STUDY REPORT

Prospective, randomized, multicenter, open label phase II study to access efficacy and safety of Lucentis® monotherapy (ranibizumab 0.5 mg intravitreal injections) compared with Lucentis® plus panretinal photocoagulation (PRP) and PRP (monotherapy) in the treatment of patients with high risk proliferative diabetic retinopathy

PROTOCOL Nº:	CRFB002DPT04T
ACRONYM:	Lucentis PDR
EudraCT Number / ClinicalTrials.gov Number:	2009-014409-15 / NCT01280929
SPONSOR:	AIBILI
REPORT VERSION Nº:	3.0
REPORT VERSION DATE:	30/10/2015

Investigator(s) : José Cunha-Vaz, João Figueira

According ICH-E3

Study Report

Approval			
Name	**Function**	**Institution**	**Date**
José Cunha-Vaz	President of Board of AIBILI and Coordinating Investigator	AIBILI	2015/10/30
João Figueira	Principal Investigator	AIBILI	2015/10/30

Authors / Reviewers			
Name	**Function**	**Role**	**Date**
Sandrina Nunes	4C Director	Reviewer	2015/10/30

Revision Log

Protocol Version	Section	Amendment	Reason for Changes	Date
0.0	All	---	Preliminary efficacy analysis. Version never released.	2014/07/18
1.0	All	---	Preliminary report. Version never released.	2014/08/18
2.0	All	---	Final Study Report.	2014/12/02
3.0	All	Efficacy and Safety evaluations were reviewed	During the elaboration of the study publication incoherence were detected on the primary outcome. Transcription errors were detected for the NVE and NVD parameters. Following SAE queries raised by Novartis, IMP holder, the safety section was updated.	2015/10/30
	2	Update of the Summary and Conclusions		
	6	Name of the statistician		
	9.5.1	Typo error		
	10.1	Update of the efficacy results		
	11.1	Update of the efficacy results	NVE, NVD and NV total reanalyed. NV regression results are presented in the primary efficacy analysis.	
	12.1;12.2; 12.3; 12.6	Update information on AE	Patient 0319 had one more AE	
	13	Update of the results		
	15	Update of the references		
	16.1.6	Copy of the publication of the study	The manuscript of the study was accepted for publication in the journal Ophthalmologica on 2015, October 28th.	

Clinical Study Report Approval Page

Protocol Number	CRFB002DPT04T

Study Title:

Prospective, randomized, multicenter, open label phase II study to access efficacy and safety of Lucentis® monotherapy (ranibizumab 0.5 mg intravitreal injections) compared with Lucentis® plus panretinal photocoagulation (PRP) and PRP (monotherapy) in the treatment of patients with high risk proliferative diabetic retinopathy

Clinical Study Report Approved by:

José Cunha-Vaz (President of Board of AIBILI and Coordinating Investigator)	Date
João Figueira (Principal Investigator)	Date

1 Table of contents for the individual clinical study report

2 Synopsis

Sponsor-Investigator Prof. Dr. José Cunha-Vaz, AIBILI	
Name of Finished Product: Lucentis®, Standard panretinal photocoagulation (PRP).	
Name of Active Ingredient: 0.5 mg ranibizumab intravitreal injection	
Title of Study: Prospective, randomized, multicenter, open label phase II study to access efficacy and safety of Lucentis® monotherapy (ranibizumab 0.5 mg intravitreal injections) compared with Lucentis® plus panretinal photocoagulation (PRP) and PRP (monotherapy) in the treatment of patients with high risk proliferative diabetic retinopathy	
Investigators: José Cunha-Vaz, João Figueira, José Henriques, Paulo Rosa, Rufino Silva	
Study centre(s): AIBILI Clinical Trial Centre (AIBILI-CEC) Espaço Médico de Coimbra (EMC) Instituto de Retina de Lisboa (IRL) Instituto Oftalmológico Gama Pinto (IOGP) ALM Oftalmolaser (ALM) CUF Porto (CUF) Hospital São João (HSJ)	
Publication (reference): Not applicable	
Studied period (years): three years **First enrolment:** 11 Nov. 2010 **Last completed:** 13 Nov. 2013	**Phase of development:** Phase II study
Objectives: The purpose of this trial was to evaluate safety and to compare the efficacy of intravitreous injection of ranibizumab alone (0.5 mg), versus combination of intravitreous injection of ranibizumab (0.5 mg) plus PRP, versus PRP alone in the regression of retinal neovascularization (NV) in eyes with high-risk proliferative diabetic retinopathy (HR-PDR)	
Methodology: This was a prospective, randomized, multicenter, open label, phase II study to access efficacy and safety of Lucentis® monotherapy (ranibizumab 0.5 mg intravitreal injections) (Group 2) compared with Lucentis® plus PRP (Group 3) and PRP (monotherapy) (Group 1) in the treatment of patients with HR-PDR.	
Number of patients (planned and analysed): Planned 54 patients (18 patients in each arm). Included 35 patients in only 4 clinical centres (AIBILI-CEC, EMC, IRL and IOGP). Analysed 35 patients.	
Diagnosis and main criteria for inclusion: Type I, or Type II diabetic subjects as defined by the WHO criteria of either, gender, and aged ≥ 18 years. HR-PDR eyes. Best corrected Visual Acuity (BCVA) at screening > 20/320 (25 letters in the ETDRS Chart) in the study eye. Clear ocular media and adequate pupillary dilatation to permit good quality fundus photography. Intraocular pressure < 21 mmHg.	
Test product, dose and mode of administration, batch number: Group 2: Trial subjects received intravitreous injections of ranibizumab (0.5 mg) every 4 weeks for a total of 3 injections at month-0, month-1 and month-2. For the next 10 months period of follow-up, if NV didn't showed regression or if there was a recurrence, subjects should receive additional injections at minimum of 4 weeks interval. If after the first 3-month period (loading phase), no signs of NV regression were observed, rescue treatment with PRP was given to the patient. Group 3: Trial subjects received a combination treatment of ranibizumab intravitreous injections plus PRP (2 weeks ± 1 week after injection), at month-0, month-1 and month-2. For the next 10 months period of follow-up, subjects should receive additional combination treatments, if NV regression was not completed and/or if there was a recurrence. The injections interval had a minimum of 4 weeks.	
Duration of treatment: One year (12 months)	
Reference therapy, dose and mode of administration, batch number: Group 1: The control eyes group received the standard photocoagulation care (PRP) at month-0, that can be repeated, after the first 3-months period, during the 12 months of follow-up according to the ETDRS study protocol.	

Criteria for evaluation:
All patients included in the study were used for the Intent to Treat (ITT) population analysis.
All patients which concluded the study were used for Per Protocol (PP) population analysis.
Efficacy:
BCVA assessments using the ETDRS charts at a test distance of 4 meters.
Optical coherence tomography (OCT) - to assess the central macular thickness (CMT).
Color Fundus photography (CFP) - to measure the NV area
Fluorescein angiography (FA) - to measure the NV area
Use of rescue treatment
Safety:
BCVA assessments using the ETDRS charts at a test distance of 4 meters
Ophthalmic examinations (slit lamp exam with biomicroscopy, fundus exam and intra ocular pressure)
Adverse events (ocular and non-ocular)

Statistical methods: Categorical variables are summarized with frequencies and percentages and numerical variables with mean, standard deviation, minimum, maximum, median and interquartile range.
A univariate analysis was performed to test statistically significance differences between study groups. The Exact Fisher test was used for categorical variables, and the Kruskal-Wallis test was used for continuous variables. To compare the evolution between visits for the NV area, BCVA and CMT the Wilcoxon test and Friedman test were used. Pairwise comparisons were performed with Bonferroni correction.

SUMMARY - CONCLUSIONS
This study showed that combined therapy (PRP+ITV group) resulted in a higher proportions of eyes with NV regression one year after the beginning of the trial but this effect was not significantly different from the remaining treatment arms which may be due to the small number of patients enrolled in the study. The occurrence of severe vitreous haemorrhage or PDR-related complications requiring vitrectomy was more frequent in eyes assigned to PRP monotherapy (30.8%). Finally, the eyes with high-risk NV assigned to ITV monotherapy did not need any laser rescue treatment during the twelve month period of follow-up.
Altogether these results suggest that ranibizumab may have a place in the treatment of NV by itself or as an adjuvant to PRP at least in diabetic type 2 patients.
Data from NVE and NVD regression was analyzed separately. We believe that the clinical implications and prognosis of these two types of NV are quite different (Rand et al., 1985) (Duh, 2008). The percentage of regression achieved was higher for NVE than NVD.
Regarding the occurrence of severe vitreous haemorrhage and/or PDR-related complications it was higher in PRP monotherapy group with a higher frequency of VH of any severity grade in the same eyes.
It is of major relevance that none of the eyes in the ITV monotherapy group needed rescue pan-retinal photocoagulation treatment. ITV showed efficacy in controlling the NV by itself during the twelve month period of the study. Considering the side effects on vision of pan-retinal photocoagulation, ITV monotherapy appears as an interesting alternative, at least for the initial period of twelve months.
Most of the ITV eyes required 5 injections (50%), but the median number did not differ significantly for eyes with combined therapy. Regarding the number of PRP performed sessions, it did not also vary significantly between eyes treated with PRP alone and PRP+ITV.

In summary:
This randomized controlled trial suggested suggests that intravitreal ranibizumab is safe and may be considered as a therapy for high-risk proliferative diabetic retinopathy eyes. The results obtained using ITV alone or in combined therapy are comparable or better than PRP alone. It remains to be demonstrated if this beneficial effect can be sustained for periods longer than twelve months.

Date of the report: 30/10/2015

3 List of tables and list of figures

List of tables

List of figures

4 List of abbreviations and definition of terms

AE	Adverse Event
BCVA	Best Corrected Visual Acuity
BMI	Body Mass Index
BPM	Beats Per Minute
CRF	Case Report/Record Form
CORC	Coimbra Ophthalmology Reading Center
DA	Disc Area
DBP	Diastolic Blood Pressure
DME	Diabetic Macular Edema
ETDRS	Early Treatment Diabetic Retinopathy Study
FPFV	First Patient First Visit
HbA_{1C}	Haemoglobin A1C
hCG	Human Chorionic Gonadotropin
HR	High-Risk
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IQR	Interquartile Range
IOP	Intraocular Pressure
IUD	Intrauterine Device
ITV	Intravitreal Injection
IRB	Institutional Review Board
LPLV	Last Patient Last Visit
NVD	Neovascularization if the Disc
NVE	Neovascularization Elsewhere
NYHA	New York Heart Association
OCT	Optical Coherence Tomography
PDR	Proliferative Diabetic Retinopathy
PRP	Panretinal Photocoagulation
SAE	Serious Adverse Event
SD	Standard Deviation
SBP	Systolic Blood Pressure
SmPC	Summary of Product Characteristics

VEGF	Endothelial Growth Factor
YAG	Yttrium Aluminium Garnet
WHO	World Health Organization

5 Ethics

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

The study and any amendments were reviewed by the National Independent Ethics Committee CEIC – Comissão de Ética para a Investigação Clínica.
The study was additionally approved by:

a. The National Data Protection Committee, CNPD – Comissão Nacional de Protecção de Dados.
b. The National Competent Authorithy (CA), INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.

Approvals are provided in appendix.

5.2 Ethical conduct of the study

This clinical study was designed, implemented and reported in accordance with the International Conference on Harmonization Harmonized Tripartite Guidelines for Good Clinical Practice (ICH-GCP), 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.

5.3 Patient information and consent

Informed consent was obtained from each subject in writing before any study procedures. The study was described by a study coordinator and/or investigator, who answered any questions, and written information was also provided. Samples of the written information were given to each subject.

A sample of the patients' information and consent form is provided in appendix.

6 Investigators and study administrative structure

The administrative structure is found below (e.g. principal investigator, affiliations and qualifications, other important staff, and Coordinating Center team).

Study Personnel

Coordinating Investigator	José Cunha-Vaz
Principal Investigators	AIBILI-CEC: João Figueira EMC: Rufino Silva IRL: José Henriques IOGP: Paulo Rosa ALM: Monteiro Grilo (no patient recruited) CUF: Ângela Carneiro (no patient recruited) HSJ: Ângela Carneiro (no patient recruited)
Coordinating Center	4C
Responsible	Sandrina Nunes
Study Statistician	Pedro Mota Veiga, Sandrina Nunes
Study Data Manager	Sónia Simões
Study Manager	Ana Pedroso
Study Monitors	Ana Pedroso / Sónia Simões
Central Reading Centre	CORC

The protocol and protocol approval page are provided in appendix.

The site personnel is described in the delegation of duties of the clinical centre in appendix.

The principal investigator approval page if provided in appendix.

7 Introduction

PRP can cause regression of retinal NV and reduce the risk of severe vision loss in people with PDR. However, this destructive treatment may be associated with side effects (e.g. pain, transient blurring, loss of peripheral and/or night vision, increased risk of macular edema and central vision loss) and it is not always efficient in the regression of the NV.
VEGF has been shown to play a role in retinal NV and retinal vascular leakage related with PDR and Diabetic Macular Edema (DME).
Anti-VEGF treatments have been hypothesized as an alternative adjunctive treatment for the management of retinal NV and macular edema related with Diabetic Retinopathy (DR).
There are few reports of retinal traction detachment in patients with PDR and fibrovascular proliferation (although it is infrequent). However, from previous clinical experience, we hypothetic that the risk of detachment only exists when there is in place a fibrovascular proliferation with retinal traction previous to the injection.

