, minimum and maximum. The frequency and percentages are reported for all categorical measures.

Graphs with the evolution of BCVA and RT assessed using SD-OCT evolution are presented for the 12 patients.

The efficacy hypotheses

- H0: there is no change in BCVA from baseline to Month-12
- H1: there is a change in BCVA from baseline to Month-12

and

- H0: there is no change in central retinal thickness assessed using SD-OCT from baseline to Month-12
- H1: there is a change in central retinal thickness assessed using SD-OCT from baseline to Month-12

were tested using Wilcoxon Signed-Rank test, due the small sample size.

SUMMARY - CONCLUSIONS

This study showed that, although no statistically significant differences were found from baseline to Month-12 (p=0.255), eyes with chronic DME not responding to prior therapies, showed improvements in BCVA (+3.7 letters), after ILUVIEN injection, with a greater BCVA improvement among pseudophakic patients (+6.8 letters) compared with phakic eyes (-2.5 letters).

Eyes also showed improvements in macular thickness (-292.83 µm) and in volume (-1.8 mm3) from baseline to Month-12, and statistically significant differences were observed for central subfield thickness (p=0.003) and for macular volume (p=0.005). This improvement were observed in 92% of the patients.

Regarding safety, as expected, statistically significant differences were observed from baseline to Month-12 for IOP (p=0.005), but only five patients showed IOP over 22 mmHg during the study. These patients were all well controlled with eye drops.

The patient with cataract worsening underwent surgery showing improvement of the edema and visual acuity at the end of the study.

No deaths occurred during the Study. One serious adverse events (SAE), not related to treatment, occurred (Myocardial infarction).

Regarding Hemoglobin A1C, no statistically significant differences were found from baseline to Month-12 (p=0.623).

This was the first study of this nature with ILUVIEN in Portugal, with patients with chronic DME not responding to prior therapies.

The reduced number of patients included in this exploratory study limited the conclusions, namely the statistical significance of results.

In conclusion, this prospective, non-randomized, multicentre, open-label phase 4 pilot study suggests that ILUVIEN is safe and may be considered effective for chronic DME patients considered insufficiently responsive to available therapies with or without intravitreal corticosteroid therapy.

Date of the report: 2016/07/29

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3 List of abbreviations and definition of terms

4C	Coimbra Coordinating Centre for Clinical Research
AIBILI	Association for Innovation and Biomedical Research on Light and Image
AE	Adverse Event
Anti-VEGF	Anti- Vascular Endothelial Growth Factor
BCVA	Best-Corrected Visual Acuity
BP	Blood Pressure
CFP	Colour Fundus Photography
CI	Coordinating Investigator
CRF	Case Report Form
DME	Diabetic Macular Edema
DR	Diabetic Retinopathy
ETDRS	Early Treatment Diabetic Retinopathy Study
FPFV	First Patient First Visit
ICH	International Conference on Harmonization
IDCT	Investigator Driven Clinical Trial
IOP	Intraocular Pressure
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ITT	Intention to treat
LPLV	Last Patient Last Visit
OCT	Optical Coherence Tomography
OD	Right Eye
OS	Left Eye
OU	Both Eyes

RT	Retinal Thickness
SAE	Serious Adverse Event
SD-OCT	Spectral Domain - Optical Coherence Tomography
SE	Study Eye
VEGF	Vascular Endothelial Growth Factor
SmPC	Summary of Product Characteristics

4 Ethics

4.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The final study protocol, including the substantial amendments and the final version of the subject information and consent form, were reviewed and approved by an Independent Ethics Committee (IEC) prior to inclusion of subjects.

The Independent Ethics Committee (IEC) is listed in annex.

4.2 Ethical conduct of the study

This study was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

The protocol, case report form (CRF) and the proposed informed consent form were reviewed and approved by a properly constituted IRB/IEC/REB before study start. A signed and dated statement that the protocol, CRF and informed consent form had been approved by the IRB/IEC/REB were given to the Sponsor before study initiation. Prior to study start, the Principal Investigator was required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions

and procedures found in the protocol and to give access to all relevant data and records to study's monitors, auditors, IRB/IEC/REB and regulatory authorities as required.

The Principal Investigator and all clinical study staff conducted the clinical study in compliance with the protocol. The Principal Investigator ensured that all personnel involved in the conduct of the study were qualified to perform their assigned responsibilities through relevant education, training and experience.

4.3 Patient information and consent

The Investigator ensured that each patient was fully informed about the nature and objective of the study and possible risks associated with participation.

Eligible patients only participated in the study after providing written (witnessed, where required by law or regulation), approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient was informed about the study to the extent possible given his/her understanding. If the patient was capable of doing so, he/she indicated assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent was obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent is documented in the patient source documents.

The Sponsor provided to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and considered appropriate for this study.

5 Investigators and study administrative structure

The Clinical Sites and their respective Principal Investigators (PIs) that participated in the Study are listed in annex. The Coordinating Investigator was João Figueira from AIBILI-CEC and the Sponsor was AIBILI.

Study Personnel

Coordinating Investigator	João Figueira
Principal Investigators	AIBILI-CEC: João Figueira
	HVFX: Miguel Amaro
	IRL: José Henriques
	HSJ: Vítor Rosas
Coordinating Centre	4C
Responsible	Sandrina Nunes
Study Statistician	Dalila Alves
Study Data Manager	Dalila Alves
Study Manager	Tiago Ferreira
Study Monitors	Sónia Simões

The protocol and protocol approval page are provided in appendix.

The principal investigator approval page if provided in appendix.

6 Introduction

The pathogenesis of DME is complex and multi-factorial, occurring mainly because of the breakdown of the blood-retinal barrier and has an increased incidence with increasing diabetes severity (Bhagat et al., 2009).

Literature suggests that between 1 in 4 and 1 in 3 eyes, with clinically significant macular edema will experience moderate visual loss (i.e., 15 letters or more on the ETDRS chart) within 3 years if left untreated (Bhagat et al., 2009).

The pathogenesis of DME involves several contributing factors including an over-expression of vascular endothelial growth factor (VEGF) and multi-factorial inflammatory processes that lead to the breakdown of the blood-retina barrier and retinal ischemia. Owing to the over expression of VEGF, anti-VEGF therapies are currently used as treatment options in DME. The standard of care and reference therapy for DME (HAS Transparency Commission

opinion on Lucentis, 2011) involves the use of laser. In the case that the DME patient still remains insufficiently responsive to laser therapy, subsequent therapy involves on-label treatments such as anti-VEGF therapy and off-label treatment with intravitreal corticosteroids (i.e., referred to herein as current clinical practice). To date, ILUVIEN has not formed part of DME clinical practice and so there is, naturally, limited experience of using ILUVIEN in Portugal. Recently, however, the Portuguese Competent Authority (INFARMED) has conceded marketing authorization and has approved reimbursement for ILUVIEN. Therefore, ILUVIEN will form one of the therapies that can be used by treating physicians in Portugal. Patients insufficiently responsive to anti-VEGF therapy (e.g., ranibizumab or bevacizumab) are usually treated with intravitreal corticosteroid, (e.g., triamcinolone acetonide or dexamethasone) on an off-label basis (Ford et al., 2013). However, the responses to corticosteroids in patients, with regard to foveal thickness and visual acuity, can decay during the course of intravitreal corticosteroids as such treatments are intended to provide a short-term release of the active and are intended to be used repeatedly (Callanan et al., 2013 and Kane et al., 2008). In contrast, ILUVIEN is administered as a single injection and delivers submicrogram levels of fluocinolone acetonide in the vitreous for up to 36 months. As a result, frequent injections (≤6 months between injections) are not required but longer-term, routine assessments of safety (e.g., intraocular pressure – IOP and cataract formation) are required (Campochiaro et al., 2012). The use of ILUVIEN has been approved by the INFARMED. This study will provide treating physicians with experience with ILUVIEN as well as monitoring its safety (and effectiveness) in a real-life chronic DME patients judged insufficiently responsive to available therapies. As ILUVIEN has 3-year duration, clinicians would like to have an indication of how patients' IOP may change with ILUVIEN. Changes in IOP are likely to differ in different individuals.

A known side effect of intravitreal corticosteroids is increased intraocular pressure. In the FAME study 38.4% of patients receiving ILUVIEN (0.2 μg/day) received IOP-lowering medication and 18.4% of ILUVIEN patients experienced an increase in IOP of greater than 30 mmHg. To mitigate the effect of IOP changes, the current study only recruited patients whose baseline IOP was ≤ 21 mmHg. Furthermore, it is likely that patients who did not experience a rise in IOP in response to prior treatment with an intravitreal corticosteroid will not experience a rise in IOP in response to ILUVIEN, which contains the corticosteroid

fluocinolone acetonide – Fac (Kane et al., 2008). Lastly, ILUVIEN, unlike short-term release corticosteroids, is designed to release low dose FAc in a sustained fashion over the course of a 36 month period (Campochiaro et al., 2013).

7 Study objectives

To assess the effect and safety of ILUVIEN in patients with chronic DME insufficiently responsive to prior available therapies with or without prior history of intraocular corticosteroid therapy.

8 Investigational plan

8.1 Overall study design and plan-description

8.1.1 Type and design of the study

This was a prospective, non-randomized, multicentre, open-label phase 4 pilot study to assess the effect and safety of ILUVIEN in chronic DME patients considered insufficiently responsive to available therapies with or without intravitreal corticosteroid therapy.

Prior to receiving ILUVIEN, patients has been judged to be insufficiently responsive to prior treatment to DME by the investigator. Prior treatment for DME include either 1) laser with or without prior history of intraocular corticosteroid therapy or 2) laser and anti-VEGF therapy with or without prior history of intraocular corticosteroid therapy.

Patients enrolled had an IOP $\leq$ 21 mmHg at screening. Those patients enrolled with prior history of treatment with an intravitreal corticosteroid will have an associated peak IOP $\leq$ 25 mmHg.

This 12 month study consisted of 8 visits. The screening visit within 14 days prior to enrolment established the patient's eligibility. At Visit 2 (day 0), one eligible eye per qualifying patient received ILUVIEN treatment. Visits 1 and 2 could be combined on the same day, if possible. Visit 3 (week 1) was to monitor the safety of the treatment procedure. The remaining visits were scheduled at months 1, 3, 6, 9, and 12 to assess the effectiveness and safety of ILUVIEN.

8.1.2 Study Procedures / Data Acquisition

The investigator explained the study purpose, procedures and the patient responsibilities to a potential study participant. The patient's willingness and ability to meet the protocol requirements was determined.

When it has been established that the patient may be eligible, prior to any study-specific procedure, written informed consent was obtained. The patient signed and dated one copy of the consent form in the presence of the investigator. The original copy was retained with the patient records and a copy was given to the patient.

After informed consent has been obtained, and prior to enrolment, the patient was evaluated to determine eligibility. Screening procedures consist of:

- Demographics, including date of birth, gender, and iris colour;
- Diabetes history, including type of diabetes, dates of diagnosis of diabetes and DME;
- Medical history and ophthalmic history, with specific attention to:
  - Last three treatments with anti-VEGF therapy prior to screening, including type and date of injections, and associated visual acuity;
  - Last treatment with intravitreal corticosteroids prior to screening, including type and date of injection, and associated maximum IOP;
  - Last treatment with laser photocoagulation for DME, including type and date of treatment, and associated visual acuity.
- Pregnancy test, if applicable
- Hemoglobin A_{1c}
- Blood pressure
- Ophthalmic examination consisting of BCVA, IOP, central subfield thickness, macular volume, and corneal thickness (via spectral SD-OCT)
- Slit lamp examination and ophthalmoscopy
- Fundus photography
- Diabetic retinopathy assessment
- Lens status (according to the AREDS 2008 Clinical Lens Opacity Grading)
- Verification that the patient satisfies all inclusion and exclusion criteria.

8.1.3 Screening Failures

Non eligible patients were considered screening failures. All data collected during the Screening Visit were registered, as well as the reason for not being eligible.

8.1.4 Study Completion

Subjects who successfully completed the study through Month-12 were considered to have completed the Study for data analysis.

8.1.5 Study Discontinuation

There was no early study termination.

8.1.6 Patient Identification

Each subject is uniquely identified by a subject identification code. This code is only used for study purposes. Upon signing the informed consent form, the subject was identified by this subject identification code. This code start with the characters "RESP" and consist of a combination of the site number and subject number. Once assigned to a subject, the subject identification code will not be reused. During the Clinical Trial and afterwards, only the Investigator was able to identify the subject based on the subject identification code.

Example: The 1st patient in clinical site 01 to sign the informed consent form was assigned the patient number "RESP-01001" and the 1st patient in clinical site 02 to sign the informed consent form was assigned the patient number "RESP-02001".

8.2 Selection of study population

Chronic DME patients considered insufficiently responsive to available therapies (laser, anti-VEGF) with or without intravitreal corticosteroid therapy.

8.2.1 Inclusion criteria

1. Patients ≥18 years of age, of either sex that have signed informed consent.
2. Chronic DME, defined as a history of macular edema with duration > 1 year having already received other treatment, based on investigator's clinical evaluation and demonstrated using fundoscopic photography and SD-OCT.

3. Patients considered as insufficiently responsive as defined as having underwent other previous treatments, including at least 3 anti-VEGF injections in the last 6 months, and the following:
    - Mean central foveal thickness (central subfield thickness) ≥ 290 μm in women and ≥ 305 μm in men in Zeiss Cirrus OR ≥ 305 μm in women and ≥ 320 μm in men in Heidelberg Spectralis, in the study eye as measured using SD-OCT;
    - Vision impairment (20/50 to 20/400 using Snellen visual acuity equivalent) related to DME;
    - If in the Investigator's opinion a further improvement is possible.

8.2.2 Exclusion criteria

1. IOP > 21 mmHg at screening (day -14) in the study eye.
2. Historical rise in IOP > 25 mmHg following treatment with an intravitreal corticosteroid in the study eye.
3. Use of ≥ 2 active agents as IOP-lowering medications to control IOP at screening in the study eye.
4. Patients that have vitreomacular traction in DME and opaque media in the study eye.
5. Patients with severe proliferative diabetic retinopathy requiring pan retinal photocoagulation in the study eye.
6. Pregnant or breastfeeding women.
7. Patients diagnosed with active angiographic central macular ischaemia prior to screening in the study eye.
8. Patients that have received pan retinal photocoagulation or undergone cataract surgery in the 3 months prior to the screening visit in the study eye.
9. Patients with contraindications:
    - Presence of pre-existing glaucoma.
    - Active or suspected ocular or periocular infection.
    - The patient is hypersensitive to the active agent or to one of the excipients.
10. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant UNLESS they are: using a highly effective method of birth control (i.e. one that results in a less than 1% per year failure rate when used consistently and

correctly, such as implants, injectables, combined oral contraceptives, and some intrauterine devices – IUDs). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) are not acceptable. Reliable contraception should be maintained throughout the study and for 30 days after study drug discontinuation.

8.2.3 Study eye

The study eye is the affected eye; for patients with bilateral DME, the study eye was the more severely affected eye fitting the inclusion/exclusion criteria. If both eyes are equally affected and eligible, the study eye was determined at the investigator's discretion.

All study data was collected for the study eye only.

8.2.4 Removal of patients from therapy or assessment

As this is a phase 4 study, no significant safety risks were expected for the subjects other than the described in the SmPC. Nevertheless, study medication was discontinued and the patient withdrawn from the study if the Investigator determined that continuing it resulted in a significant safety risk for that patient.

Subjects could voluntarily withdraw from the study for any reason at any time. They are considered withdrawn if they stated an intention to withdraw, or failed to return for visits, or became lost to follow up for any other reason. If a patient chose to stop treatment, the Investigator encouraged the patient to return for a last visit as soon as possible, according with the patient's availability in order to undergo, if possible, an Early Termination Visit (same procedures as in the Discharge Visit).

If a subject was withdrawn from the study, or withdrew his/her consent, all data collected until the time of withdrawal was used in the analyses.

8.3 Treatments

8.3.1 Treatments administered

All patients received ILUVIEN 190 micrograms intravitreal implant in applicator with an initial release rate of 0.2 microgram per day. The implant was administered by injection

according to the method of administration defined in the SmPC. Only one eye of each patient was treated with ILUVIEN. The other (non-study) eye received ocular treatment at the discretion of the investigator.

8.3.2 Identity of investigational product

All patients received ILUVIEN 190 micrograms intravitreal implant.

The sponsor supplied ILUVIEN to be used in this study. The implant is an injectable intraocular sustained-release drug delivery system for FAc preloaded into a one-time use sterile applicator. Each implant contains 0.19 mg of FAc as the active ingredient within a cylindrical polyimide tube 3.5 mm long with an internal diameter of 0.34 mm. Inactive ingredients are polyimide, polyvinyl alcohol (PVA) and silicone adhesive. The polyimide tube and silicone adhesive are impermeable to FAc, while the cured PVA coated end of the tube act as a diffusion port allowing the drug to be released. The implant is to be injected through the pars plana into the vitreous using the applicator.

8.3.3 Selection of doses in the study

The implant was supplied sterile as an individual unit in the applicator. Designed to allow precision insertion of the needle to an exact depth through the sclera, the applicator is equipped with an 8.5 mm long 25 gauge needle attached to a hub. The implant is preloaded inside the applicator. The applicator has a two-step button to control the movement of the implant as it is being positioned for insertion, with grips on the handle to prevent the gloved hand of the physician from slipping during insertion. There is also a gauge on the applicator to assist with measuring the distance of the insertion site from the limbus. The applicator has a clear window so that the physician can confirm that the implant is loaded inside the applicator. The needle is attached to a hub to prevent over-insertion and the length of the needle also allows better visualization during the procedure. The applicator has been placed inside a molded tray and a Tyvek® lid was applied and then heat sealed. This is considered primary packaging and provides a 12 sterile barrier. The sealed tray was placed inside a carton (secondary packaging). The carton and contents were terminally sterilized using a validated gamma irradiation cycle. The cartons were stored in a secure, locked location accessible only to authorized study personnel, and maintained at room temperature. The study drug and

labelling was supplied by the Sponsor to the Investigator. The Investigator designated a pharmacy at the clinical site to apply the label to the study drug.

8.3.4 Selection and timing of dose for each patient

All treatments were performed on Day 0. Patients received an intraocular injection of ILUVIEN in the study eye. Topical antibiotic was prescribed for all patients for 3-5 days following the treatment day.

8.3.5 Blinding

Not applicable.

8.3.6 Prior and concomitant therapy

With regard to concomitant medications, the type, start date and stop date ("or ongoing"), reason for use and site of medications used at screening visit or during the study were collected on the CRF.

The Investigator instructed the patient to notify the centre about any new medications he/she took after the start of the study drug. All medications (other than study drug) and significant non-drug therapies administered after the patient started treatment with study medication were listed on the CRF.

8.3.7 Treatment compliance

Due to the route of administration and sustained delivery of ILUVIEN, treatment compliance is ensured.

8.4 Efficacy and safety variables

8.4.1 Efficacy and safety measurements assessed and flow chart

Effectiveness assessments:

Variables for assessing effectiveness include BCVA and retinal thickness parameters assessed using SD-OCT (i.e., central subfield thickness and macular volume).

Safety assessments:

Ocular safety was assessed by evaluating ocular AE, BCVA, IOP, Hemoglobin A_{1c}, slit lamp exams, ophthalmoscopy, and concomitant ocular medications and therapies.

Systemic safety was assessed by evaluating non-ocular AE and concomitant non-ocular medications and therapies.

Table 1. Scheduled Visits

Study phase	Screening Phase	Treatment Phase						
Visit Number	1*	2*	3	4	5	6	7	8 (Discharge Visit)
Day	-14	**0**	7	**30**	90	**180**	270	**360**
Study Month/Week	-	**0**	-	**1**	3	**6**	9	**12**
Procedure								
Medical/ophthalmic history[1]	X							
Pregnancy test for women of childbearing potential	X							
Hemoglobin A1c	X							X
Blood Pressure	X							
ILUVIEN administration		X						
Demographic	X							
Diabetes history	X							
Ophthalmic examination[2]	X		X	X	X	X	X	X
BCVA	X		X	X	X	X	X	X
IOP	X		X	X	X	X	X	X
SD-OCT	X		X	X	X	X	X	X
Inclusion / Exclusion criteria	X							
Fundus photography	X					X		X
Diabetic retinopathy assessment	X					X		X
Concomitant medications and non-drug therapies		X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X
Study completion forms								X

* V1 and V2 can be combined on the same day.
[1] Specify previous intravitreal injections
[2] Ophthalmic examination includes slit lamp examination, and dilated ophthalmoscopy.

8.4.2 Appropriateness of measurements

The efficacy and safety parameters selected were the standard parameters used for this indication and for this type of patient population.

8.4.3 Primary efficacy variables

- BCVA (letters)
- SD-OCT
    - Central subfield thickness
    - Macular volume

8.4.4 Safety variables

Ocular safety will be assessed by evaluating

- Ocular AEs, including SAEs occurring at any time during the trial;
- BCVA (letters);
- IOP;
- Hemoglobin A1c;
- Slit lamp examination - normal/abnormal and specification for Cornea, Conjunctiva, Iris, Anterior Chamber and Lens;
- Ophthalmoscopy - normal/abnormal and specification for Vitreous, Retina, Macula, Choroid, Optic Nerve and other;
- Concomitant ocular medications and therapies.

Systemic safety will be assessed by evaluating non-ocular AEs, and concomitant non-ocular medications and therapies.

8.5 Data quality assurance

Designated staff entered the information required by the protocol onto the CRF, provided by the Coordinating Centre. The clinical centre was responsible for reviewing the CRF for completeness and accuracy and instruct personnel to make any required corrections or additions.

After receiving all completed CRF and after the verification of the data, the Study Database was declared complete and accurate, and was locked making data available for data analysis.

8.6 Statistical methods planned in the protocol and determination of sample size

8.6.1 Statistical and analytical plans

Tables of summary statistics for variables related with medical/ophthalmic history, hemoglobin A1c, vital signs, demographic, diabetes history, ophthalmic examination, BCVA, IOP, SD-OCT, fundus photography, concomitant medications and non-drug therapies and AEs are presented.

Continuous variables are summarized using the following statistics: mean, median, standard deviation, interquartile range, minimum and maximum. The frequency and percentages are reported for all categorical measures.

Graphs with the evolution of BCVA and RT assessed using SD-OCT evolution are presented for the 12 patients.

The efficacy hypotheses

- H0: there is no change in BCVA from baseline to Month-12
- H1: there is a change in BCVA from baseline to Month-12

and

- H0: there is no change in central retinal thickness assessed using SD-OCT from baseline to Month-12
- H1: there is a change in central retinal thickness assessed using SD-OCT from baseline to Month-12

were tested using Wilcoxon Signed-Rank test, due the small sample size.