The Macugen Diabetic Retinopathy Study Group reported that during the clinical trial testing pegaptanib in the treatment of DME, most subjects with retinal NV at screening assigned to pegaptanib showed regression of NV by week 36 [Adamis, 2006]. These findings suggest a direct effect of pegaptanib upon retinal NV in patients with diabetes mellitus.
Gonzalez *et al.* ([Gonzalez, 2007] and [Gonzalez, 2009]) performed a clinical trial comparing the regression of PDR, in 10 eyes treated with pegaptanib, versus 10 eyes treated with PRP, and concluded that pegaptanib appears to effectively induce regression of PDR and decrease the anatomic extent of DME. Use of pegaptanib may reduce the need for and/or extent of PRP in PDR thus optimizing therapeutic results while diminishing iatrogenic effects inherent to retinal ablation.

In a previous study we injected ranibizumab prior to surgery in patients with severe PDR, that were submitted later to a posterior vitrectomy, to reduce NV and minimize the risk of an intraoperatory haemorrhage caused by the manipulation of the fibrovascular membranes. In total, we injected and submitted to surgery 15 eyes with the above mentioned condition, with excellent results. The results of the first 10 eyes were presented in 2008 in the congress of the Portuguese Society of Ophthalmology (Figueira J., 51º Congresso Português de Oftalmologia, Dez. 2008, Porto, Portugal).

This study was designed to evaluate the safety and determine the efficacy of ranibizumab (0.5 mg) in monotherapy, PRP monotherapy or combination therapy (ranibizumab 0.5 mg plus PRP) in patients with Type I or Type II diabetes mellitus and with HR-PDR.

Where HR-PDR was defined as:

- NV in de Disc (NVD) ≥ 1/4 DA (disc area) or NV elsewhere (NVE) ≥ 1/2 DA or
- NVE < 1/2 DA + vitreous and/or pre-retinal haemorrhage and/or rubeosis and/or traccional retinal detachment.
- NVD <1/4 DA + vitreous and/or pre-retinal haemorrhage and/or rubeosis and/or traccional retinal detachment.

Data from this study will be used to support Portuguese Guidelines for the treatment of Type I or Type II diabetes mellitus patients at HR-PDR.

8 Study objectives

The primary objective of this study was to demonstrate superiority of one of the treatment groups: ranibizumab 0.5 mg monotherapy, PRP monotherapy or combination therapy (ranibizumab 0.5 mg plus PRP) over a 12-month treatment period in the following:

1. Regression of NV.

Regression of NV from screening to the 12 months visit (primary endpoint), was measured by an independent reading center in disc area (DA) units (decimal DA units), based on CFP (retinography) and FA.
Regression of NV was defined as any decrease in the area of NV.

Secondary objectives were:

1. Changes from screening in BCVA
2. Changes from screening in macular retinal thickness (CMT) by OCT
3. Recurrence of NV
4. Number of treatments needed
5. Additional focal or grid laser for DME
6. Drug safety profile
7. Need for vitrectomy due to occurrence of vitreous haemorrhage or retinal detachment relative to the three treatment groups.

9 Investigational plan

9.1 Overall study design and plan-description

This was a prospective, randomized, multicenter, open label, phase II study to access efficacy and safety of Lucentis® monotherapy (ranibizumab 0.5 mg intravitreal injections) compared with Lucentis® PRP and PRP (monotherapy) in the treatment of patients with HR-PDR.

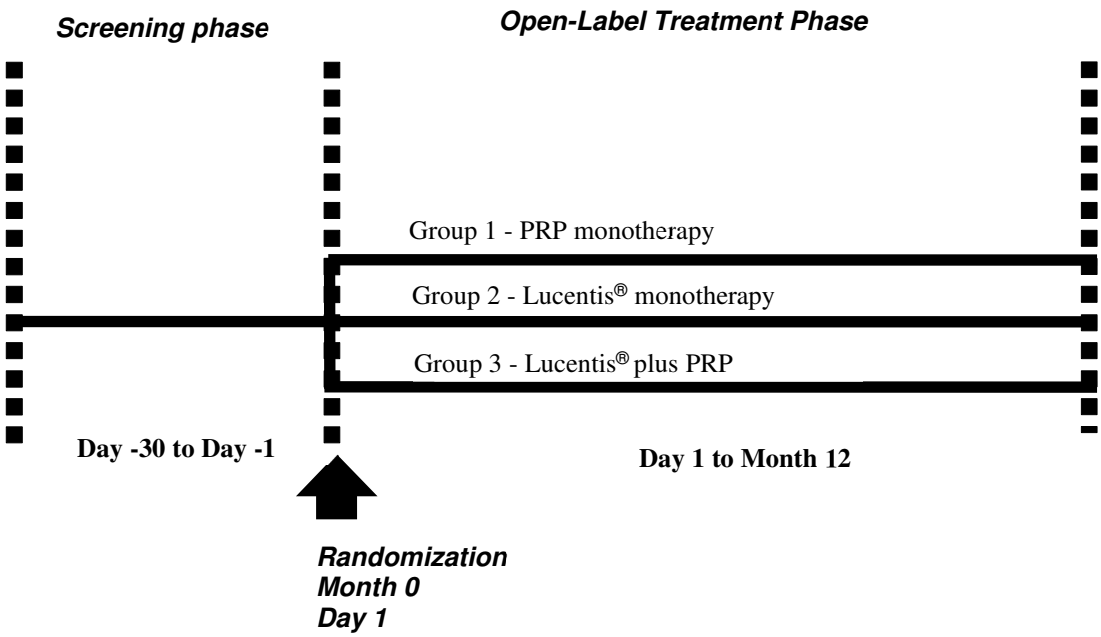
Patients who signed informed consent participated in a screening period, lasting 1 to 30 days, to evaluate patient eligibility.

If patient's eligibility was confirmed, patients were randomized at month 0 in a 1:1:1 ratio to one of the three treatment groups, i.e. standard photocoagulation (PRP) (Group 1), ranibizumab (0.5 mg) intravitreal injections (Group 2), or combination treatment of ranibizumab (0.5 mg) intravitreal injections plus PRP (Group 3) for 12 months (Fig.9-1).

Randomized patients entered a treatment phase during 12 months. Visits to assess safety and efficacy were scheduled at 4 week intervals (monthly visits) during the period of the study. The assessment to address the primary objective was performed at screening, at the end of months 3, 6 and 12.

Patients that withdrawn from the study prior to completion of the 12-month treatment phase were asked to return at month 12 for a final evaluation.

Figure 9-1 Study design



9.2 Discussion of study design, including the choice of control groups

The control group (Group 1 – PRP) was chosen based on the standard treatment for HR-PDR. A loading dose of 3 intravitreal injections during the first 3 months was considered for the study groups (Group 2 and Group 3) because it is the recommended loading dose for patients treated with Lucentis ®. The monthly follow-up was chosen in order to follow and evaluate the disease evolution and any potential need of treatment. Efficacy was assessed only after month-3 because this is the time needed for treatment effect.

9.3 Selection of study population

The study population was recruited by each principal investigator from their clinical practice. The study population consisted of a representative group of male and female outpatients (≥ 18 years old) who met all the following inclusion and none of the exclusion criteria.

9.3.1 Inclusion criteria

Patients eligible for inclusion in this study fulfill all of the following criteria:

1. HR-PDR eyes (as defined in section 7).
2. BCVA at screening > 20/320 (25 letters in the ETDRS Chart) in the study eye.
3. Clear ocular media and adequate pupillary dilatation to permit good quality fundus photography.
4. Intraocular pressure < 21 mmHg.

GENERAL CRITERIA

5. Type I, or Type II diabetic subjects as defined by the WHO criteria of either gender, and aged ≥ 18 years.
6. Women must be using effective contraception, be post-menopausal for at least 12 months prior to trial entry, or surgically sterile.
7. Ability to provide written informed consent.
8. Ability to return for all trial visits.

9.3.2 Exclusion criteria

Patients eligible for inclusion in this study fulfill none of the following criteria:

1. Eyes with prior scatter (panretinal) or focal/grid photocoagulation, within the previous 6 months.
2. Fibrovascular proliferation with retinal traction.
3. Other cause of retinal NV (retinal vein occlusion, radiation retinopathy or others).
4. Atrophy/scarring/fibrosis/ hard exudates involving the center of the macula.
5. Subjects who have received YAG laser, or peripheral retinal cryoablation, or laser retinopexy (for retinal tears only), or focal/grid photocoagulation, within the previous 6 months.

6. Significant media opacities, which might interfere with visual acuity, assessment of toxicity or fundus photography.
7. Subjects should not be entered if there is likelihood that they will require cataract surgery within the following 1 year.
8. Any intraocular surgery within 6 months before trial enrolment.
9. Previous vitrectomy.
10. HbA_{1C} level $\geq$11% or recent signs of uncontrolled diabetes.
11. Any of the following underlying systemic diseases:

    • History or evidence of severe cardiac disease, e.g. NYHA Functional Class III or IV, clinical or medical history of unstable angina, acute coronary syndrome, myocardial infarction, or revascularization procedure within 6 months prior to screening, or ventricular tachyarrhythmia requiring treatment.

    • History or evidence of clinically significant peripheral vascular disease such as intermittent claudication or prior amputation.

    • Clinically significant impaired renal function (serum creatinine >2.5 mg/dL or s/p renal transplant or receiving dialysis).

    • Clinically significant impaired hepatic function.

    • Stroke (within 12 months of trial entry).

    • Any major surgical procedure within one month before trial enrolment.

12. Previous radiation to the head in the region of the study eye.
13. Any prior treatment with an investigational agent for diabetic retinopathy or anti-VEGF therapy (including intravitreal, subconjunctival or subtenons corticosteroids) during the past 90 days for any other condition.
14. Known serious allergies to fluorescein used in angiography, or to components of Lucentis® formulation.
15. Systolic BP > 170 mmHg (2 different readings) or diastolic BP > 100 mmHg (2 different readings).
16. Acute ocular or periocular infection.
17. Previous filtering surgery (e.g., trabeculectomy) or placement of a glaucoma drainage devise (e.g., tube-shunt surgery).
18. Use of other investigational drugs at the time of enrollment.
19. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
20. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
21. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL).

22. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant UNLESS they are: women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner; women whose partners have been sterilized by vasectomy or other means 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 was maintained throughout the study and for 30 days after study drug discontinuation.

No additional exclusions were applied by the investigator, in order to ensure that the study population was representative of all eligible patients.

9.3.3 Removal of patients from therapy or assessment

If a patient discontinued prematurely the study at any time either at his or her request or at the investigator's discretion, the reason(s) for withdrawal was recorded on the relevant page of the Case Report Form (CRF) and source document. Patients who withdraw from the study prematurely underwent a termination visit (at month-12), if possible.

If such withdrawal occurred, or if the patient fails to return for visits, the investigator determined the primary reason for a patient's premature withdrawal from the study and recorded this information on the CRF.

Patients could be withdrawn at any time if the investigator concluded that it was in the patient's best interest for any reason. Protocol violations do not lead to patient withdrawal unless they indicate a significant risk to the patient's safety.

Patients could voluntarily withdraw from the study for any reason at any time. They were considered withdrawn if they state an intention to withdraw, or fail to return for visits, or become lost to follow-up for any other reason

9.4 Treatments

9.4.1 Treatments administered

Patients were assigned to one of the following three treatment groups in a ratio of 1:1:1, i.e.:

- Group 1: Control eyes group receiving the standard photocoagulation care (PRP) at month-0, that can be repeated, after the first 3-months period, during the 12 months of follow-up according to the ETDRS study protocol.
- Group 2: Trial subjects receiving intravitreous injections of ranibizumab (0.5 mg) every 4 weeks for a total of 3 injections at month-0, month-1 and month-2. For the next 10 months period of follow-up, if NV didn't showed regression or if there was a recurrence, subjects should receive additional injections at minimum of 4 weeks interval. If after the first 3-month period (loading phase), no signs of neovascularization regression were observed, rescue treatment with PRP was given to the patient.

- Group 3: Trial subjects receiving a combination treatment of ranibizumab intravitreous injections plus PRP (2 weeks ± 1 week after injection), at month-0, month-1 and month-2. For the next 10 months period of follow-up, subjects should receive additional combination treatments, if NV regression was not completed and/or if there was a recurrence. The injections interval had a minimum of 4 weeks.

9.4.2 Identity of investigational product(s)

- 0.5 mg ranibizumab (labeled Lucentis® 0.5mg/0.05ml)
- Panretinal laser photocoagulation (PRP)

Ranibizumab was used according to the Summary of Products Characteristics (SmPC).

Ranibizumab is formulated as a sterile solution aseptically filled in a sterile glass vial. Each vial contains ranibizumab in an aqueous solution (pH 5.5) with histidine, trehalose, and polysorbate 20. The vial contains no preservative and is suitable for single use only. Ranibizumab was stored according to the label instructions contained on the Specific SmPC for Portugal and was kept in a secure locked facility.

Once it was used marketed Lucentis®, each vial was labeled with the appropriate information stating that the medication was for use in this clinical trial only. Medication labels complied with the legal requirements and were printed in the local language. The storage conditions for study drug was described on the medication label.

Additionally was stamped outside the Lucentis® box a label with the statement that the medication was intended to be used only in the designed clinical trial and that one vial was used for one patient only.

Each center was provided with sufficient supplies of ranibizumab for treatment use to allow completion of the study.

The laser treatment technique was applied following ETDRS guidelines to a particular patient was at the discretion of the treating physician.

9.4.3 Method of assigning patients to treatment groups

At Visit 2, month-0, all patients who fulfill all the inclusion/exclusion criteria were given the lowest available number on the randomization list. This number assigns them to one of the treatment groups. The investigator entered the randomization number on the CRF.

The randomization numbers were generated using a procedure to ensure that treatment assignment was unbiased and concealed from patients and investigator staff. A randomization list was produced by AIBILI using a validated system that automates the random assignment of treatment groups to randomization numbers in the specified ratio.

The randomization scheme was reviewed by Biostatistics Personnel and locked by them after approval.

Each site received initially 3 numbered envelopes corresponding to three treatments/randomization numbers. After confirmed patient eligibility, investigator opened the envelope with the lowest randomization number to assign a treatment to a patient. The opened envelope was signed and dated by the investigator. Patient number and initials was written on

the opened envelope to confirm assignment of this specific treatment to a specific patient. Once a envelope was assigned to a patient it was not reused.

The randomization number was recorded on the CRF.

9.4.4 Selection of doses in the study

The selection of doses in the study was done according to the Lucentis® SmPC.

9.4.5 Selection and timing of dose for each patient

The selection of doses in the study was done according to the Lucentis® SmPC.

- Group 2: Trial subjects received intravitreous injections of ranibizumab (0.5 mg) every 4 weeks for a total of 3 injections at month-0, month-1 and month-2. For the next 10 months period of follow-up, if NV didn't showed regression or if there was a recurrence, subjects received additional injections at minimum of 4 weeks interval. If after the first 3-month period (loading phase), no signs of NV regression were observed, rescue treatment with PRP was given to the patient.
- Group 3: Trial subjects received a combination treatment of ranibizumab intravitreous injections plus PRP (2 weeks ± 1 week after injection), at month-0, month-1 and month-2. For the next 10 months period of follow-up, subjects received additional combination treatments, if NV regression was not completed and/or if there was a recurrence. The injections interval had a minimum of 4 weeks.

9.4.6 Blinding

This was a randomized, open-label study. Blinding was not applicable.

9.4.7 Prior and concomitant therapy

Any concomitant medications including prescription drugs or over-the-counter preparations used by a patient since the date of enrolment (screening visit) until the conclusion of the study participation (except for routine medications given for ocular procedures required by the protocol, i.e. fluorescein, dilating drops, topical antibiotic, topical anesthetic) were recorded on the Concomitant medications CRF page including start and stop dates and reason for use.

The following treatments were not allowed during the study (for both eyes):

- Treatment with anti-angiogenic drugs (pegaptanib sodium, anecortave acetate, bevacizumab, etc.) or intravitreal corticosteroids in either eye.
- Systemic medications known to be toxic to the lens, retina or optic nerve, including Deferoxamine, Chloroquine/ hydroxychloroquine (Plaquenil), Tamoxifen, Phenothiazines and Ethambutol.
- Treatment with glitazones when newly started during the study.

Concerning the fellow eye, the following treatment was not allowed during the study:

- Anti-VEGF therapy.

The fellow eye may only receive gold standard (laser photocoagulation) for the treatment of PDR or DME.

The investigator instructed the patient to notify the study site about any new medications he/she took after the start of the study. All medications (other than study drug and routine medications given for ocular procedures required by the protocol) and significant non-drug therapies (including physical therapy and blood transfusions) administered after visit 1 and after the patient starts treatment with study drug was recorded on the Concomitant medications CRF page.

9.4.8 Treatment compliance

Treatment was performed at site. Treatment compliance was not applicable.

9.5 Efficacy and safety variables

9.5.1 Efficacy and safety measurements assessed and flow chart

Table 9 1 lists all of the assessments performed during the study and indicates with an "X" the visits when they were performed and with an "(X)" the visits were treatment could be performed if needed.

Patients should be seen for all visits on the designated day or as close as possible.

At a minimum, patients were contacted for safety evaluations during the 30 days following the last dose of study drug or last completed visit (whichever is later), including final contact at the 30-day point. Documentation of attempts to contact the patient were recorded in the patient record.

For group 2 safety contacts were performed up to 1 year after completing the study.

Efficacy assessments

The following assessments were performed to assess ranibizumab efficacy on retinal structure, visual function and NV:

- BCVA with ETDRS chart at 4 meters,
- OCT,
- CFP,
- FA,
- Use of rescue treatment.

Safety assessments

Safety assessments consisted of monitoring and recording all adverse events (ocular and non-ocular) and serious adverse events (ocular and non-ocular), ophthalmic examinations (slit lamp exam with biomicroscopy, fundus exam and intra ocular pressure), and visual acuity assessments.

Table 9-1. Evaluation and visit schedule.

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Study phase	Screening phase	Open label treatment phase												
Study Month		0	1	2	3	4	5	6	7	8	9	10	11	12
Study Day	-30 to - 1	1	30	60	90	120	150	180	210	240	270	300	330	360
Procedure														
Informed Consent	X													
Medical History and Demographics	X													
Inclusion/Exclusion	X													
Vital Signs	X				X									X
Laboratory Tests	X													X
Urine Pregnancy Test*	X													
HbA_{1C}	X													
Best-Corrected Visual Acuity	X				X			X						X
Ophthalmic Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Color Fundus Photography	X				X			X						X
Fluorescein Angiography	X				X			X						X
Optical Coherence Tomography	X				X			X						X
Lucentis**		X	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
PRP		X			(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
Lucentis plus		X	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Discharge														X

* For patients of childbearing potential.

** For patients in group 2 rescue treatment with PRP was allowed after the loading phase (first 3-months period).

9.5.2 Appropriateness of measurements

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

9.5.3 Primary efficacy variable(s)

The primary efficacy variable was defined as the regression of NV from screening to the 12 month visit, measured by an independent reading center in DA units based on CFP and FA. Regression of NV was defined as any decrease of the area of NV.

9.6 Data quality assurance

CFP and FA used to measure the area of NV (primary outcome) were analysed centrally by an independent central reading centre (Coimbra Ophthalmology Reading Center - CORC).

AIBILI monitors reviewed the CRFs entered by the investigational staff for completeness and accuracy and instructed the site personnel to make any required corrections or additions. Queries were sent by AIBILI designated staff to the investigational site using an electronic data query (e-mail). Designated investigator site staff were required to respond to the query by mail and AIBILI made necessary changes. Investigator site staff printed the response provided to AIBILI, sign and date, and file the answers in the investigator file.

Data from the CRFs were entered into the study database by AIBILI staff using single data entry. Verification was performed manually by a separate member of AIBILI by comparing the CRF to the data entered into the database.

After these actions were completed and the database was declared to be complete and accurate, it was locked and data was made available for data analysis.

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

9.7.1 Statistical and analytical plans

The ITT and PP sets were used for the primary efficacy analysis according to the following null (H0) and alternative (H1) hypotheses:

- H0: there is no difference between groups (PRP, Ranibizumab and Ranibizumab+PRP groups) in the proportion of subjects with total NV regression at month-12 (i.e. in the proportion of subjects with absence of NV at month-12).
- H1: there is a difference between these groups.

The hypothesis was tested using the Exact Fisher test with a statistical adjustment for multiple between-treatment comparisons (i.e., PRP vs. Ranibizumab and Ranibizumab+PRP). An alpha level of 0.05 was considered (corrected to 0.016 for the 3 groups under analysis). The Kruskal-Wallis test was used to compare NV areas between groups at month-0, month-3, month-6 and month-12 and the Friedman test was computed to evaluate statistically significant changes from baseline of NV areas in each group. Multiple comparations, with Bonferroni correction, were done with Mann-Whitney and Wilcoxon tests.

For the secondary efficacy analysis, changes from baseline in BCVA and CMT were compared between groups, as well as recurrence of neovascularization, number of treatments needed, additional focal or grid laser for DME, drug safety profile and the need for vitrectomy due to occurrence of vitreous haemorrhage or retinal detachment relative to the three treatment groups. The Kruskal-Wallis test was used to compare BCVA and CMT between groups at month-0, month-3, month-6 and month-12 and the Friedman test was computed to evaluate statistically significant changes from baseline of BCVA and CMT in each group. Multiple comparations, with Bonferroni correction, were done with Mann-Whitney and Wilcoxon tests. Mann-Whitney test was used to compare the number of PRP treatments between Group 1 and Group 3 and the number of ITV treatment between Group 2 and Group 3. The Exact Fisher test was performed in the remaining cases.

If the ITT and the PP analyses yield the same results, the PP provided supportive evidence of the magnitude of treatment effect among patients who received the treatment. If the results of the 2 methods differ, exploratory analyses were performed to evaluate the factors that contribute to the differences.

9.7.2 Determination of sample size

The sample size calculation was based on the primary efficacy analysis in the proportion of subjects with NV regression at month-12.

For this study 54 subjects were planned for inclusion (18 subjects per treatment arm) to achieve a statistical power of 90%.

Sample size was computed using the SampleSize software (SPSS Inc., Version 2.0) and estimates from previous studies ([ETDRS, 1991], [Adamis, 2006], [Gonzalez, 2007] and [Gonzalez, 2009]). The following considerations were made:

- 25% improvement rate for the PRP group
- 90% improvement rate for the Ranibizumab and the Ranibizumab+PRP groups,
- 2-sided alpha level of 0.01,
- 10% dropout rate, for the 12-months follow-up period.

9.8 Changes in the conduct of the study or planned analyses

The statistical planning was reviewed due to the low recruitment rate, only 35 patients were recruited instead of 54 patients as initially planned.

The centres HSJ (1), CUF (2), and ALM (3) didn't recruited patients and IOGP (5) recruited only one patient.
Non-parametric tests were used due to the non-normal distribution of the data.
For nominal and/or categorical variables the Exact Fisher test was used and for numerical variables the Mann-Whitney test, Wilcoxon test, Kruskal-Wallis test and Friedman test were performed.
Also, due to the small sample size, an additional analysis was conducted on the primary efficacy outcome. A new variable was computed to identify patients with or without NV regression. This new variable takes into account the area of NV and the development of any completion related with NV progression.

Patients "**Without NV regression**" were defined as:

1. Patients with no decrease in the area of NV (i.e. with an increase or with constant area NV)
   OR
2. Patients with vitreous haemorrhage or retinal haemorrhage or pre-rubeosis or tractional retinal detachment (collected from the CFP and FA)
   OR
3. Patients with vitreous haemorrhage or rubeosis (collected from Adverse Events form)

Patients "**With NV regression**" were defined as:

1. Patients with a decreased area of NV
   AND
2. Patients without criteria 2 or 3 of "Without NV regression"

10 Study Patients

10.1 Disposition of patients

Patients disposition by treatment arm are presented in.

Table 10-1. Patient disposition.

	Total	Group 1	Group 2	Group 3
Patients				
Planned	54	18	18	18
Screened	43	---	---	---
Failed inclusion criteria	8	---	---	---
Eligible / Randomized	35	13	10	12
Exposed	35	13	10	12
Completed – 12-months visit	30	11	9	10
Discontinued	5	2	1	2
Discontinued due to disease worsening	2	2	0	0
Main cause of discontinuation				
Death	0	---	---	---
Adverse event(s)	3	2	0	1
Lack of efficacy	0	---	---	---
Protocol violation(s)	0	---	---	---
Administrative reasons	0	---	---	---
Other	2	0	1	1

10.2 Protocol deviations

Protocol deviations are listed in Appendix.

The major protocol deviation was related with the recruitment.

The recruitment period was extended from November 2010 to November 2012 (2 years). Even though, only 35 patients were recruited from the 54 initially planned.

11 Efficacy evaluation

11.1 Data sets analyzed

Subjects were grouped according to the treatment administered (n=35). First group corresponds to standard PRP, which included 13 subjects at screening, the second group corresponds to Ranibizumab (0.5 mg), which included at screening 10 subjects and the third group to Ranibizumab+PRP with 12 subjects (Table 11-1).
There were few missing data and therefore, the present analysis includes cases with missing data.
The CONSORT Flow Chart is presented in Figure 11-1.

Table 11-1. Analysis populations.

	Total	Group 1	Group 2	Group 3
Analysis population	---	---	---	---
Intent-to-treat (ITT)	35	13	10	12
Safety (> 1 evaluation)	35	13	10	12
Per protocol (PP)	30	11	9	10
Evaluable patients (PP1)[1]	30	11	9	10

[1] Population considered: Per Protocol plus 2 patients that discontinued due to disease worsening.