An alpha of 0.05 was considered in all analyses.

Statistical analyses were performed on Stata version 12.1 StataCorp LP, College Station, Texas, USA).

8.6.2 Determination of sample size

Twelve (12) patients were considered for this study, two sites with 3 patients, one site with 4 patients and one site with 2 patients. Being a pilot study no sample size was estimated.

8.7 Changes in the conduct of the study or planned analyses

No changes have been made in the conduct of the planned analyses.

9 Study Patients

9.1 Disposition of patients

Patients disposition are presented in Table 2.

Table 2. Patient disposition

Patients	*Total*
Planned	12
Screened	16
Failed inclusion criteria	4
Eligible	12
Completed	12
Discontinued	0

9.2 Protocol deviations

The protocol deviations are provided in appendix.

10 Efficacy evaluation

10.1 Data sets analysed

All effectiveness variables were analysed using the intent-to-treat (ITT) population. The ITT population include all enrolled patients who have a valid baseline assessment. The method of last observation carried forward was used to impute values for missing data. All effectiveness variables are summarised using this data set.

Summaries of data without data imputation, i.e., observed cases, were also generated.

10.2 Demographic and Other baseline characteristics

The baseline characteristics are summarized for the ITT population. These data are presented in tabular summaries (Table 3 to Table 27) to describe the patients enrolled into the study.

10.2.1 Demographic characteristics

Table 3. Age

	Mean	*Sd*	*Min*	*Max*	*P50*	*P25*	*P75*
Age (years)	69.58	9.32	58	87	69	60.5	75.5

Table 4. Gender

Gender	*Female*		*Male*		*Total*	
	No.	%	No.	%	No.	%
	4	33.33	8	66.67	12	100

Table 5. Iris Colour

Iris Colour	*BLUE*		*BROWN*		*Total*	
	No.	%	No.	%	No.	%
	1	8.33	11	91.67	12	100

10.2.2 Lens status

Table 6. Lens status

Lens Status	*PHAKIC*		*PSEUDOPHAKIC*		*Total*	
	No.	%	No.	%	No.	%
	4	33.33	8	66.67	12	100

10.2.3 Vital Signs

Table 7. Vital Signs

Vital Signs	*Mean*	*Sd*	*Min*	*Max*	*P50*	*P25*	*P75*
Systolic blood pressure	153	21.64	116	192	150	142.5	165.5
Diastolic blood pressure	77.08	8.74	64	93	75.5	72	84

10.2.4 Diabetes/Metabolic related parameters

Table 8. Hemoglobin A_{1C}

	Mean	*Sd*	*Min*	*Max*	*P50*	*P25*	*P75*
HbA_{1C}	6.87	1.25	5.4	8.8	6.6	5.8	8.5

Table 9. Diabetes type

Diabetes type	*Type 1*		*Type 2*		*Total*	
	No.	%	No.	%	No.	%
	0	0	12	100	12	100

Table 10. Diabetes duration

	Mean	*Sd*	*Min*	*Max*	*P50*	*P25*	*P75*
Diabetes duration (years)	19.09	11.08	3	41	20	10	25

Table 11. DME duration

	Mean	*Sd*	*Min*	*Max*	*P50*	*P25*	*P75*
DME duration (years)	3.42	3.09	1	10	2.5	1	4

10.2.5 Diabetic retinopathy

Table 12. Diabetic retinopathy assessment

DR Severity	None		Moderate		Severe		Proliferative		Laser		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
	3	25	2	16.67	1	8.33	1	8.33	5	41.67	12	100

10.2.6 BCVA

Table 13. BCVA (letters)

	Mean	*Sd*	*Min*	*Max*	*P50*	*P25*	*P75*
Standard ETDRS	48.75	10.86	26	61	50.5	41.5	58.5

10.2.7 SD-OCT

Table 14. SD-OCT assessment

	Mean	*Sd*	*Min*	*Max*	*P50*	*P25*	*P75*
Central subfield thickness	650.5	140.94	424	910	655.5	527	752.5
Macular volume	11.61	2.01	9.17	14.93	11.01	9.95	13.1
Corneal thickness	570	36.51	530	610	570	540	600

10.2.8 Fundus Photography assessment

Table 15. Fundus photography

PHOTO TAKEN	*No*		*Yes*		*Total*	
	No.	%	No.	%	No.	%
	0	0	12	100	12	100

10.2.9 Ophthalmological Examination

Table 16. Slit Lamp Exam

Patients with any abnormality	*No*		*Yes*		*Total*	
	No.	%	No.	%	No.	%
	8	66.67	4	33.33	12	100
Total	8	66.67	4	33.33	12	100

Table 17. Slit Lamp Exam Abnormalities

	N	***%***
Eye disorders	**3**	**60.0%**
Cataract nuclear	1	20.0%
Pterygium	1	20.0%
Corneal pigmentation	1	20.0%
Surgical and medical procedures	**2**	**40.0%**
Intraocular lens implant	2	40.0%
Total	**5**	**100.0%**

Table 18. Ophthalmoscopy

Patients with any abnormality	*No*	*No*	*Yes*	*Yes*	*Total*	*Total*
	No.	%	No.	%	No.	%
	2	16.67	10	83.33	12	100
Total	2	16.67	10	83.33	12	100

Table 19. Ophthalmoscopy Abnormalities

	N	***%***
Eye disorders	**22**	**73.3%**
Diabetic retinal oedema	7	23.3%
Diabetic retinopathy	7	23.3%
Macular fibrosis	2	6.7%
Macular oedema	1	3.3%
Vitreous degeneration	1	3.3%
Retinal haemorrhage	2	6.7%
Retinal aneurysm	1	3.3%
Retinal pigmentation	1	3.3%
Surgical and medical procedures	**7**	**23.3%**

Photocoagulation	3	10.0%
Retinal laser coagulation	4	13.3%
Investigations	**1**	**3.3%**
Optic nerve cup/disc ratio	1	3.3%
Grand Total	**30**	**100.0%**

Table 20. Intraocular Pressure measurement

	Mean	*Sd*	*Min*	*Max*	*P50*	*P25*	*P75*
IOP	14.58	2.94	10	20	14.5	13	16.5

10.2.10 Medical and ophthalmic history

Table 21. Listing of medical history

	N	***%***
Blood and lymphatic system disorders	**1**	**2.6%**
Hypercoagulation	1	2.6%
Cardiac disorders	**2**	**5.1%**
Arrhythmia	1	2.6%
Cardiac disorder	1	2.6%
Gastrointestinal disorders	**1**	**2.6%**
Abdominal hernia	1	2.6%
Infections and infestations	**1**	**2.6%**
Onychomycosis	1	2.6%
Metabolism and nutrition disorders	**17**	**43.6%**
Dyslipidaemia	3	7.7%
Hypercholesterolaemia	3	7.7%
Hyperuricaemia	1	2.6%
Type 2 diabetes mellitus	10	25.6%
Nervous system disorders	**1**	**2.6%**
Cerebrovascular accident	1	2.6%
Psychiatric disorders	**2**	**5.1%**
Bipolar disorder	1	2.6%
Insomnia	1	2.6%
Skin and subcutaneous tissue disorders	**1**	**2.6%**

Psoriasis	1	2.6%
Social circumstances	**2**	**5.1%**
Menopause	2	5.1%
Surgical and medical procedures	**3**	**7.7%**
Cholecystectomy	1	2.6%
Foot operation	1	2.6%
Prostatic operation	1	2.6%
Vascular disorders	**8**	**20.5%**
Hypertension	8	20.5%
Total	**39**	**100.0%**

Table 22. Listing of ocular history

	N	*%*
Eye disorders	**37**	**100.0%**
Cataract	7	18.9%
Cataract cortical	2	5.4%
Cataract nuclear	2	5.4%
Cataract operation	3	8.1%
Diabetic retinal oedema	6	16.2%
Diabetic retinopathy	9	24.3%
Intraocular lens implant	4	10.8%
Macular oedema	3	8.1%
Vitreous haemorrhage	1	2.7%
Grand Total	**37**	**100.0%**

Table 23. Previous treatments

		n (%)
Previous Treatments	Laser + anti-VEGF + Corticosteroids	4 (33.3)
	Laser + anti-VEGF	5 (41.7)
	Anti-VEGF alone	3 (25.0)

Table 24. Previous laser sessions, anti-VEGF injections and corticosteroids treatments

	Mean (SD)
Previous laser sessions	4.4 (4.2)
Previous anti-VEGF injections	4.0 (2.9)
Previous corticosteroids treatments	2.0 (1.4)

10.2.11 Inclusion and Exclusion criteria

Table 25. Inclusion / exclusion criteria

FULFILL ALL CRITERIA	*No*		*Yes*		*Total*	
	No.	%	No.	%	No.	%
	4	25	12	75	16	100

Table 26. Listing of excluded subjects with exclusion reason

Patient ID	*Exclusion reason*
RESP-03001	CRT lower than 320 µm
RESP-03003	BCVA better than 20/50
RESP-03004	BCVA better than 20/50
RESP-04001	IOP >21 mmHg at screening (day -14) in the study eye

10.2.12 Study Eye

Table 27. Study eye

STUDY EYE	*Right Eye*		*Left Eye*		*Total*	
	No.	%	No.	%	No.	%
	6	50	6	50	12	100

10.3 Measurements of treatment compliance

No compliance monitoring was performed according to the approved protocol.

10.4 Efficacy results and tabulations of individual patient data

10.4.1 Analysis of efficacy

The following tables (Table 28 to Table 30) and figures (Figure 1 to Figure 3) show the efficacy results.

Although BCVA score has improved from baseline to Month-12, this improvement was not statistically significant (p=0.255).

Statistically significant differences were observed from baseline to Month-12 for Central subfield thickness (p=0.003) and for macular volume (p=0.005).

Table 28. BCVA (letters)

	Mean	*Sd*	*Min*	*Max*	*P50*	*P25*	*P75*	*p-value*[1]
Screening	48.75	10.86	26	61	50.5	41.5	58.5	
Week 1	53.58	12.14	27	76	55	48	60	
Month 1	54.58	12.09	27	74	57.5	46.5	61	
Month 3	55.5	16.42	15	79	60.5	49	65	0.255
Month 6	55.5	17.53	12	79	60.5	55.5	63	
Month 9	53.17	16.03	17	74	58	47	62	
Month 12	52.42	15.12	25	77	55.5	43	63	

[1] Wilcoxon signed-rank test between screening and month 12

For sub analysis by lens status, see 10.4.2.6 Examination of Subgroups section.