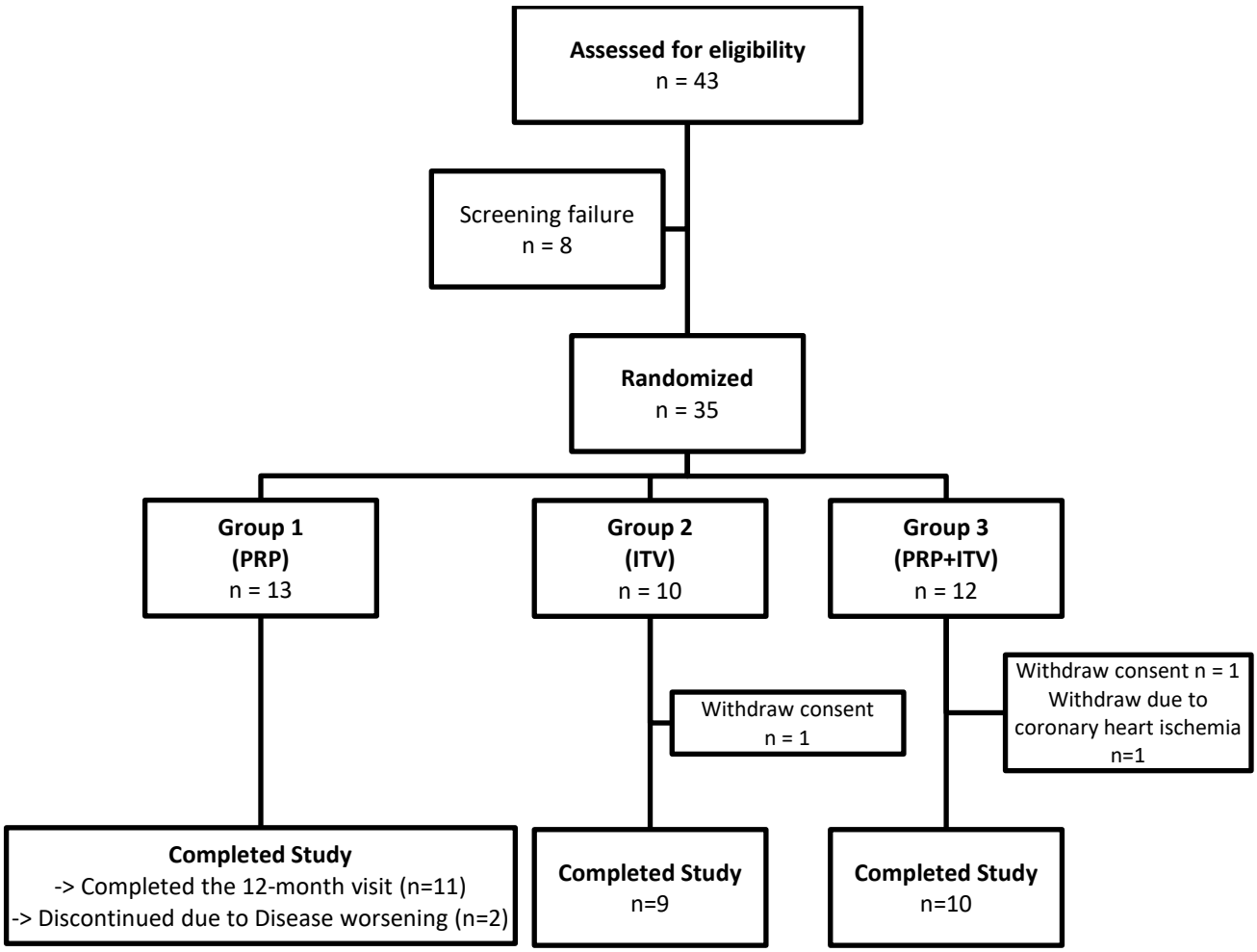


Figure 11-1. CONSORT flow chart.

11.1.1 Demographic and other screening characteristics

Screening characteristics are described in Table 11-2 (ITT population) and Table 11-3 (PP population). All patients were Type 2 diabetes. In general no statistical differences were found between study groups, statistical differences were found only for the study eye in the ITT population.

Table 11-2. Screening summary by treatment group (ITT population)

	Group 1		Group 2		Group 3		p
	No.	%	No.	%	No.	%	
Study eye[1]							
OD	8	61.5	1	10.0	6	50.0	0.038*
OS	5	38.5	9	90.0	6	50.0	
Sex[1]							
F	3	23.1	4	40.0	2	16.7	0.557
M	10	76.9	6	60.0	10	83.3	
Age (years)[2]							
Mean ± SD (Range)	52.08 ± 14.2 (27 - 76)		59.40 ± 6.43 (51 - 67)		54.50 ± 11.2 (31 - 70)		0.382
Median (IQR)	54 (44 - 59)		61 (52 - 65)		57 (49.5 - 61.5)		
Height (cm) [2]							
Mean ± SD (Range)	167.42 ± 7.59 (154 - 179)		162.40 ± 9.00 (150 - 178)		169.00 ± 5.36 (160 - 176)		0.182
Median (IQR)	168 (163.5 - 171)		161.5 (155 - 169)		168 (165.5 - 175)		
Weight (Kg) [2]							
Mean ± SD (Range)	82.83 ± 9.44 (70 - 98)		84.80 ± 8.80 (65 - 98)		84.50 ± 13.71 (56 - 106)		0.713
Median (IQR)	80 (76.5 - 91)		86 (82 - 90)		89 (75.5 - 93)		
BMI (kg/m^2) [2]							
Mean ± SD (Range)	29.61 ± 3.41 (25.16 - 36.96)		32.57 ± 6.09 (25.08 - 42.98)		29.52 ± 4.24 (20.32 - 34.67)		0.457
Median (IQR)	28.56 (27.34 - 31.82)		31.5 (27.14 - 36.21)		28.9 (27 - 33.13)		
HbA1C (%)[2]							
Mean ± SD (Range)	8.08 ± 1.47 (6.2 - 11)		7.83 ± 1.20 (6.4 - 9.7)		7.94 ± 1.31 (6.6 - 10.3)		0.975
Median (IQR)	8 (6.8 - 8.7)		7.55 (7 - 8.9)		7.2 (6.7 - 9)		
Heart rate (bpm)[2]							
Mean ± SD (Range)	78.15 ± 11.94 (65 - 107)		77.5 ± 11.32 (58 - 94)		79.75 ± 7.85 (66 - 92)		0.824
Median (IQR)	79 (68 - 81)		79 (68 - 83)		80 (76 - 85.5)		
SBP (mm/Hg) [2]							
Mean ± SD (Range)	145.15 ± 19.11 (110 - 173)		154.4 ± 12.36 (140 - 177)		137.5 ± 16.49 (110 - 169)		0.060
Median (IQR)	146 (138 - 159)		151 (145 - 161)		140 (127.5 - 146.5)		
DBP (mm/Hg) [2]							
Mean ± SD (Range)	80.85 ± 11.62 (64 - 100)		78.40 ± 7.43 (66 - 94)		79.00 ± 10.30 (64 - 98)		0.930
Median (IQR)	80 (70 - 90)		79 (74 - 81)		79.5 (70 - 86)		
IOP (mm/Hg)[2]							
Mean ± SD (Range)	16.00 ± 1.41 (13 - 18)		16.30 ± 2.06 (14 - 20)		15.17 ± 1.85 (11 - 17)		0.588
Median (IQR)	16 (16 - 17)		16 (15 - 16)		16 (14 - 16.5)		
NVE (DA)[2]							
Mean ± SD (Range)	4.9 ± 7.6 (0 - 26.5)		2.3 ± 2.9 (0.0 - 9.2)		3.8 ± 5.7 (0.0 - 18.0)		0.988
Median (IQR)	1.2 (0.5 - 8.2)		1.1 (0.6 - 2.1)		1.4 (0.3 - 5.8)		
NVD (DA)[2]							
Mean ± SD (Range)	1.5 ± 2.6 (0 - 8.2)		0.6 ± 1.2 (0 - 4.0)		1.0 ± 1.7 (0.0 - 6.0)		0.624
Median (IQR)	0.3 (0.0 - 0.8)		0.1 (0.0 - 0.5)		0.4 (0.0 - 1.3)		
NV Total (DA)[2]							
Mean ± SD (Range)	6.4 ± 9.2 (0.5 - 31.5)		2.9 ± 2.9 (0.5 - 9.5)		4.9 ± 7.0 (0.3 – 24.0)		0.988
Median (IQR)	1.6 (0.6 - 9.8)		1.8 (0.8 - 4.6)		1.7 (0.8 - 6.6)		
BCVA letters (#)[2]							
Mean ± SD (Range)	70.15 ± 17.00 (20 - 90)		74.7 ± 9.20 (55 - 85)		70.92 ± 12.66 (39 - 87)		0.777
Median (IQR)	76 (71 - 78)		76.5 (73 - 79)		76 (64 - 79)		
Macular retinal thickness (µm)[2]							
Mean ± SD (Range)	329.33 ± 92.61 (215 - 561)		323.30 ± 62.14 (249 - 411)		377.00 ± 168.04 (225 - 842)		0.836
Median (IQR)	317 (275.5 - 351)		319.5 (256 - 378)		331 (290 - 408)		

[1] Fisher Exact test; [2] Kruskal-Wallis test; * $p < 0.05$

Table 11-3. Screening summary by treatment group (PP population)

	Group 1		Group 2		Group 3		p
	No.	%	No.	%	No.	%	
Study eye[1]							
OD	7	63.64	1	11.1	4	40	0.066
OS	4	36.36	8	88.9	6	60	
Sex[1]							
F	3	27.27	4	44.4	2	20	0.542
M	8	72.73	5	55.6	8	80	
Age (years)[2]							
Mean ± SD	51.91 ± 15.32 (27 - 76)		59.00 ± 6.69 (51 - 67)		52.60 ± 11.33 (31 - 70)		0.511
Median (IQR)	54 (52 - 65)		59 (47 - 57)		56.5 (51 - 63)		
Height (cm) [2]							
Mean ± SD	167.40 ± 8.30 (154 - 179)		161.89 ± 9.39 (150 - 178)		167.70 ± 4.88 (160 - 175)		0.285
Median (IQR)	168 (155 - 169)		161 (165 - 170)		168 (161 - 170)		
Weight (Kg) [2]							
Mean ± SD	82.60 ± 10.02 (70 - 98)		85.11 ± 9.28 (65 - 98)		84.10 ± 15.07 (56 - 106)		0.821
Median (IQR)	80 (83 - 90)		86 (71 - 93)		90 (79 - 92)		
BMI (kg/m^2) [2]							
Mean ± SD	29.52 ± 3.49 (25.16 -		32.92 ± 6.35 (25.08 -		29.81 ± 4.61 (20.32 -		0.546
Median (IQR)	28.56 (27.14 - 36.21)		33.59 (26.56 - 33.3)		30.62 (27.14 - 33.73)		
HbA1C (%)[2]							
Mean ± SD	8.25 ± 1.51 (6.2 - 11)		7.71 ± 1.21 (6.4 - 9.7)		7.89 ± 1.37 (6.6 - 10.3)		0.795
Median (IQR)	8.6 (6.8 - 9.6)		7.4 (7 - 7.7)		7.15 (6.7 - 9)		
Heart rate (bpm)[2]							
Mean ± SD	78.91 ± 12.42 (65 - 107)		78.56 ± 11.47 (58 - 94)		79.00 ± 8.19 (66 - 92)		0.914
Median (IQR)	79 (68 - 81)		80 (72 - 83)		80 (74 - 83)		
SBP (mm/Hg) [2]							
Mean ± SD	145.55 ± 17.67 (110 - 173)		152.67 ± 11.75 (140 - 177)		136.10 ± 17.79 (110 - 169)		0.079
Median (IQR)	146 (138 - 159)		148 (145 - 160)		140 (120 - 145)		
DBP (mm/Hg) [2]							
Mean ± SD	82.82 ± 11.27 (70 - 100)		77.89 ± 7.69 (66 - 94)		78.90 ± 10.47 (64 - 98)		0.654
Median (IQR)	82 (70 - 90)		78 (74 - 80)		79.5 (70 - 83)		
IOP (mm/Hg)[2]							
Mean ± SD	15.91 ± 1.51 (13 - 18)		15.89 ± 1.69 (14 - 20)		15.10 ± 1.91 (11 - 17)		0.681
Median (IQR)	16 (15 - 17)		16 (15 - 16)		16 (14 - 16)		
NVE (DA)[2]							
Mean ± SD	5.0 ± 8.1 (0 - 26.5)		1.9 ± 2.8 (0 - 9.2)		4.5 ± 6.1 (0 - 18)		0.891
Median (IQR)	1.2 (0.5 - 9.0)		0.8 (0.6 - 2.1)		1.5 (0.3 - 9.8)		
NVD (DA)[2]							
Mean ± SD	0.7 ± 1.5 (0 - 5)		0.6 ± 1.3 (0 - 4)		1.2 ± 1.8 (0 - 6)		0.404
Median (IQR)	0.0 (0.0 - 0.7)		0.0 (0.0 - 0.5)		0.5 (0.0 - 1.8)		
NV Total (DA)[2]							
Mean ± SD	5.6 ± 9.5 (0.5 - 31.5)		2.6 ± 2.9 (0.5 - 9.5)		5.7 ± 7.5 (0.3 - 24.0)		0.790
Median (IQR)	1.2 (0.5 - 9.8)		1.5 (0.8 - 2.1)		2.6 (0.9 - 10.0)		
BCVA letters (#)[2]							
Mean ± SD	69.45 ± 18.51 (20 - 90)		75.89 ± 8.91 (55 - 85)		73.30 ± 8.31 (62 - 87)		0.708
Median (IQR)	76 (61 - 79)		77 (74 - 79)		76 (65 - 79)		
Macular retinal thickness (µm) [2]							
Mean ± SD	334.30 ± 101.07 (215 -		313.56 ± 57.23 (249 - 390)		345.50 ± 82.98 (225 - 508)		0.800
Median (IQR)	322.5 (268 - 355)		300 (256 - 372)		331 (310 - 357)		

[1] Fisher Exact test; [2] Kruskal-Wallis test; * $p < 0.05$

11.2 Efficacy results and tabulations of individual patient data

11.2.1 Analysis of efficacy

The results presented in this section are for the ITT population and PP population. For some primary analyses related with NV regression the 2 cases in group 1 that discontinued due to NV worsening were included (PP1 population).

11.2.1.1 Primary efficacy analysis

The following tables (Table 11-4 and Table 11-5) show the efficacy results regarding treatment for the primary efficacy variable, area of NV, based on the regression or worsening of the NV at the end of the study. For this analysis the PP1 population was considered. No statistically significant differences were found between groups in the proportion of subjects with NVE, NVD and NV Total regression.

Table 11-4. Primary efficacy parameter: NV regression by groups (PP1 population equivalent to the PP1 population)

		Group 1		Group 2		Group 3		p[1]
		No.	%	No.	%	No.	%	
NVE	*No change*	*0*	*0*	*1*	*11.1*	*1*	*10.0*	
	Without Regression	4	30.8	2	22.2	0	0	
	With Regression	9	69.2	6	66.7	9	90.0	0.223
NVD	*No change*	*4*	*30.8*	*4*	*44.5*	*2*	*20.0*	
	Without Regression	4	30.8	2	22.2	1	10.0	
	With Regression	5	38.4	3	33.3	7	70.0	0.539
NV Total	*No change*	-	-	-	-	-	-	
	Without Regression	5	38.5	3	33.3	0	0	
	With Regression	8	61.5	6	66.7	10	100	0.075

[1] Exact Fisher's test

Table 11-5. Primary efficacy parameter: NV regression by groups (PP population)

		Group 1		Group 2		Group 3		p[1]
		No.	%	No.	%	No.	%	
NVE	*No change*	*0*	*0*	*1*	*11.1*	*1*	*10.0*	
	Without Regression	2	18.2	2	22.2	0	0	
	With Regression	9	81.8	6	66.7	9	90.0	0.467
NVD	*No change*	*4*	*36.4*	*4*	*44.5*	*2*	*20.0*	
	Without Regression	2	18.2	2	22.2	1	10.0	
	With Regression	5	45.4	3	33.3	7	70.0	0.650
NV Total	*No change*	-	-	-	-	-	-	
	Without Regression	3	27.3	3	33.3	0	0	
	With Regression	8	72.7	6	66.7	10	100	0.166

[1] Exact Fisher's test

The evolution of the NV area in the 3 treatments groups for months 0, 3, 6 and 12 is presented in the Table 11-6 and Table 11-7. At screening, month-6 and month-12, no statistically significant differences were found between groups. Statistical differences between groups ($p \leq 0.044$) were found at month-3 for the NVE and NV total for the ITT population, and for the NV total area for the PP population.

In Group 1, statistically significant differences were observed between visits for NVD and NV total ($p \leq 0.043$). In Group 2, statistically significant differences between visits were found for the three NV areas ($p \leq 0.039$). In Group 3, statistically significant differences between visits were found for the three NV areas ($p \leq 0.014$). These results were similar for both ITT and PP populations.

Table 11-6. Primary efficacy parameter (Area of NV) by groups and visits (ITT population)

		Group 1		Group 2		Group 3		
		Mean ± SD	**Median (IQR)**	**Mean ± SD**	**Median (IQR)**	**Mean ± SD**	**Median (IQR)**	p[1]
NVE	Screening	4.9 ± 7.6	1.2 (0.5-8.2)	2.4 ± 2.9	1.1 (0.6-2.1)	3.9 ± 5.7	1.4 (0.4-5.9)	0.988
	Month 3	3.5 ± 4.6	1.2 (0.2-6.5)	0.2 ± 0.3	0 (0-0.2)	0.4 ± 0.6	0.1 (0-0.6)	0.044
	Month 6	3.6 ± 6.3	0.8 (0.2-4.3)	0.8 ± 0.7	1 (0.3-1)	1.0 ± 2.0	0.3 (0-0.9)	0.333
	Month 12	3.1 ± 5.8	0.1 (0-4.9)	1.5 ± 2.9	0.2 (0-1.6)	0.4 ± 0.5	0.1 (0-0.7)	0.837
	p[2]	0.126		0.039		0.014		
NVD	Screening	1.5 ± 2.6	0.3 (0-0.8)	0.6 ± 1.2	0.1 (0-0.5)	1.0 ± 1.7	0.4 (0-1.3)	0.647
	Month 3	1 ± 2.2	0.3 (0-1)	0.1 ± 0.2	0 (0-0)	0.1 ± 0.1	0 (0-0)	0.105
	Month 6	0.9 ± 2.3	0 (0-0.7)	0.1 ± 0.3	0 (0-0)	0.2 ± 0.2	0 (0-0.3)	0.647
	Month 12	0.2 ± 0.4	0 (0-0.6)	0.2 ± 0.4	0 (0-0.4)	0.2 ± 0.2	0.1 (0-0.3)	0.961
	p[2]	0.010		<0.001		<0.001		
NV Total	Screening	6.4 ± 9.2	1.6 (0.6-9.8)	2.9 ± 2.9	1.8 (0.8-4.6)	4.9 ± 7.0	1.7 (0.8-6.7)	0.988
	Month 3	4.5 ± 5.8	1.5 (0.4-8.3)	0.3 ± 0.3	0.2 (0-0.3)	0.5 ± 0.6	0.3 (0-0.8)	0.018
	Month 6	4.5 ± 7.1	1.1 (0.3-6.7)	1.0 ± 0.7	1 (0.8-1.3)	1.1 ± 2.0	0.6 (0-1)	0.430
	Month 12	3.3 ± 5.7	0.4 (0-4.9)	1.7 ± 3.1	0.4 (0.2-1.6)	0.5 ± 0.5	0.4 (0.1-0.9)	0.804
	p[2]	0.043		0.012		0.006		

[1] Kruskal Wallis test (between groups); [2] Friedman test (within visits)

Table 11-7. Primary efficacy parameter (Area of NV) by groups and visits (PP population)

		Group 1		Group 2		Group 3		
		Mean ± SD	**Median (IQR)**	**Mean ± SD**	**Median (IQR)**	**Mean ± SD**	**Median (IQR)**	p[1]
NVE	Screening	5.0 ± 8.1	1.2 (0.5-9)	2.0 ± 2.8	0.8 (0.6-2.1)	4.5 ± 6.1	1.5 (0.3-9.8)	0.891
	Month 3	3.1 ± 4.6	0.9 (0.2-5.1)	0.2 ± 0.3	0 (0-0.2)	0.3 ± 0.6	0.1 (0-0.4)	0.083
	Month 6	3.3 ± 6.5	0.6 (0.1-1.7)	0.8 ± 0.7	1 (0.3-1)	1.0 ± 2.0	0.3 (0-0.9)	0.442
	Month 12	3.1 ± 5.8	0.1 (0-4.9)	1.5 ± 2.9	0.2 (0-1.6)	0.4 ± 0.5	0.1 (0-0.7)	0.837
	p[2]	0.126		0.039		0.014		
NVD	Screening	0.7 ± 1.5	0 (0-0.7)	0.6 ± 1.3	0 (0-0.5)	1.2 ± 1.8	0.5 (0-1.8)	0.443
	Month 3	0.4 ± 0.5	0.2 (0-0.8)	0.1 ± 0.2	0 (0-0)	0.1 ± 0.2	0 (0-0)	0.227
	Month 6	0.3 ± 0.4	0 (0-0.6)	0.1 ± 0.3	0 (0-0)	0.2 ± 0.2	0 (0-0.3)	0.819
	Month 12	0.2 ± 0.4	0 (0-0.6)	0.2 ± 0.4	0 (0-0.4)	0.2 ± 0.2	0.1 (0-0.3)	0.961
	p[2]	0.010		<0.001		<0.001		
NV Total	Screening	5.6 ± 9.5	1.2 (0.6-9.8)	2.6 ± 2.9	1.5 (0.8-2.1)	5.7 ± 7.5	2.6 (0.9-10)	0.79.0
	Month 3	3.5 ± 4.8	1.4 (0.3-6.4)	0.3 ± 0.3	0.2 (0-0.3)	0.4 ± 0.6	0.3 (0-0.4)	0.036
	Month 6	3.6 ± 6.6	0.6 (0.1-2.2)	1.0 ± 0.7	1 (0.8-1.3)	1.1 ± 2.0	0.6 (0-1)	0.567
	Month 12	3.3 ± 5.7	0.4 (0-4.9)	1.7 ± 3.1	0.4 (0.2-1.6)	0.5 ± 0.5	0.4 (0.1-0.9)	0.804
	p[2]	0.043		0.012		0.006		

[1] Kruskal Wallis test (between groups); [2] Friedman test (within visits)

Multiple comparisons were performed with Bonferroni correction. For the NVE area statistical differences were found between Group 1 and Group 2 in both ITT and PP populations ($p \leq 0.048$) (Table 11-8 and Table 11-9). Group 1 showing a higher NVE area than Group 2.

For NVD area statistical differences were found between Group 1 and Group 3 ($p = 0.028$) in the ITT population. Group 1 showing a higher NVD area than Group 3.

For the NV total area statistical differences were found between Group 1 and Group 2 and Group 1 and Group 3 for the both ITT and PP populations. Group 1 showing higher NV total area than Group 2 ($p=0.012$) and Group 1 showing higher NV total area than Group 3 ($p \leq 0.026$)

Table 11-8. Resume of treatment pairwise comparisons of NV area at month 3 (ITT population)

		Group 1	Group 2	Group 3
NVE	Group 1			
	Group 2	0.025 (Group 1> Group 2)		
	Group 3	0.042 (Group 1> Group 3)	0.539	
NVD	Group 1			
	Group 2	0.064		
	Group 3	0.028 (Group 1> Group 3)	0.756	
NV Total	Group 1			
	Group 2	0.012 (Group 1> Group 2)		
	Group 3	0.021 (Group 1> Group 3)	0.554	

Table 11-9. Resume of treatment pairwise comparisons of NV area at month 3 (PP1 population)

		Group 1	Group 2	Group 3
NVE	Group 1			
	Group 2	0.025 (Group 1> Group 2)		
	Group 3	0.048 (Group 1> Group 3)	0.627	
NVD	Group 1			
	Group 2	0.064		
	Group 3	0.054	0.909	
NV Total	Group 1			
	Group 2	0.012 (Group 1> Group 2)		
	Group 3	0.026 (Group 1> Group 3)	0.611	

Multiple comparisons (with Bonferroni correction[1]) are shown in Table 11-10 and Table 11-11. The results are similar in both ITT and PP populations.
In Group 1 no statistical significant differences were found ($p \geq 0.008$).
In Group 2 a statistical significant decrease for the NV total was found between screening and month-3 ($p = 0.008$).
In group 3 a statistical decrease for the NV total was found between screening and month-3 ($p \leq 0.005$), and for the NVD in the ITT population between screening and month-3 ($p = 0.006$).

[1] With Bonferroni correction reference p-value was 0.05 divided by the number of comparisons done. In this case four visits were compared, corresponding to six comparisons. The reference p-value was 0.008.

Table 11-10. Resume of visits pairwise comparisons of NV area by treatment (ITT population)

		SCR - M3	M3 - M6	M6 - M12
NVE	Group 1	0.028	0.783	0.443
	Group 2	0.009	0.042	0.812
	Group 3	0.011	0.500	0.367
NVD	Group 1	0.968	0.156	0.589
	Group 2	0.045	0.566	0.473
	Group 3	0.006	0.500	0.873
NV Total	Group 1	0.076	0.665	0.448
	Group 2	0.008	0.043	0.859
	Group 3	0.003	0.262	0.412

Table 11-11. Resume of visits pairwise comparisons of NV area by treatment (PP1 population)

		SCR - M3	M3 - M6	M6 - M12
NVE	Group 1	0.028	0.783	0.443
	Group 2	0.009	0.042	0.812
	Group 3	0.011	0.500	0.367
NVD	Group 1	0.968	0.156	0.589
	Group 2	0.048	0.473	0.473
	Group 3	0.011	0.509	0.873
NV Total	Group 1	0.076	0.665	0.448
	Group 2	0.008	0.043	0.859
	Group 3	0.005	0.262	0.412

Figure 11-2 and Figure 11-3 show the NV areas by visits, by groups and by patients for the ITT and PP populations. For the three groups the three NV areas decrease from baseline to month-12.