Table 29. Central subfield thickness

	Mean	*Sd*	*Min*	*Max*	*P50*	*P25*	*P75*	*p-value*[1]
Screening	650.5	140.94	424	910	655.5	527	752.5	
Week 1	447.25	180.54	271	832	381	331	515.5	
Month 1	406.08	192.97	162	845	403.5	251.5	483	
Month 3	323.17	106.48	148	502	333	244	382.5	0.003
Month 6	356.17	174.67	143	857	331.5	288	378.5	
Month 9	421.17	159.77	176	736	394.5	344	487.5	
Month 12	357.67	169.55	138	743	306	258.5	422	

[1] Wilcoxon signed-rank test between screening and month 12

Table 30. Macular Volume

	Mean	*Sd*	*Min*	*Max*	*P50*	*P25*	*P75*	*p-value*[1]
Screening	11.61	2.01	9.17	14.93	11.01	9.95	13.1	
Week 1	10.60	2.04	8.7	15.06	10.04	9.27	11.29	
Month 1	10.23	2.10	8.27	15.9	9.51	9.22	10.68	
Month 3	9.45	1.12	7.91	11.82	9.10	8.83	9.93	0.005
Month 6	9.79	2.33	7.94	16.47	8.93	8.71	10.03	
Month 9	10.16	2.17	8.1	14.61	9.24	8.99	10.53	
Month 12	9.81	1.89	7.75	14.48	9.09	8.80	10.30	

[1] Wilcoxon signed-rank test between screening and month 12

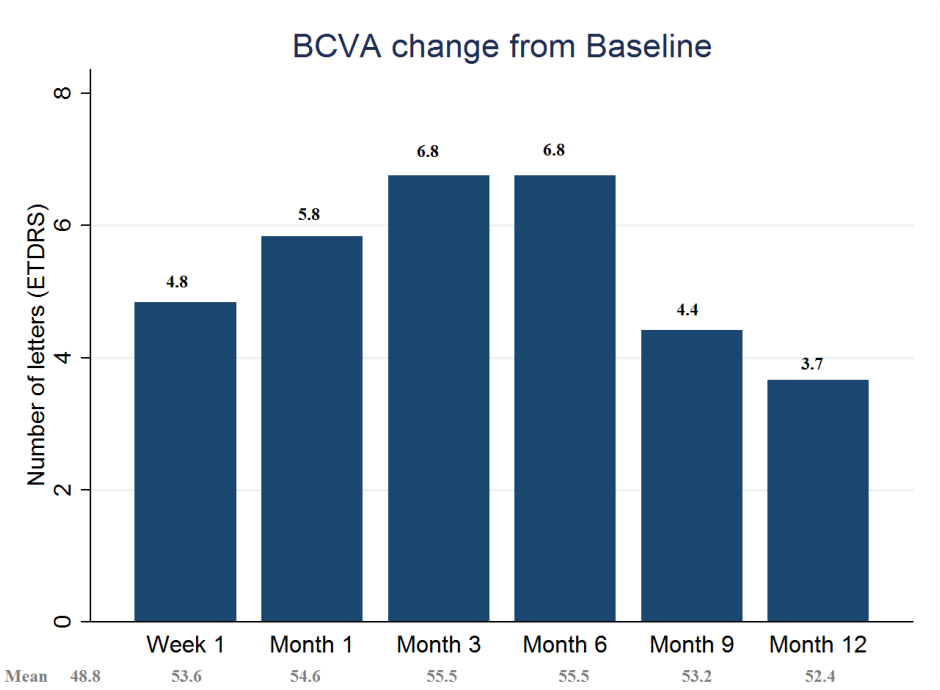


Figure 1. Improvement from screening of BCVA (letters).

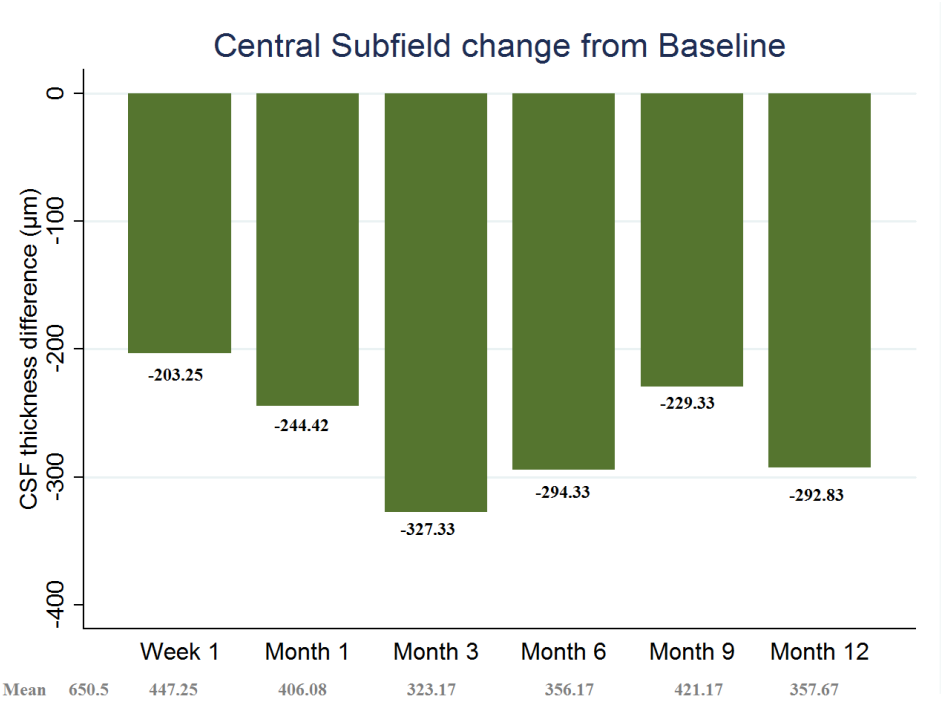


Figure 2. Improvement from screening of Central subfield thickness (µm).

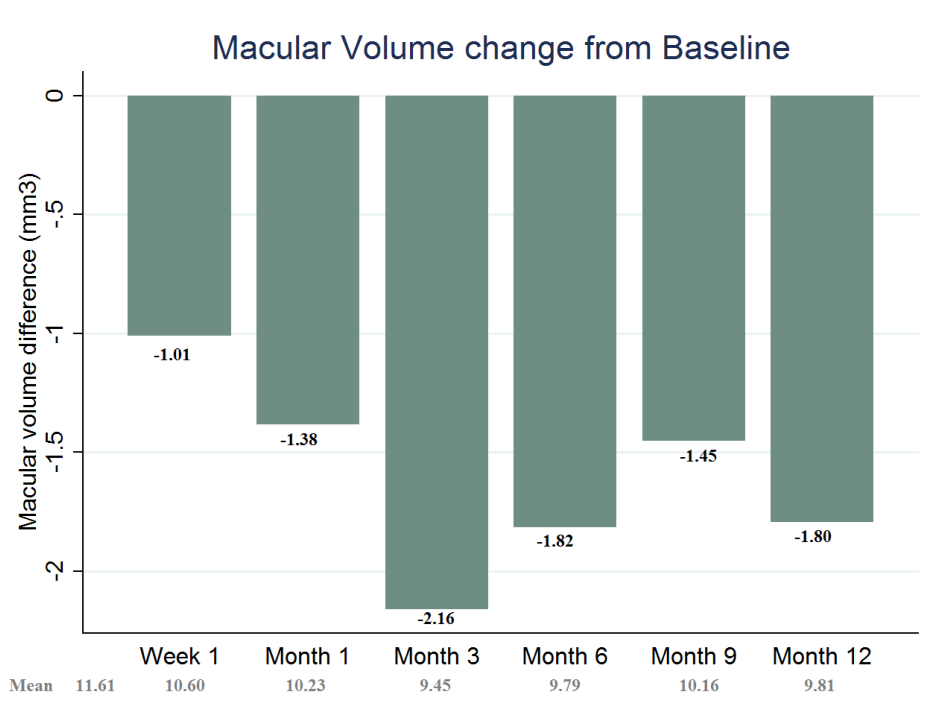


Figure 3. Improvement from screening of Macular Volume (mm^3).

10.4.2 Statistical / Analytical Issues

10.4.2.1 Adjustments for Covariates

Due to the exploratory nature of the study no adjustments were done.

10.4.2.2 Handling of Dropouts or Missing Data

The method of last observation carried forward will be used to impute values for missing data.

No data will be excluded due to protocol violations.

10.4.2.3 Interim Analyses and Data Monitoring

Interim analysis was carried out on an 'as needed' basis, e.g., congresses, periodic safety updates. The interim analysis was exploratory adjusted to the analysis period in question.

10.4.2.4 Multicentre Studies

All study parameters were acquired using Standard Operations Procedures to reduce inter-centres variability and to allow for the data analysis without corrections or conversions.

10.4.2.5 Multiple Comparisons/Multiplicity

Due to the exploratory nature of the study no adjustments were done.

10.4.2.6 Examination of Subgroups

BCVA changes were analysed, by lens status, and results are presented in Table 31, Figure 4 and Figure 5.

Pseudophakic patients had a higher mean letter gain at Month 12, of 6.8 letters (p=0.058) but no statistically significant differences were found from screening to Month 12, for both pseudophakic eyes (66.7%) and phakic eyes (33.3%).

Table 31. BCVA (letters), by lens status

	Phakic Eyes		*Pseudophakic Eyes*		*p-value*[1]
	Mean ± SD	**Median (IQR)**	**Mean ± SD**	**Median (IQR)**	
Screening	46.5 ± 15.55	50 (34.5 – 58.5)	49.88 ± 8.81	50.5 (43.5 – 57)	0.799
Week 1	51.75 ± 20.81	55 (36 – 67.5)	54.5 ± 6.57	55 (52 – 60)	0.734
Month 1	51.75 ± 20.32	53 (36 – 67.5)	56 ± 6.78	57.5 (52 – 60.5)	0.932
Month 3	49.25 ± 27.89	51.5 (27.5 – 71)	58.63 ± 7.54	60.5 (53.5 – 64.5)	0.734
Month 6	45 ± 29.50	44.5 (21.5 – 68.5)	60.75 ± 3.96	61.5 (59 – 63)	0.268
Month 9	44.75 ± 25.59	44 (24 – 65.5)	57.38 ± 7.89	58.5 (56 – 62)	0.307
Month 12	44 ± 23.42	37 (27.5 – 60.5)	56.63 ± 7.96	58.5 (51.5 – 63)	0.235
p-value[2]	0.715		0.058		

[1] Wilcoxon-Mann-Whitney test (between groups); [2] Wilcoxon signed-rank test between screening and month 12

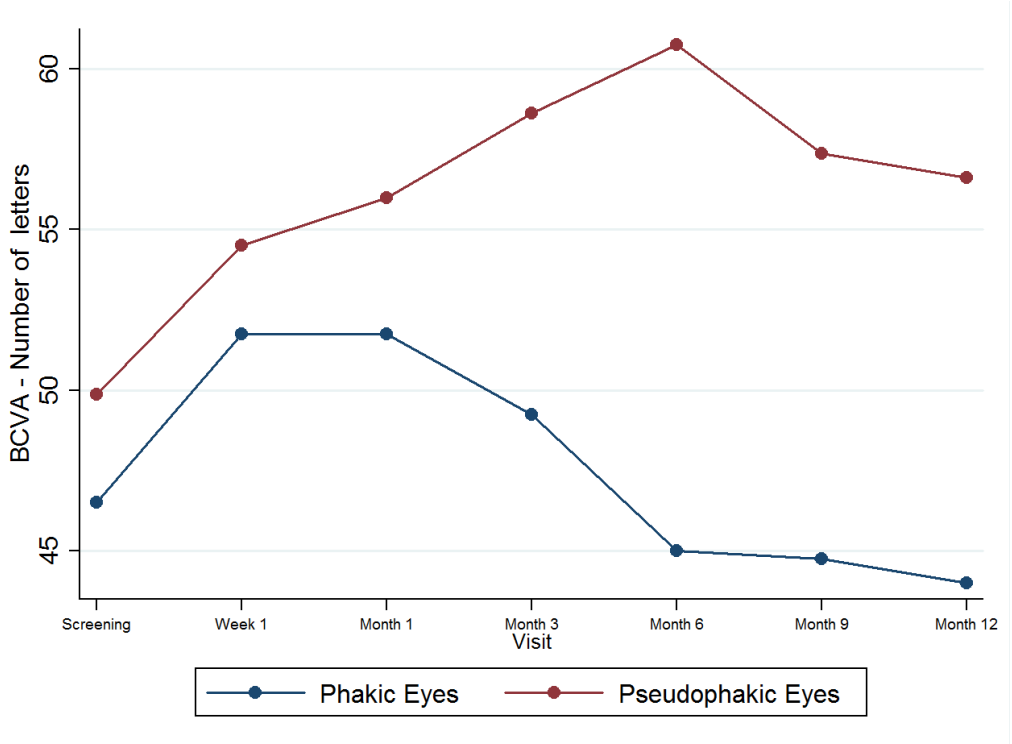


Figure 4. BCVA (letters), by lens status.