Figure 11-2. Primary efficacy parameter: NV areas by groups and visits (ITT population) – mean value

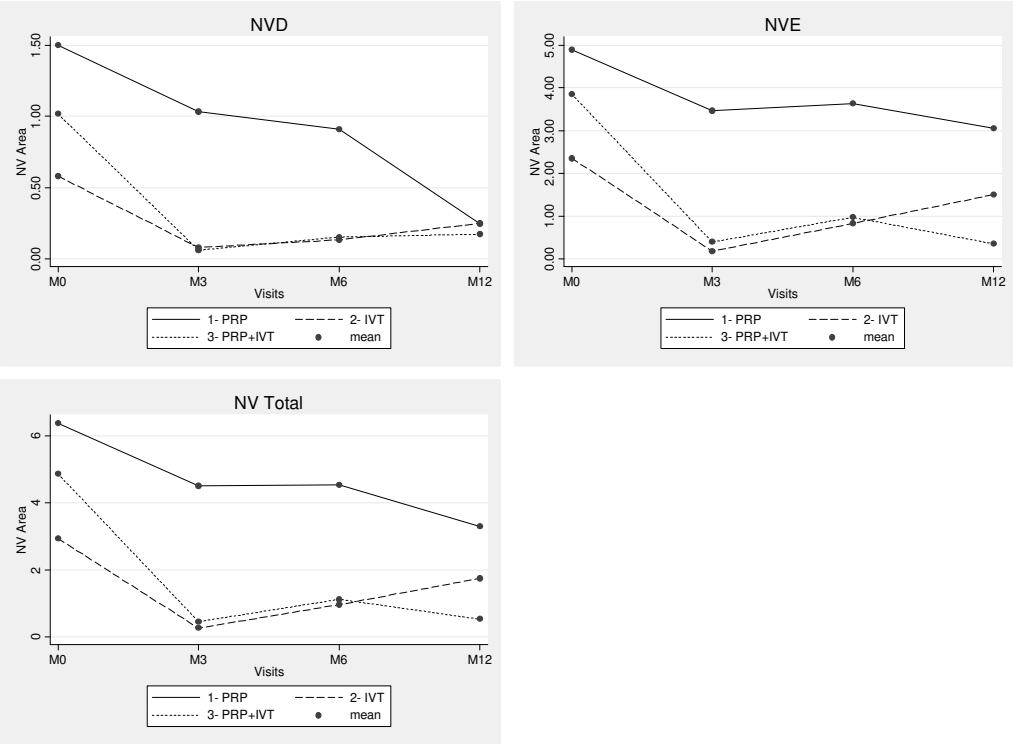


Figure 11-3. Primary efficacy parameter: NV area by groups and visits (PP population) – mean value

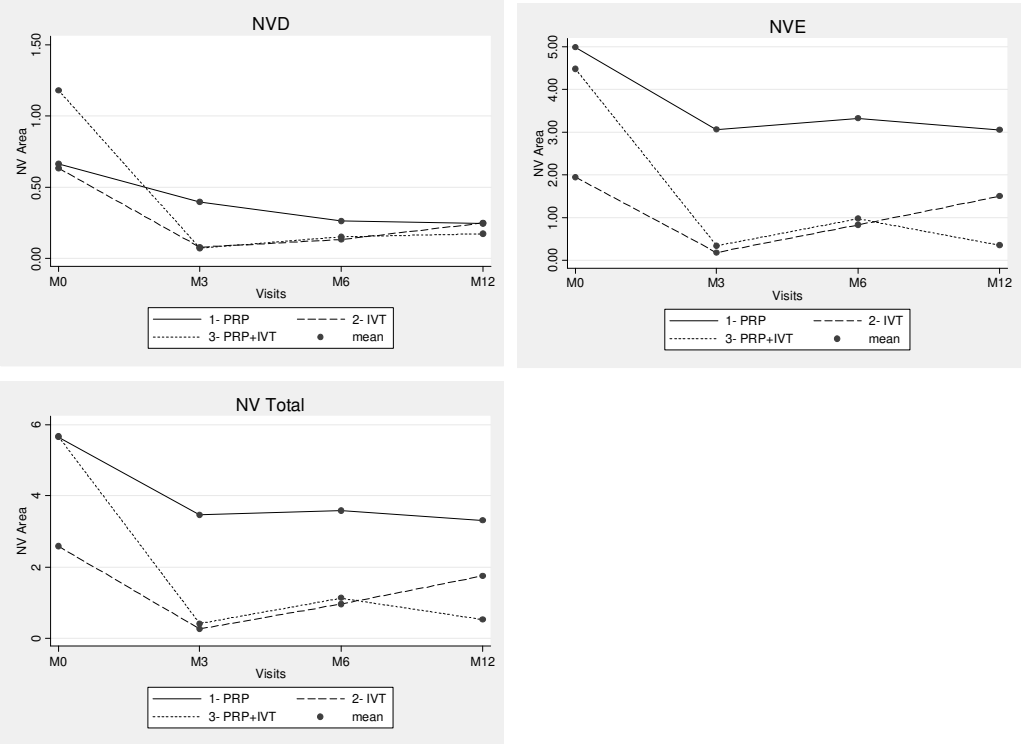


Figure 11-4. Primary efficacy parameter: NVE area by patients, groups and visits (ITT population)

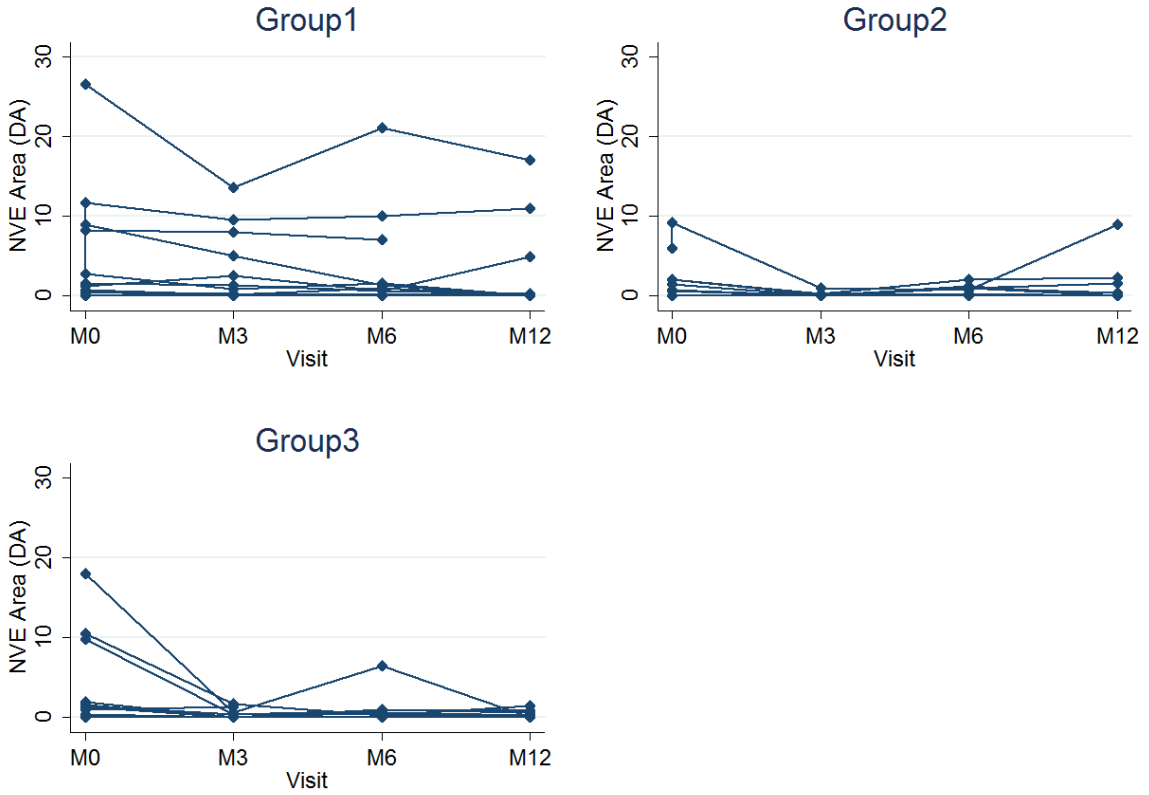


Figure 11-5. Primary efficacy parameter: NVE area by patients, groups and visits (PP population)

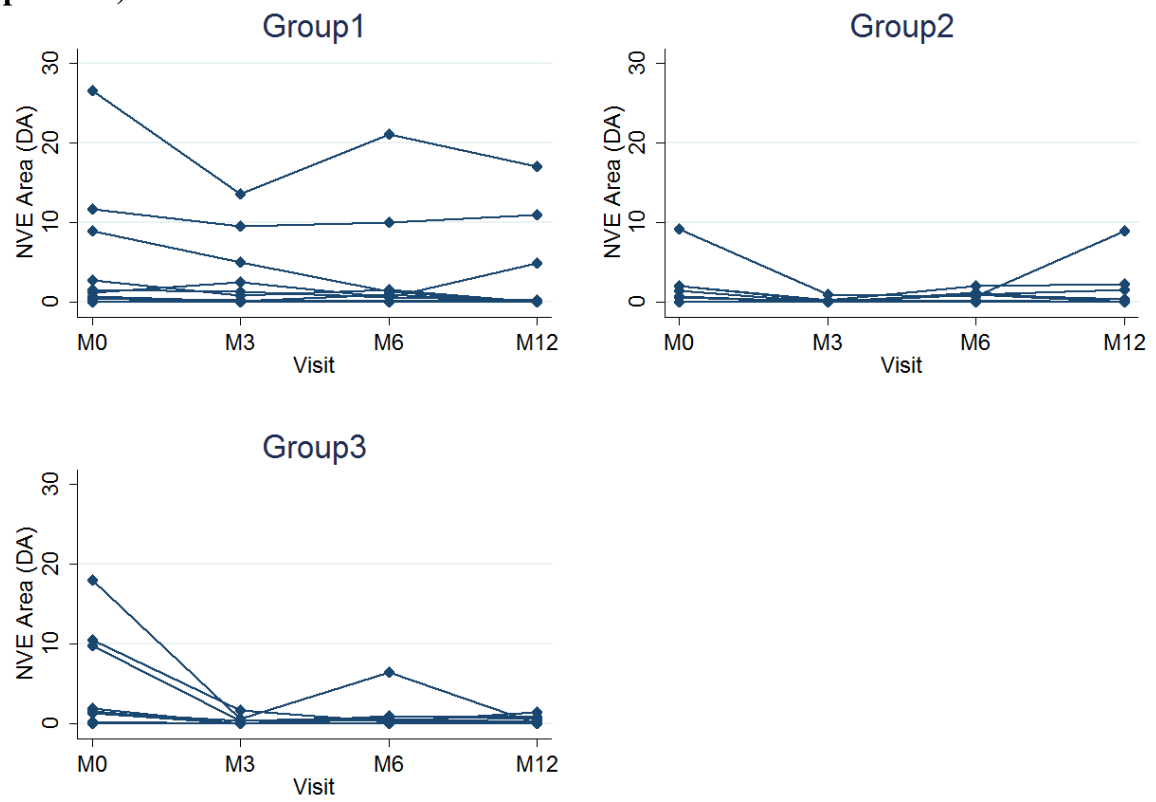


Figure 11-6. Primary efficacy parameter: NVD area by patients, groups and visits (ITT population)

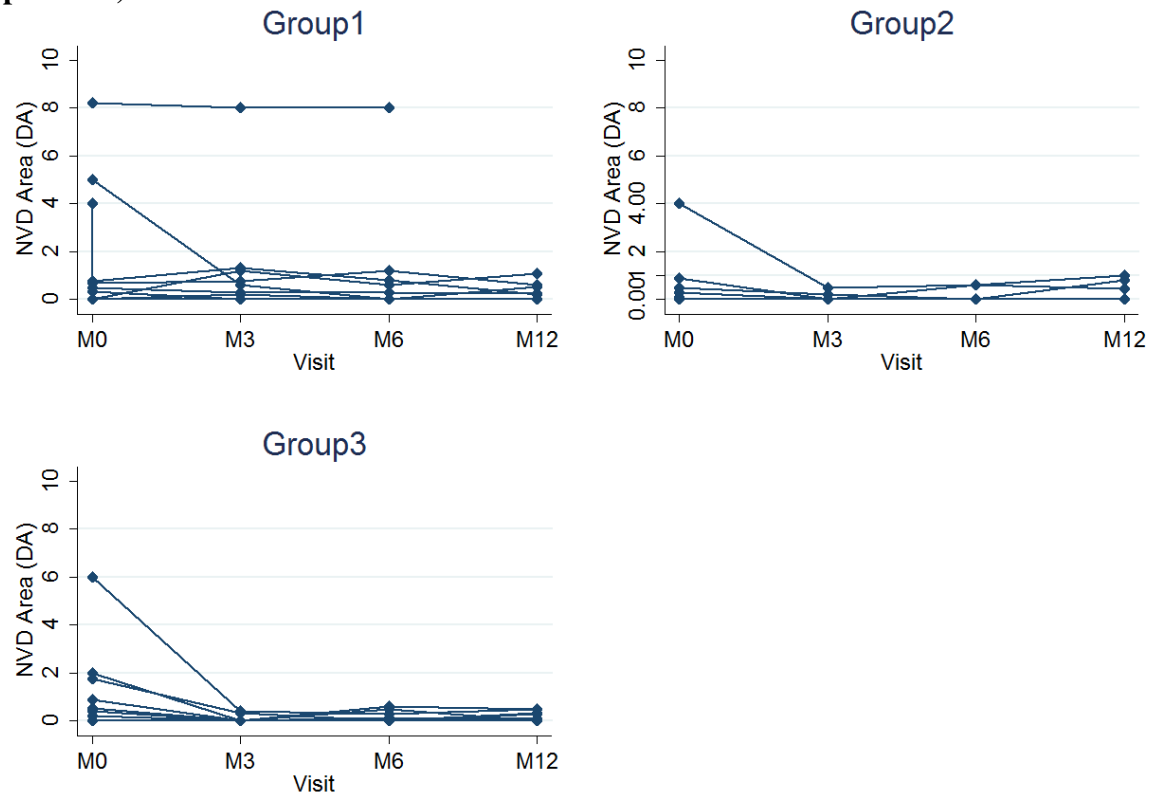


Figure 11-7. Primary efficacy parameter: NVD area by patients, groups and visits (PP population)

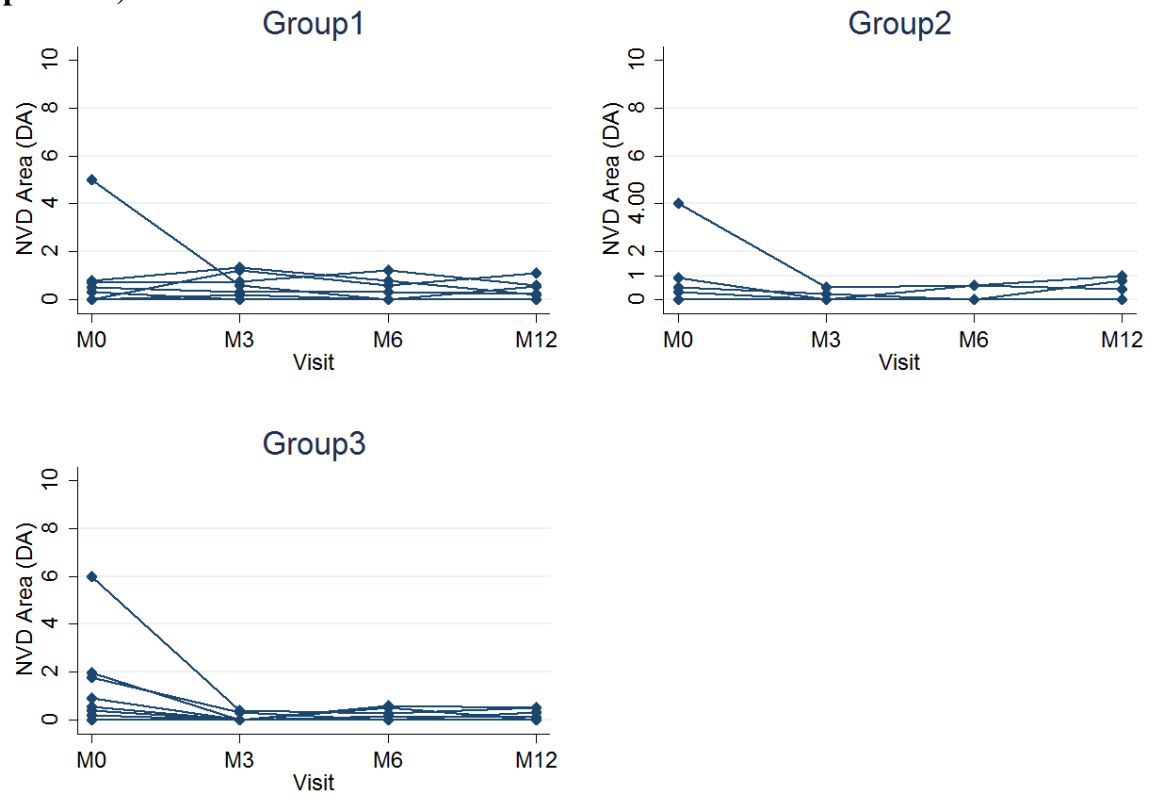


Figure 11-8. Primary efficacy parameter: NV total area by patients, groups and visits (ITT population)

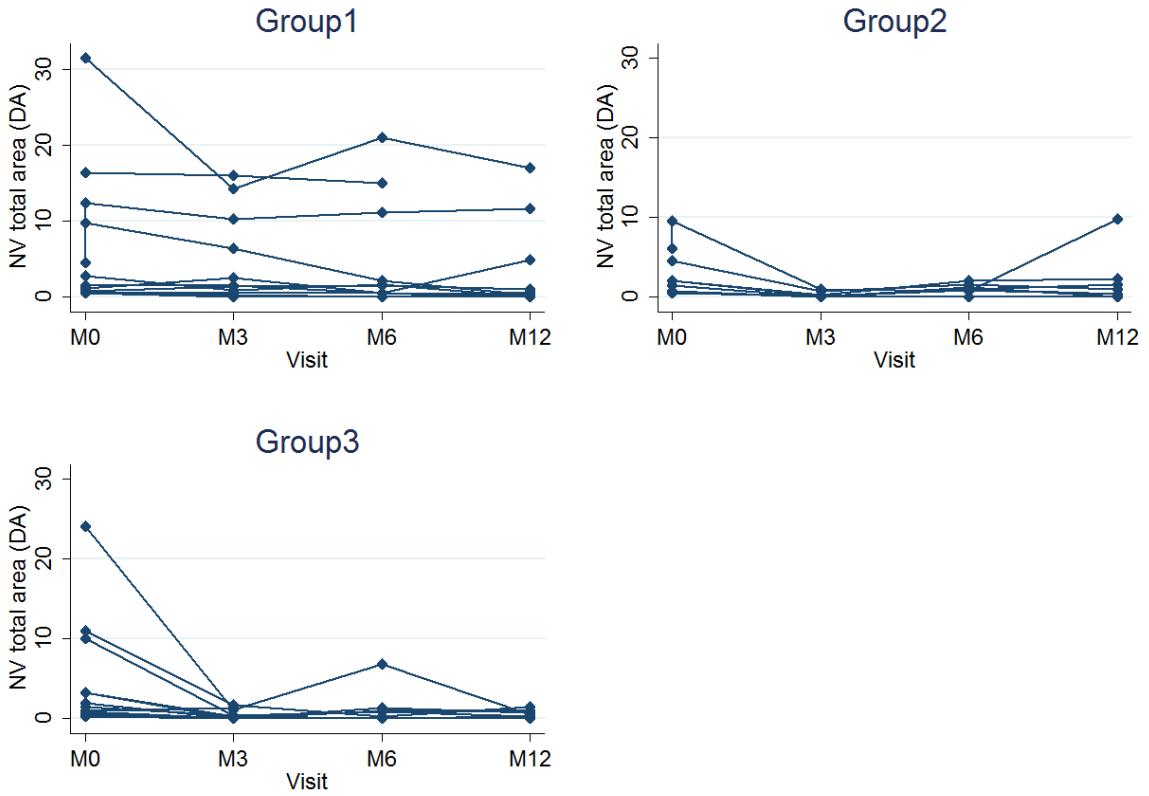
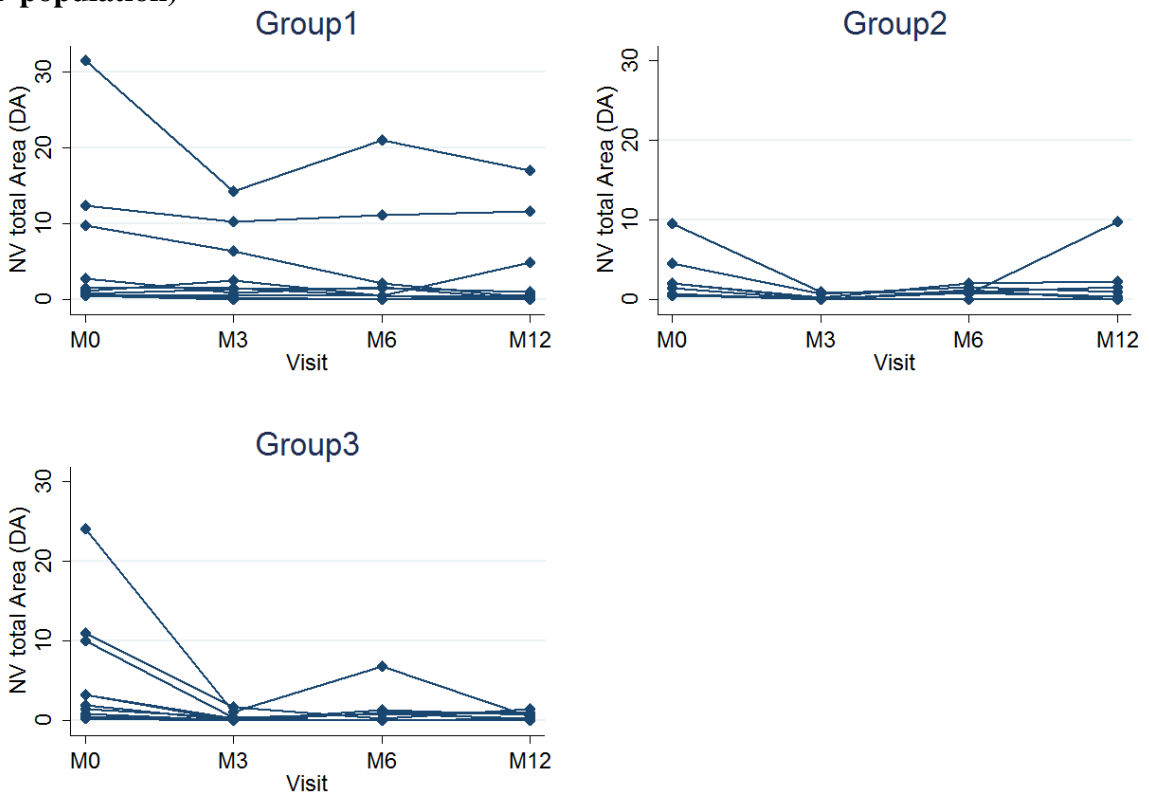


Figure 11-9. Primary efficacy parameter: NV total area by patients, groups and visits (PP population)



NV areas differences from screening and the remains visits are shown in Table 11-12 and Table 11-13. There was no statistically significant differences between groups for the three NV areas changes from screening to month-3.
Group 1 showed a statistically significant change from screening in the NVE and NV total areas ($p \leq 0.007$).
Group 2 showed a statistically significant change from screening in the NVD area ($p = 0.024$).
Group 3 showed a statistically significant change from screening in the three NV areas ($p = 0.008$).

Table 11-12. Primary efficacy parameter (Changes from screening in NV areas) by groups and visits (ITT population)

		Group 1		Group 2		Group 3		
		Mean ± SD	**Median (IQR)**	**Mean ± SD**	**Median (IQR)**	**Mean ± SD**	**Median (IQR)**	p[1]
NVE	Month 3	-1.8 ± 3.8	-0.4 (-2;-0.2)	-1.8 ± 2.5	-0.8 (-1.9;-0.6)	-3.5 ± 5.5	-1.2 (-5.3;-0.2)	0.607
	Month 6	-1.6 ± 2.4	-0.8 (-1.5;-0.3)	-1.1 ± 2.8	0 (-0.8;0.3)	-3.5 ± 4.7	-1 (-8.9;-0.3)	0.152
	Month 12	-1.9 ± 3.9	-0.7 (-2.8;-0.1)	-0.4 ± 0.9	-0.6 (-0.6;0)	-4.1 ± 6.0	-1.2 (-8.9;-0.3)	0.202
	p[2]	0.007		0.085		0.002		
NVD	Month 3	-0.3 ± 1.4	0 (-0.2;0.1)	-0.6 ± 1.1	0 (-0.3;0)	-1.0 ± 1.6	-0.4 (-1.2;0)	0.065
	Month 6	-0.4 ± 1.5	0 (-0.2;0)	-0.5 ± 1.2	0 (-0.5;0)	-1.0 ± 1.8	-0.5 (-1.4;0)	0.166
	Month 12	-0.4 ± 1.6	0 (-0.3;0)	-0.4 ± 1.1	0 (-0.5;0)	-1.0 ± 1.7	-0.5 (-1.4;0)	0.247
	p[2]	0.058		0.024		0.002		
NV Total	Month 3	-2.0 ± 5.0	-0.5 (-2;0)	-2.3 ± 2.6	-1.5 (-1.9;-0.8)	-4.4 ± 6.7	-1.5 (-6.3;-0.6)	0.183
	Month 6	-2.0 ± 3.4	-0.8 (-1.3;-0.5)	-1.6 ± 2.8	-0.5 (-1.2;-0.3)	-4.5 ± 5.8	-1.5 (-9.1;-0.6)	0.244
	Month 12	-2.3 ± 5.1	-0.6 (-2.8;0.1)	-0.8 ± 1.3	-0.6 (-1.5;0.2)	-5.1 ± 7.3	-1.8 (-9.1;-0.8)	0.178
	p[2]	0.004		0.055		0.002		

[1] Kruskal Wallis test; [2] Friedman

Table 11-13. Primary efficacy parameter (Changes from screening of NV areas) by groups and visits (PP population)