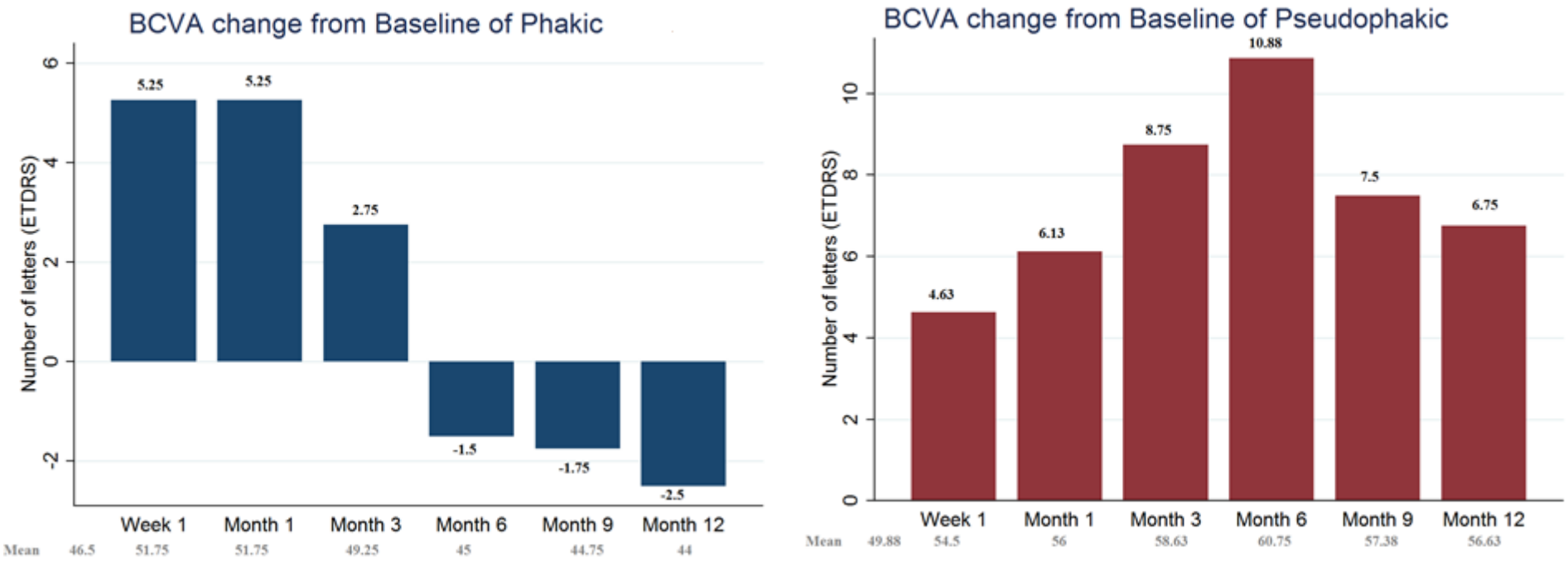


Figure 5. Change from screening of BCVA (letters), by lens status.

10.4.3 Efficacy conclusions

Although no statistically significant differences were found from baseline to Month-12 (p=0.255), eyes with chronic DME not responding to prior therapies showed improvements in BCVA (+3.7 letters), after ILUVIEN injection, with a greater BCVA improvement among pseudophakic patients (+6.8 letters).

Eyes showed also improvements in macular thickness (-292.83 µm) and in volume (-1.8 mm^3) from baseline to Month-12, and statistically significant differences were observed for central subfield thickness (p=0.003) and for macular volume (p=0.005).

11 Safety evaluation

All safety variables were analysed using the safety population. The safety population include data from all enrolled patients who received ILUVIEN and from whom at least one safety measurement was obtained. No data were excluded due to protocol violations.

11.1 Extent of exposure

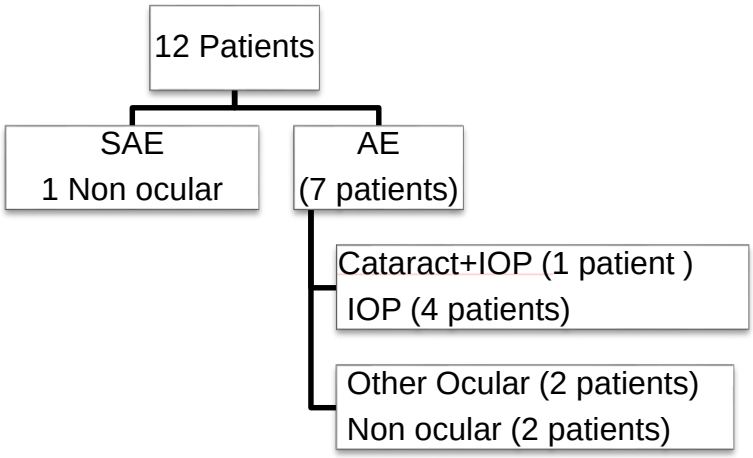
Twelve (12) patients have been enrolled into the RESPOND study.

11.2 Adverse events (AEs)

AEs are summarised by presenting the number and percentage of patients having at least one occurrence of any AE during the study, having at least one occurrence of an AE within each system organ class and a list of AEs by patients, i.e., the following is provided

- Frequency distribution of AEs;
- Frequency distribution of AEs by body system and preferred term;
- Listing of AEs by patients.

11.2.1 Brief summary of adverse events



11.2.2 Display of adverse events

The frequency distribution of AEs by body system and preferred term is presented in Table 32. Of the 5 patients that had ocular hypertension, 4 (80%) are phakic.

Table 32. Frequency distribution of AEs by body system and preferred term

	N	***%***
Cardiac disorders	**1**	**8.3%**
Myocardial infarction	1	8.3%
Eye disorders	**8**	**66.7%**
Cataract	1	8.3%
Keratitis	1	8.3%
Ocular hypertension	5	41.7%
Vitreous haemorrhage	1	8.3%
Infections and infestations	**1**	**8.3%**
Conjunctivitis	1	8.3%
Injury, poisoning and procedural complications	**1**	**8.3%**
Facial bones fracture	1	8.3%
Nervous system disorders	**1**	**8.3%**
Dizziness	1	8.3%
Total	**12**	**100.0%**

11.2.3 Listing of adverse events by patient

Table 33 presents the list of all adverse events per patient.

Table 33. Listing of adverse events by patient

	N	*%*
RESP-01001	**2**	**11.8%**
Eye disorders	**1**	**5.9%**
Ocular hypertension	1	5.9%
Nervous system disorders	**1**	**5.9%**
Dizziness	1	5.9%
RESP-01002	**2**	**11.8%**
Eye disorders	**2**	**11.8%**
Ocular hypertension	2	11.8%
RESP-01003	**5**	**29.4%**
Eye disorders	**5**	**29.4%**
Cataract	1	5.9%
Ocular hypertension	4	23.5%
RESP-01004	**2**	**11.8%**
Eye disorders	**2**	**11.8%**
Ocular hypertension	2	11.8%
RESP-02001	**1**	**5.9%**
Cardiac disorders	**1**	**5.9%**
Myocardial infarction	1	5.9%
RESP-03005	**2**	**11.8%**
Eye disorders	**1**	**5.9%**
Ocular hypertension	1	5.9%
Injury, poisoning and procedural complications	**1**	**5.9%**
Facial bones fracture	1	5.9%
RESP-03006	**1**	**5.9%**
Eye disorders	**1**	**5.9%**
Keratitis	1	5.9%
RESP-04003	**2**	**11.8%**
Eye disorders	**1**	**5.9%**
Vitreous haemorrhage	1	5.9%
Infections and infestations	**1**	**5.9%**
Conjunctivitis	1	5.9%
Total	**17**	**100.0%**

11.2.4 Analysis of adverse events

The most frequent AE that occurred during the study was ocular hypertension (41.7% of AEs). Intraocular pressure measurements of patients with ocular hypertension adverse events, by lens status, are presented in Figure 6.

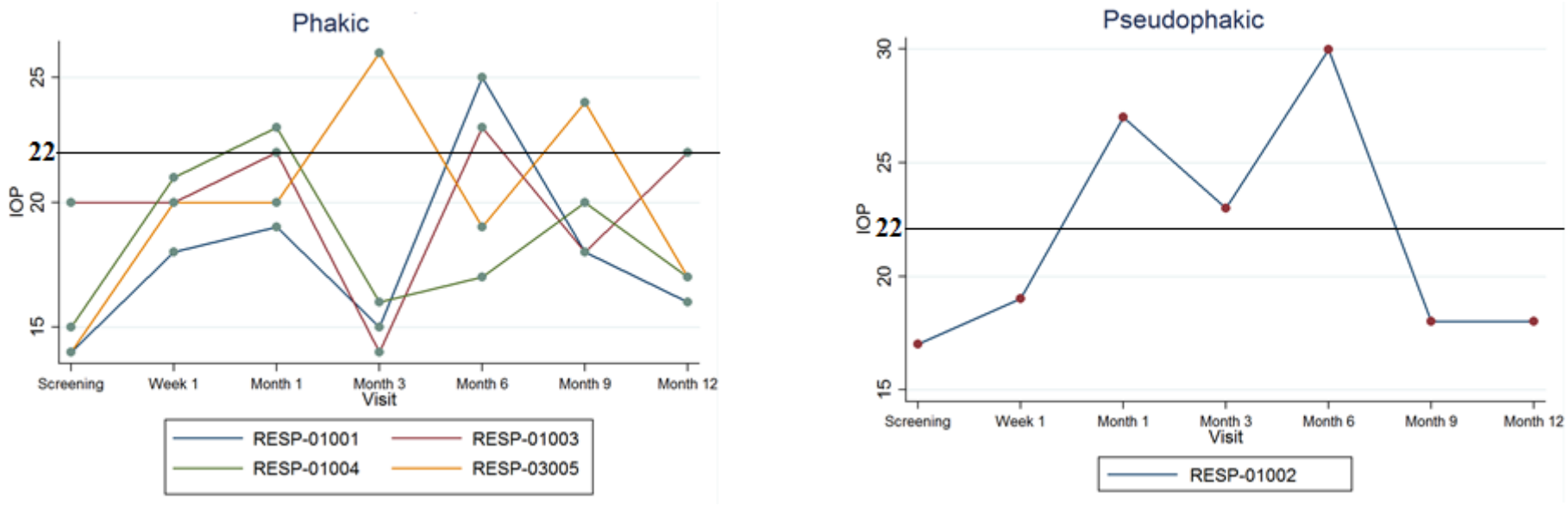


Figure 6. IOP of patients with Ocular hypertension adverse event, by lens status.

The patients with IOP over 22 mmHg were well controlled with eye drops.

The patient with cataract worsening underwent surgery showing improvement of the edema and visual acuity.

11.3 Deaths, other serious adverse events and other significant adverse events

No deaths occurred during the Study.

One serious adverse events (SAE) occurred (Myocardial infarction).

11.4 BCVA (letters)

In Table 34 and in Figure 7 are presented the results regarding BCVA (letters). No statistically significant differences were found from baseline to Month-12 (p=0.255).

In Figure 8 are presented the results regarding BCVA (letters), by lens status.

Table 34. BCVA (letters)

	Mean	*Sd*	*Min*	*Max*	*P50*	*P25*	*P75*	*p-value*[1]
Screening	48.75	10.86	26	61	50.5	41.5	58.5	
Week 1	53.58	12.14	27	76	55	48	60	
Month 1	54.58	12.09	27	74	57.5	46.5	61	
Month 3	55.5	16.42	15	79	60.5	49	65	0.255
Month 6	55.5	17.53	12	79	60.5	55.5	63	
Month 9	53.17	16.03	17	74	58	47	62	
Month 12	52.42	15.12	25	77	55.5	43	63	

[1] Wilcoxon signed-rank test between screening and month 12

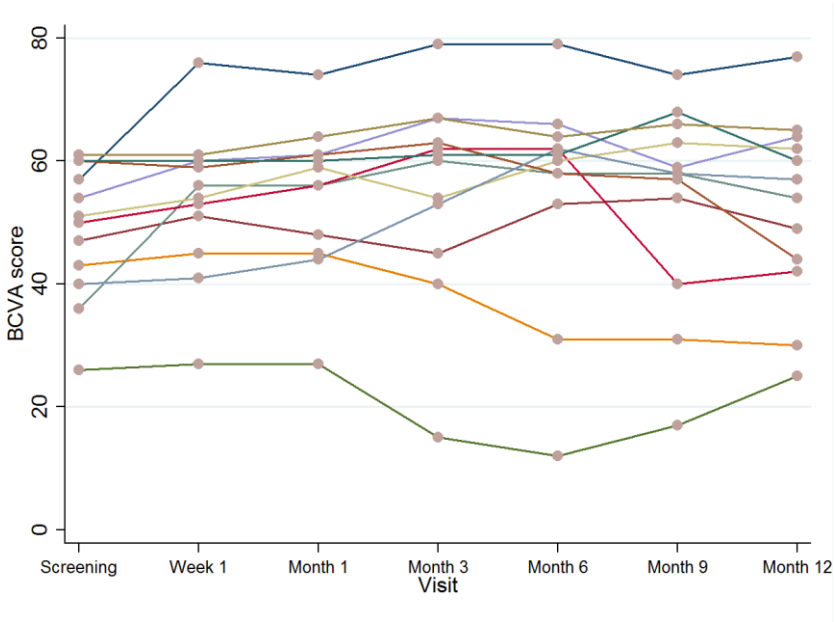


Figure 7. BCVA (letters), by patient.

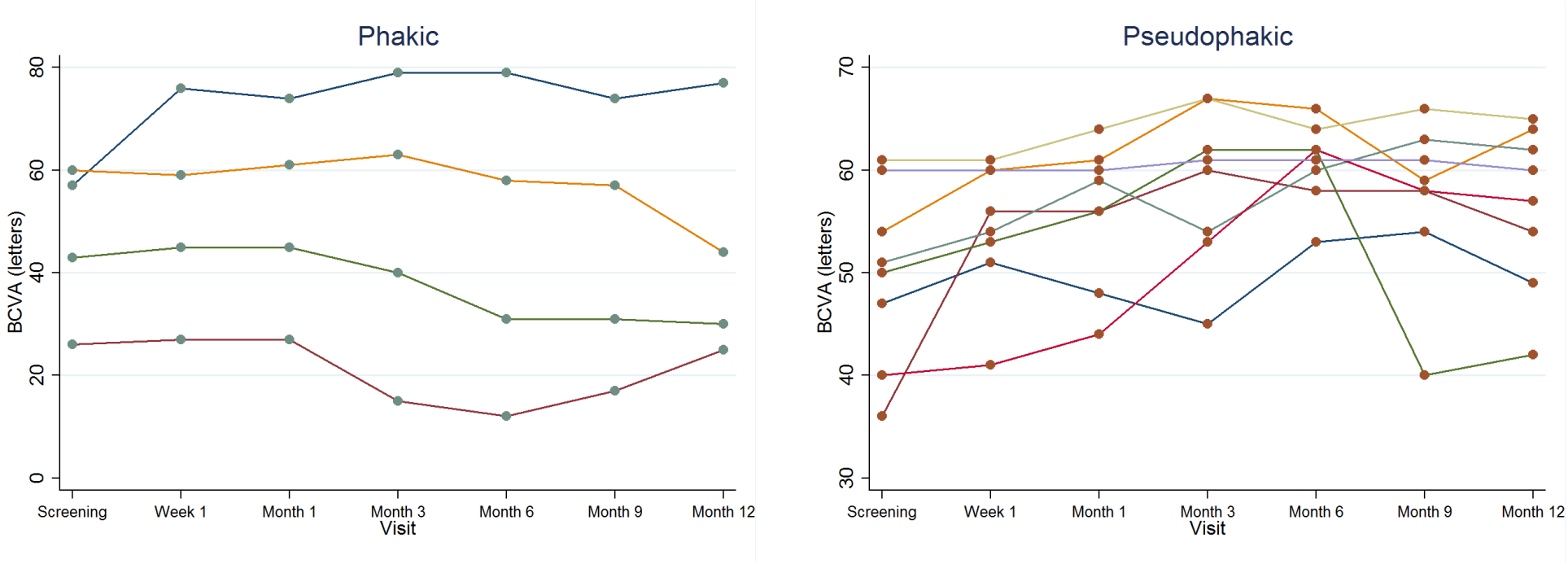


Figure 8. BCVA (letters), by patient and lens status.

11.5 Intraocular Pressure

In Table 35 and Table 36 and in Figure 9 are presented the safety results regarding the Intraocular Pressure measurement. Statistically significant differences were observed from baseline to Month-12 for IOP (p=0.005).

In Figure 10 are presented the results regarding the Intraocular Pressure measurement, by lens status.

Table 35. Intraocular Pressure measurement

	Mean	*Sd*	*Min*	*Max*	*P50*	*P25*	*P75*	*p-value*[1]
Screening	14.58	2.94	10	20	14.5	13	16.5	
Week 1	17	3.91	10	22	18.5	13.5	20	
Month 1	19.08	4.36	11	27	19.5	16.5	21.5	
Month 3	17.67	3.73	13	26	17.5	15	18.5	0.005
Month 6	19.83	4.53	14	30	19	17.5	22	
Month 9	17.25	3.25	12	24	18	15	18.5	
Month 12	17.17	2.21	14	22	17	15.5	18	

[1] Wilcoxon signed-rank test between screening and month 12

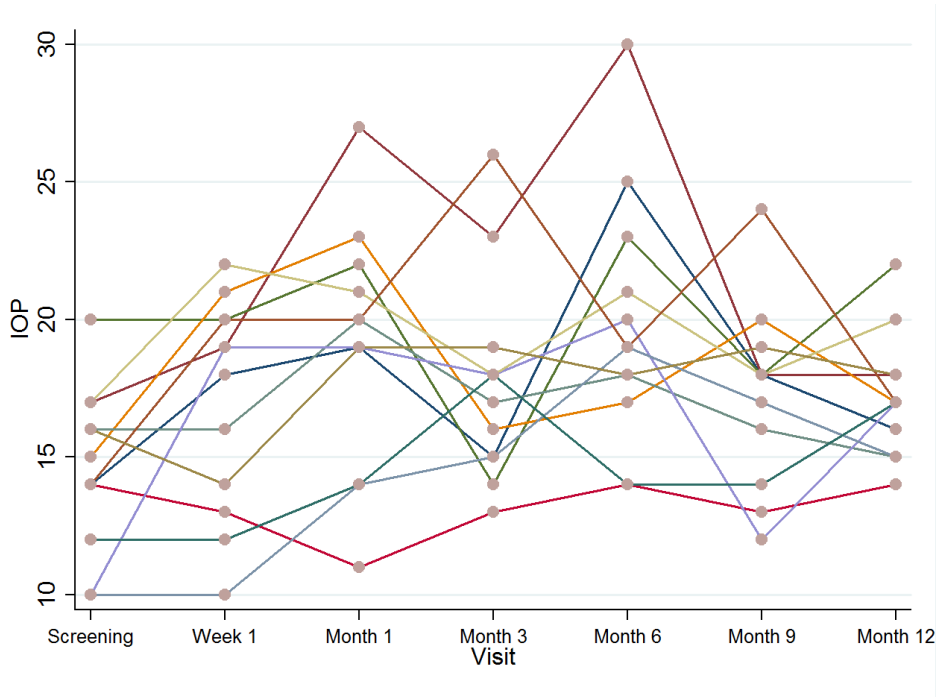


Figure 9. Intraocular Pressure measurement, by patient.

Table 36. Frequency table of Intraocular Pressure measurement, by visit

IOP	*Screening*		*Week 1*		*Month 1*		*Month 3*		*Month 6*		*Month 9*		*Month12*	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
≤22	12	100	12	100	10	83.3	10	83.3	9	75	11	91.7	12	100
>22	0	0	0	0	2	16.7	2	16.7	3	25	1	8.3	0	0
Total	12	100	12	100	12	100	12	100	12	100	12	100	12	100

The patients with IOP over 22 mmHg were well controlled with eye drops.

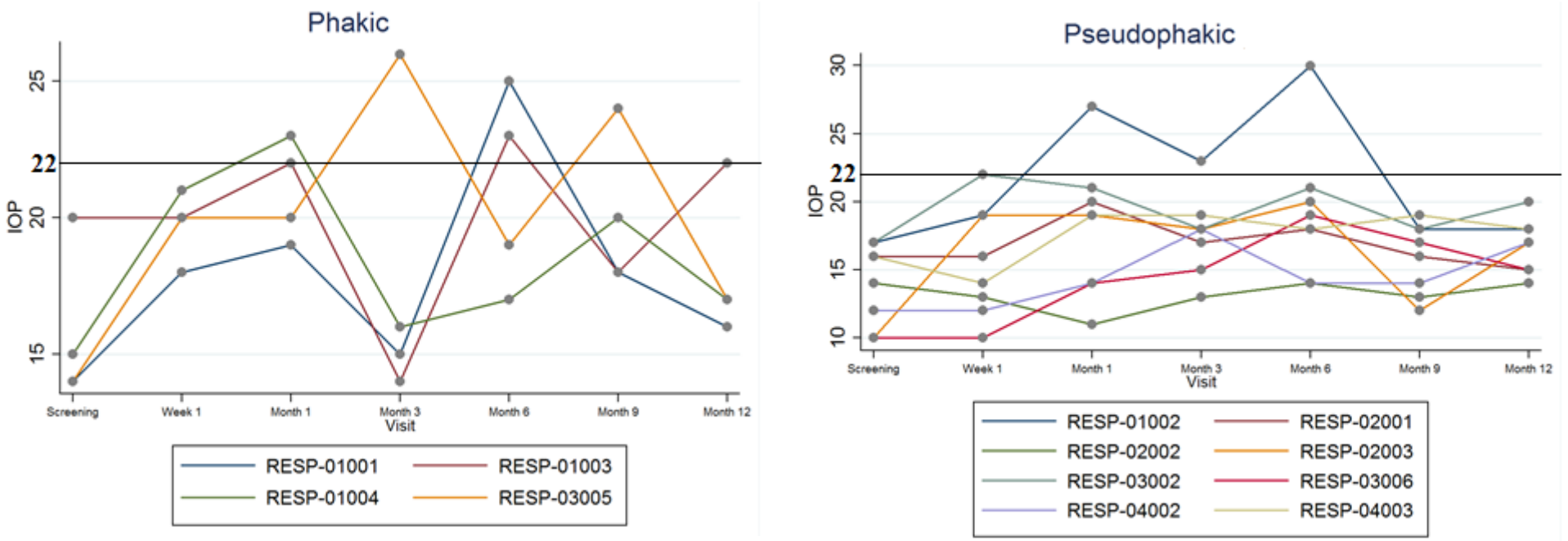


Figure 10. Intraocular Pressure measurement, by lens status.

11.6 Hemoglobin A_{1C}

In Table 37 are presented the results regarding Hemoglobin A_{1C}. No statistically significant differences were found from baseline to Month-12 (p=0.623).

Table 37. Hemoglobin A_{1C}

	Mean	*Sd*	*Min*	*Max*	*P50*	*P25*	*P75*	*p-value*[1]
Screening	6.87	1.25	5.4	8.8	6.6	5.8	8.5	0.623
Month 12	*6.9*	*1.14*	*5.5*	*9.2*	*6.8*	*5.8*	*7.9*	

[1] Wilcoxon signed-rank test between screening and month 12

11.7 Slit lamp examination

Slit lamp examination results are presented in Table 38.

Table 38. Slit lamp examination

	SCREENING		*WEEK 1*		*MONTH 1*		*MONTH 3*		*MONTH 6*		*MONTH 9*		*MONTH 12*	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Eye disorders	**3**	**60.0%**	**3**	**60.0%**	**3**	**60.0%**	**3**	**60.0%**	**3**	**60.0%**	**3**	**50.0%**	**3**	**50.0%**
Cataract nuclear	1	20.0%	1	20.0%	1	20.0%	1	20.0%	1	20.0%	1	16.7%	1	16.7%
Pterygium	1	20.0%	1	20.0%	1	20.0%	1	20.0%	1	20.0%	1	16.7%	1	16.7%
Corneal pigmentation	1	20.0%	1	20.0%	1	20.0%	1	20.0%	1	20.0%	1	16.7%	1	16.7%
Surgical and medical procedures	**2**	**40.0%**	**2**	**40.0%**	**2**	**40.0%**	**2**	**40.0%**	**2**	**40.0%**	**3**	**50.0%**	**3**	**50.0%**
Intraocular lens implant	2	40.0%	2	40.0%	2	40.0%	2	40.0%	2	40.0%	3	50.0%	3	50.0%
Total	**5**	**100.0%**	**5**	**100.0%**	**5**	**100.0%**	**5**	**100.0%**	**5**	**100.0%**	**6**	**100.0%**	**6**	**100.0%**

No safety concerns on slit lamp examinations were found.

11.8 Ophthalmoscopy

Ophthalmoscopy results are presented in Table 39.

Table 39. Ophthalmoscopy

	SCREENING		*WEEK 1*		*MONTH 1*		*MONTH 3*		*MONTH 6*		*MONTH 9*		*MONTH 12*	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Eye disorders	**22**	**73.3%**	**21**	**72.4%**	**21**	**72.4%**	**21**	**72.4%**	**21**	**72.41%**	**22**	**73.3%**	**22**	**73.3%**
Diabetic retinal oedema	7	23.3%	6	20.7%	5	17.2%	5	17.2%	5	17.2%	5	16.7%	5	16.7%
Diabetic retinopathy	7	23.3%	7	24.1%	7	24.1%	7	24.1%	7	24.1%	7	23.3%	7	23.3%
Macular fibrosis	2	6.7%	2	6.9%	2	6.9%	2	6.9%	2	6.9%	2	6.7%	2	6.7%
Macular oedema	1	3.3%	1	3.4%	2	6.9%	2	6.9%	2	6.9%	2	6.7%	2	6.7%
Retinal oedema	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	3.3%	1	3.3%
Vitreous degeneration	1	3.3%	1	3.4%	1	3.4%	1	3.4%	1	3.4%	1	3.3%	1	3.3%
Retinal haemorrhage	2	6.7%	2	6.9%	2	6.9%	2	6.9%	2	6.90%	2	6.7%	2	6.7%
Retinal aneurysm	1	3.3%	1	3.4%	1	3.4%	1	3.4%	1	3.45%	1	3.3%	1	3.3%
Retinal pigmentation	1	3.3%	1	3.4%	1	3.4%	1	3.4%	1	3.45%	1	3.3%	1	3.3%
Surgical and medical procedures	**7**	**23.3%**	**7**	**24.1%**	**7**	**24.1%**	**7**	**24.1%**	**7**	**24.1%**	**7**	**23.3%**	**7**	**23.3%**
Photocoagulation	3	10.0%	3	10.3%	3	10.3%	3	10.3%	3	10.3%	3	10.0%	3	10.0%
Retinal laser coagulation	4	13.3%	4	13.8%	4	13.8%	4	13.8%	4	13.8%	4	13.3%	4	13.3%
Investigations	**1**	**3.3%**	**1**	**3.4%**	**1**	**3.4%**	**1**	**3.4%**	**1**	**3.45%**	**1**	**3.3%**	**1**	**3.3%**
Optic nerve cup/disc ratio	1	3.3%	1	3.4%	1	3.4%	1	3.4%	1	3.45%	1	3.3%	1	3.3%
Grand Total	**30**	**100.0%**	**29**	**100.0%**	**29**	**100.0%**	**29**	**100.0%**	**29**	**100.0%**	**30**	**100.0%**	**30**	**100.0%**

No safety concerns on ophthalmoscopy examinations were found.

11.9 Concomitant medications and Therapies

Table 40 presents the list of all the concomitant medications.

Table 40. Concomitant medications

	N	*%*
ALIMENTARY TRACT AND METABOLISM	**25**	**28.7%**
DRUGS FOR ACID RELATED DISORDERS	**3**	**3.4%**
DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	3	3.4%
Proton pump inhibitors	3	3.4%
DRUGS USED IN DIABETES	**21**	**24.1%**
BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS	18	20.7%
Alpha glucosidase inhibitors	2	2.3%
Biguanides	4	4.6%
Combinations of oral blood glucose lowering drugs	5	5.7%
Dipeptidyl peptidase 4 (DPP-4) inhibitors	3	3.4%
Other blood glucose lowering drugs, excl. insulins	1	1.1%
Sulfonylureas	3	3.4%
INSULINS AND ANALOGUES	3	3.4%
Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting	2	2.3%
Insulins and analogues for injection, long-acting	1	1.1%
VITAMINS	**1**	**1.1%**
VITAMIN A AND D, INCL. COMBINATIONS OF THE TWO	1	1.1%
Vitamin D and analogues	1	1.1%
ANTIINFECTIVES FOR SYSTEMIC USE	**1**	**1.1%**
ANTIBACTERIALS FOR SYSTEMIC USE	**1**	**1.1%**
BETA-LACTAM ANTIBACTERIALS, PENICILLINS	1	1.1%
Combinations of penicillins, incl. beta-lactamase inhibitors	1	1.1%

BLOOD AND BLOOD FORMING ORGANS	**5**	**5.7%**
ANTITHROMBOTIC AGENTS	**5**	**5.7%**
ANTITHROMBOTIC AGENTS	5	5.7%
Platelet aggregation inhibitors excl. heparin	4	4.6%
Vitamin K antagonists	1	1.1%
CARDIOVASCULAR SYSTEM	**27**	**31.0%**
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	**11**	**12.6%**
ACE INHIBITORS, COMBINATIONS	2	2.3%
ACE inhibitors and calcium channel blockers	1	1.1%
ACE inhibitors and diuretics	1	1.1%
ACE INHIBITORS, PLAIN	4	4.6%
ACE inhibitors, plain	4	4.6%
ANGIOTENSIN II ANTAGONISTS, COMBINATIONS	2	2.3%
Angiotensin II antagonists and diuretics	2	2.3%
ANGIOTENSIN II ANTAGONISTS, PLAIN	3	3.4%
Angiotensin II antagonists, plain	3	3.4%
CALCIUM CHANNEL BLOCKERS	**3**	**3.4%**
SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS	3	3.4%
Dihydropyridine derivatives	3	3.4%
CARDIAC THERAPY	**1**	**1.1%**
VASODILATORS USED IN CARDIAC DISEASES	1	1.1%
Organic nitrates	1	1.1%
DIURETICS	**4**	**4.6%**
HIGH-CEILING DIURETICS	4	4.6%
Sulfonamides, plain	4	4.6%
LIPID MODIFYING AGENTS	**7**	**8.0%**

LIPID MODIFYING AGENTS, PLAIN	7	8.0%
HMG CoA reductase inhibitors	7	8.0%
PERIPHERAL VASODILATORS	**1**	**1.1%**
PERIPHERAL VASODILATORS	1	1.1%
Purine derivatives	1	1.1%
DERMATOLOGICALS	**3**	**3.4%**
ANTIFUNGALS FOR DERMATOLOGICAL USE	**1**	**1.1%**
ANTIFUNGALS FOR TOPICAL USE	1	1.1%
Other antifungals for topical use	1	1.1%
ANTIPSORIATICS	**2**	**2.3%**
ANTIPSORIATICS FOR SYSTEMIC USE	1	1.1%
Retinoids for treatment of psoriasis	1	1.1%
ANTIPSORIATICS FOR TOPICAL USE	1	1.1%
Other antipsoriatics for topical use	1	1.1%
GENITO URINARY SYSTEM AND SEX HORMONES	**1**	**1.1%**
UROLOGICALS	**1**	**1.1%**
DRUGS USED IN BENIGN PROSTATIC HYPERTROPHY	1	1.1%
Alpha-adrenoreceptor antagonists	1	1.1%
MUSCULO-SKELETAL SYSTEM	**3**	**3.4%**
ANTIGOUT PREPARATIONS	**1**	**1.1%**
ANTIGOUT PREPARATIONS	1	1.1%
Preparations inhibiting uric acid production	1	1.1%
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	**2**	**2.3%**
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS	2	2.3%
Other antiinflammatory and antirheumatic agents, non-steroids	1	1.1%
Propionic acid derivatives	1	1.1%

NERVOUS SYSTEM	**10**	**11.5%**
ANALGESICS	**1**	**1.1%**
OTHER ANALGESICS AND ANTIPYRETICS	1	1.1%
Anilides	1	1.1%
ANTIEPILEPTICS	**3**	**3.4%**
ANTIEPILEPTICS	3	3.4%
Fatty acid derivatives	1	1.1%
Other antiepileptics	2	2.3%
OTHER NERVOUS SYSTEM DRUGS	**1**	**1.1%**
ANTIVERTIGO PREPARATIONS	1	1.1%
Antivertigo preparations	1	1.1%
PSYCHOLEPTICS	**5**	**5.7%**
ANTIPSYCHOTICS	2	2.3%
Benzamides	1	1.1%
Diazepines, oxazepines, thiazepines and oxepines	1	1.1%
ANXIOLYTICS	3	3.4%
Benzodiazepine derivatives	2	2.3%
Diphenylmethane derivatives	1	1.1%
SENSORY ORGANS	**12**	**13.8%**
OPHTHALMOLOGICALS	**12**	**13.8%**
ANTIGLAUCOMA PREPARATIONS AND MIOTICS	9	10.3%
Beta blocking agents	5	5.7%
Carbonic anhydrase inhibitors	3	3.4%
Prostaglandin analogues	1	1.1%
ANTIINFECTIVES	1	1.1%
Fluoroquinolones	1	1.1%

ANTIINFLAMMATORY AGENTS	1	1.1%
Corticosteroids, plain	1	1.1%
ANTIINFLAMMATORY AGENTS AND ANTIINFECTIVES IN COMBINATION	1	1.1%
Corticosteroids and antiinfectives in combination	1	1.1%
Total	**87**	**100.0%**

11.9.1 Ocular Procedures

Table 41 presents the list of the ocular procedures.

Table 41. Ocular Procedures

	N	***%***
Surgical and medical procedures	**8**	**100.0%**
Cataract operation	1	12.5%
Intra-ocular injection	6	75%
Retinal laser coagulation	1	12.5%
Total	**8**	**100.0%**

11.10 Clinical laboratory evaluation

11.10.1 Listing of individual laboratory measurements by patient and each abnormal laboratory value

Table 42 and presents the list of individual laboratory measurements of HbA_{1C}, by patient and by visit.

Table 42. Individual laboratory measurements of HbA_{1C} at Screening and at Month 12, by patient [1]

Patient number	Screening	Month 12
RESP-01001	5.4 (Normal)	5.8 (Normal)
RESP-01002	6.5 (Normal)	**8.2 (Abnormal)**
RESP-01003	6.8 (Normal)	6.8 (Normal)
RESP-01004	**8.5 (Abnormal)**	6.2 (Normal)
RESP-02001	6.9 (Normal)	5.5 (Normal)
RESP-02002	5.6 (Normal)	6.6 (Normal)
RESP-02003	6.6 (Normal)	7 (Normal)
RESP-03002	5.8 (Normal)	5.8 (Normal)
RESP-03005	**8.8 (Abnormal)**	**9.2 (Abnormal)**
RESP-03006	6 (Normal)	6.9 (Normal)
RESP-04002	**8.7 (Abnormal)**	**7.9 (Abnormal)**
RESP-04003[2]	-	-

[1] HbA_{1c} considered abnormal if $HbA_{1c} \geq 7.5$

[2] Missing data

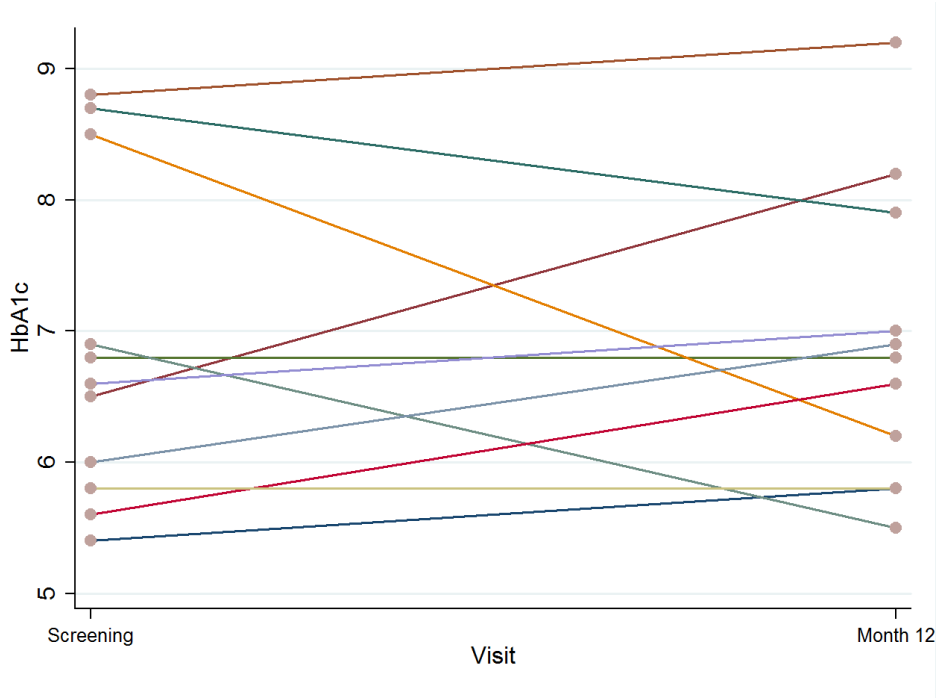


Figure 11. HbA_{1c}, by patient.

11.11 Safety conclusions

The most frequent AE that occurred during the study was Ocular hypertension (58.8% of AE).

No deaths occurred during the Study. One serious adverse events (SAE) occurred (Myocardial infarction).

Statistically significant differences were observed from baseline to Month-12 for IOP (p=0.005). The patients with IOP over 22 mmHg were well controlled with eye drops.

Improvements in BCVA from baseline to Month-12 (+3.7 letters) were not statistically significant (p=0.255).

No safety concerns on slit lamp and ophthalmoscopy examinations were found.

Regarding Hemoglobin A_{1C}, no statistically significant differences were found from baseline to Month-12 (p=0.623).

12 Discussion and overall conclusions

This study showed that, although no statistically significant differences were found from baseline to Month-12 (p=0.255), eyes with chronic DME not responding to prior therapies, showed improvements in BCVA (+3.7 letters), after ILUVIEN injection, with a greater BCVA improvement among pseudophakic patients (+6.8 letters) compared with phakic eyes (-2.5 letters).

Eyes also showed improvements in macular thickness (-292.83 µm) and in volume (-1.8 mm^3) from baseline to Month-12, and statistically significant differences were observed for central subfield thickness (p=0.003) and for macular volume (p=0.005). This improvement were observed in 92% of the patients.

Regarding safety, as expected, statistically significant differences were observed from baseline to Month-12 for IOP (p=0.005), but only five patients showed IOP over 22 mmHg during the study. These patients were all well controlled with eye drops.

The patient with cataract worsening underwent surgery showing improvement of the edema and visual acuity at the end of the study.

No deaths occurred during the Study. One serious adverse events (SAE), not related to treatment, occurred (Myocardial infarction).

Regarding Hemoglobin A_{1C}, no statistically significant differences were found from baseline to Month-12 (p=0.623).

This was the first study of this nature with ILUVIEN in Portugal, with patients with chronic DME not responding to prior therapies.

The reduced number of patients included in this exploratory study limited the conclusions, namely the statistical significance of results.

In conclusion, this prospective, non-randomized, multicentre, open-label phase 4 pilot study suggests that ILUVIEN is safe and may be considered effective for chronic DME patients considered insufficiently responsive to available therapies with or without intravitreal corticosteroid therapy.

13 Tables, figures and graphs referred to but not included in the text

All the tables are referred in the report.

14 Reference list

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15 Appendices

15.1 Study information

15.1.1 Protocol and protocol amendments

The following Protocol version and amendment is attached to this report:

Table 43. Protocol version and amendment

Protocol No.	*Version (date)*
4C-2014-06	1.0 (2014-09-24)

15.1.2 Sample case report form (unique pages only)

The sample Case Report Form is attached to this report.

15.1.3 List of IECs or IRBs

Table 44. List of IEC

Country	*Ethics Committee*
PORTUGAL	CEIC – Comissão de Ética para a Investigação Clínica Avenida do Brasil, 53 – Pav. 17-A 1749-004 Lisboa Portugal

15.1.4 List and description of investigators and other important participants in the study

Table 45. List and description of investigators in the study

Clinical Site	*Name*	*Role*
CEC - AIBILI	João Figueira	Coordinating Investigator
Hospital V. Franca de Xira	Miguel Amaro	Principal Investigator
Instituto Retina de Lisboa	José Henriques	Principal Investigator
Hospital S. João	Vítor Rosas	Principal Investigator

15.1.5 Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement

The protocol approval pages are attached to this report.

15.1.6 Audit certificates (if available)

Not applicable.

15.1.7 Documentation of statistical methods

The statistical methods are described in the main text of this report.

15.1.8 Publications based on the study

This Study has been presented in poster format by the Coordinating Investigator, João Figueira, at 17-20/09/2015 in the 15th EURETINA Congress, Nice, France; at 18/09/2015 in the Alimera Sciences Symposium, Nice, France; and at 01-05/05/2016 at ARVO – The Association for Research in Vision and Ophthalmology, Seattle, USA.

15.2 Patient data listings

15.2.1 Protocol deviations

Site	*Patient Number*	*Visit Number*	*Status*	*Deviation Description*
01	all	all	Closed	Subject numbers incorrectly created
02	all	all	Closed	Subject numbers incorrectly created
03	all	all	Closed	Subject numbers incorrectly created
02	RESP-02001	M3	Closed	Visit performed outside defined time window
02	RESP-02002	M1	Closed	Visit performed outside defined time window
02	RESP-02002	M3	Closed	Visit performed outside defined time window

02	RESP-02002	M6	Closed	Visit performed outside defined time window
02	RESP-02002	M9	Closed	Visit performed outside defined time window
02	RESP-02002	M12	Closed	Visit performed outside defined time window
03	RESP-03005	M12	Closed	Visit performed outside defined time window
04	RESP-04003	M3	Closed	Visit performed outside defined time window
04	RESP-04003	M6	Closed	Visit performed outside defined time window
04	RESP-04003	M9	Closed	Visit performed outside defined time window
04	RESP-04003	M12	Closed	Visit performed outside defined time window
02	all	all	Closed	Corneal Thickness not measured
02	all	all	Closed	Cup disk ratio not measured
02	all	Screening	Closed	DR severity not assessed.
02	all	M6	Closed	DR severity not assessed.
02	all	M12	Closed	DR severity not assessed.
02	RESP-02001	Screening	Closed	Patient did not perform at least 3 anti-VEGF treatments in the last 6 months
02	RESP-02002	Screening	Closed	Patient did not perform at least 3 anti-VEGF treatments in the last 6 months
02	RESP-02003	Screening	Closed	Patient did not perform at least 3 anti-VEGF treatments in the last 6 months
03	RESP-03002	Screening	Closed	Two of the last three anti-VEGF are prior to the last 6 months.
03	RESP-03005	Screening	Closed	One of the last three anti-VEGF are prior to the last 6 months.
03	RESP-03006	Screening	Closed	Patient did not perform at least 3 anti-VEGF treatments in the last 6 months
03	RESP-03006	Screening	Closed	The anti-VEGF are prior to the last 6 months.

03	all	all	Closed	Corneal Thickness not measured
03	RESP-03006	M12	Closed	Central subfield thickness and macular volume not measured.
04	all	all	Closed	Corneal Thickness not measured
04	all	all	Closed	Cup disk ratio not measured
04	RESP-04003	Screening	Closed	HbA1c not measured
04	RESP-04003	M12	Closed	HbA1c not measured

15.3 Disposition of Patients by Centre

Table 46. Patient disposition by Centre

Clinical Site	*Patients*	*Total*
AIBILI-CEC	Included	4
	Screening failures	0
	Drop outs	0
Hospital V. Franca de Xira	Included	3
	Screening failures	2
	Drop outs	0
Instituto Retina de Lisboa	Included	3
	Screening failures	0
	Drop outs	0
Hospital S. João	Included	2
	Screening failures	1
	Drop outs	0