		Group 1		Group 2		Group 3		
		Mean ± SD	**Median (IQR)**	**Mean ± SD**	**Median (IQR)**	**Mean ± SD**	**Median (IQR)**	p[1]
NVE	Month 3	-1.9 ± 3.9	-0.6 (-2.2;-0.2)	-1.8 ± 2.5	-0.8 (-1.9;-0.6)	-4.1 ± 5.8	-1.4 (-8.7;-0.3)	0.607
	Month 6	-1.7 ± 2.5	-0.6 (-1.7;-0.1)	-1.1 ± 2.8	0 (-0.8;0.3)	-3.5 ± 4.7	-1 (-8.9;-0.3)	0.152
	Month 12	-1.9 ± 3.9	-0.7 (-2.8;-0.1)	-0.4 ± 0.9	-0.6 (-0.6;0)	-4.1 ± 6.0	-1.2 (-8.9;-0.3)	0.202
		0.007		0.085		0.002		
NVD	Month 3	-0.3 ± 1.4	0 (-0.2;0.2)	-0.6 ± 1.1	0 (-0.3;0)	-1.1 ± 1.7	-0.5 (-1.4;0)	0.065
	Month 6	-0.4 ± 1.5	0 (-0.2;0)	-0.5 ± 1.2	0 (-0.5;0)	-1.0 ± 1.8	-0.5 (-1.4;0)	0.166
	Month 12	-0.4 ± 1.6	0 (-0.3;0)	-0.4 ± 1.1	0 (-0.5;0)	-1.0 ± 1.7	-0.5 (-1.4;0)	0.247
		0.058		0.024		0.002		
NV Total	Month 3	-2.2 ± 5.2	-0.6 (-2.1;0)	-2.3 ± 2.6	-1.5 (-1.9;-0.8)	-5.2 ± 7.1	-2.4 (-9.2;-0.9)	0.183
	Month 6	-2.1 ± 3.6	-0.6 (-1.2;-0.5)	-1.6 ± 2.8	-0.5 (-1.2;-0.3)	-4.5 ± 5.8	-1.5 (-9.1;-0.6)	0.244
	Month 12	-2.3 ± 5.1	-0.6 (-2.8;0.1)	-0.8 ± 1.3	-0.6 (-1.5;0.2)	-5.1 ± 7.3	-1.8 (-9.1;-0.8)	0.178
		0.004		0.055		0.002		

[1] Kruskal Wallis test; [2] Friedman

Table 11-14 and Table 11-15 show number of the cases with any decrease of the NV area by groups. No statistically significant differences were found between groups in the proportion of subjects with any decrease in the three NV total areas, except for the NV total in the PP population (p = 0.039).

Table 11-14. Primary efficacy parameter: Any decrease of NV by groups (ITT population)

		Group 1		Group 2		Group 3		p[1]
		No.	%	No.	%	No.	%	
NVE	Without any decrease	3	25.0	5	55.6	3	25.0	
	With any decrease	9	75.0	4	44.4	9	75.0	0.311
NVD	Without any decrease	9	75.0	6	66.7	4	33.3	
	With any decrease	3	25.0	3	33.3	8	66.7	0.142
NV Total	Without any decrease	5	41.7	3	33.3	1	8.3	
	With any decrease	7	58.3	6	66.7	11	91.7	0.218

[1] Exact Fisher's test

Table 11-15. Primary efficacy parameter: Any decrease of NV by groups (PP population)

		Group 1		Group 2		Group 3		p[1]
		No.	%	No.	%	No.	%	
NVE	Without any decrease	3	27.3	5	55.6	2	20.0	
	With any decrease	8	72.7	4	44.4	8	80.0	0.303
NVD	Without any decrease	9	81.8	6	66.7	3	30.0	
	With any decrease	2	18.2	3	33.3	7	70.0	0.052
NV Total	Without any decrease	5	45.5	3	33.3	0	0	
	With any decrease	6	54.5	6	66.7	10	100	0.039

[1] Exact Fisher's test

11.2.1.2 Secondary efficacy analysis

In this section we analyse the secondary efficacy parameters (BCVA, CMT, Complete remission of NV, Recurrence of NV, Relapse of NV, Regression of NV, and number of treatments needed).

11.2.1.2.1 BCVA

Table 11-16 and Table 11-17 show BCVA progression during the study, by group. No significant differences were observed between groups for all the study visits and no statistical differences were found between visits in each group. The results are similar in the ITT and PP populations.

Table 11-16. Secondary efficacy parameter: BCVA letters by groups and visits (ITT population)

	Group 1	Group 2	Group 3	p[1]
	Mean ± SD / Median (IQR)	Mean ± SD / Median (IQR)	Mean ± SD / Median (IQR)	
Screening	70.2 ± 17 / 76 (71 - 78)	74.7 ± 9.2 / 76.5 (73 - 79)	70.9 ± 12.7 / 76 (64 - 79)	0.777
Month 3	59.9 ± 25 / 67 (60 - 77)	72.4 ± 4.6 / 73 (69 - 74)	73.2 ± 10.5 / 78 (63 - 81)	0.173
Month 6	69.5 ± 17.9 / 74 (64 - 82)	74.6 ± 9.5 / 75 (71 - 79)	72.5 ± 12.3 / 77 (63 - 82)	0.924
Month 12	65.9 ± 16.4 / 69 (60.5 - 78.5)	72.2 ± 8.4 / 68 (67 - 77)	70.8 ± 11.3 / 74 (59 - 80)	0.841
p[2]	0.548	0.207	0.844	

[1] Kruskal Wallis test (between groups); [2] Friedman test (within visits)

Table 11-17. Secondary efficacy parameter: BCVA letters by groups and visits (PP population)

	Group 1	Group 2	Group 3	p[1]
	Mean ± SD / Median (IQR)	Mean ± SD / Median (IQR)	Mean ± SD / Median (IQR)	
Screening	69.5 ± 18.5 / 76 (61 - 79)	75.9 ± 8.9 / 77 (74 - 79)	73.3 ± 8.3 / 76 (65 - 79)	0.708
Month 3	67.9 ± 15.4 / 68 (62 - 77)	72.4 ± 4.6 / 73 (69 - 74)	72.3 ± 10.6 / 77.5 (63 - 80)	0.556
Month 6	69.5 ± 17.9 / 74 (64 - 82)	74.6 ± 9.5 / 75 (71 - 79)	72.5 ± 12.3 / 77 (63 - 82)	0.924
Month 12	68.8 ± 13.6 / 69 (62 - 79)	72.2 ± 8.4 / 68 (67 - 77)	72.7 ± 9.9 / 74 (67 - 80)	0.882
p[2]	0.731	0.218	0.685	

[1] Kruskal Wallis test (between groups); [2] Friedman test (within visits)

Figure 11-10, Figure 11-11 and Figure 11 12 show the BCVA by visits, by groups and by patients.

Figure 11-10. Secondary efficacy parameter (BCVA letters) by groups, by visits and by populations (ITT and PP) – mean value

Figure 11-11. Secondary efficacy parameter: BCVA letters by patients, groups and visits (ITT population)

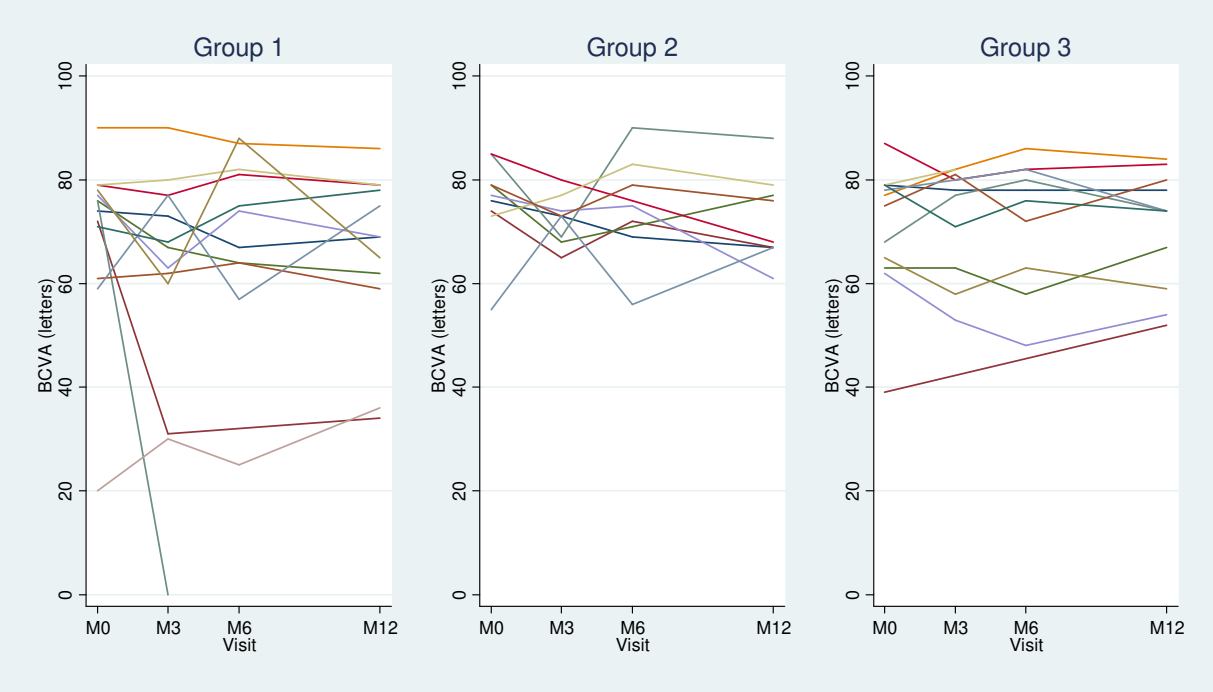
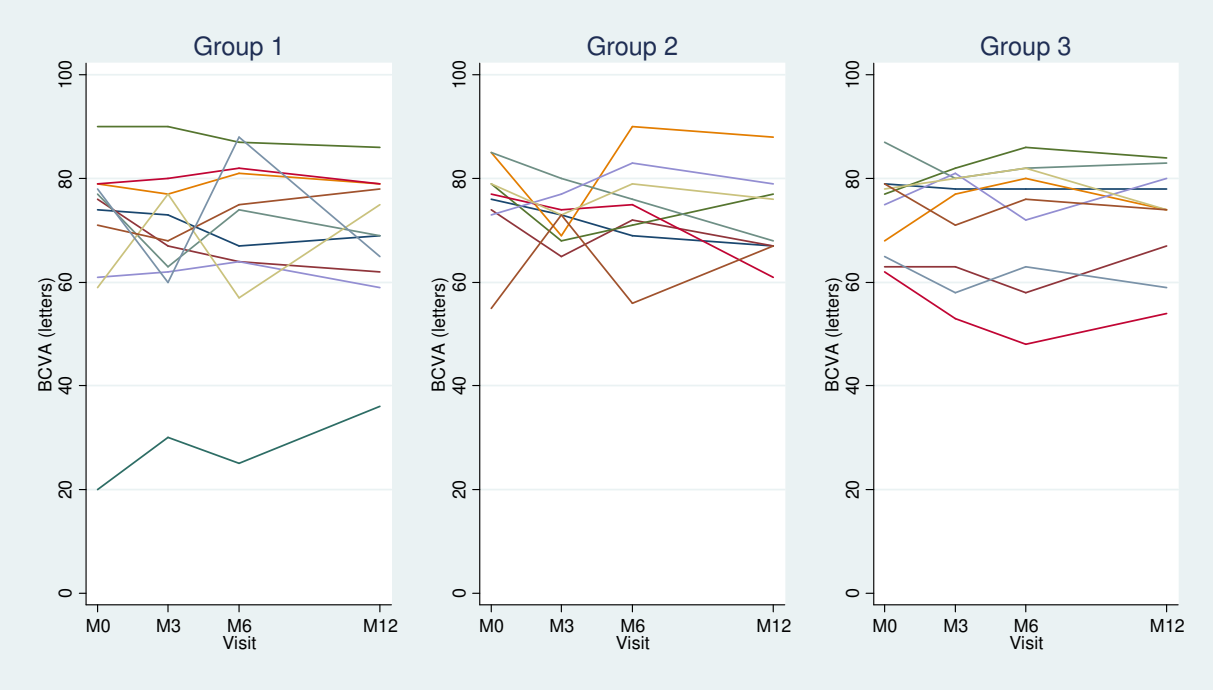


Figure 11-12. Secondary efficacy parameter: BCVA letters by patients, groups and visits (PP population)



Analysing BCVA changes from screening to the remains study visits (Table 11-18 and Table 11-19), there was no statistically significant differences between groups for the changes of BCVA from screening to months 3, 6 and 12.

Table 11-18. Secondary efficacy parameter (Changes from screening of BCVA letters) by groups and visits (ITT population)

	Group 1	Group 2	Group 3	p[1]
	Mean ± SD / Median (IQR)	Mean ± SD / Median (IQR)	Mean ± SD / Median (IQR)	
Month 3	-10.3 ± 24.4 / -2 (-14 / 1)	-3.4 ± 9.8 / -5 (-9 / -3)	-0.6 ± 6.3 / 0 (-7 / 5)	0.447
Month 6	1.6 ± 12 / 2 (-5 / 7)	2.1 ± 10.3 / 3 (-4 / 6)	0.2 ± 4.9 / 2 (-5 / 4)	0.751
Month 12	-0.6 ± 10.3 / -2 (-5 / 3)	-2.3 ± 7.3 / -3 (-5 / -2)	0.2 ± 5.8 / -1 (-4 / 6)	0.603

[1] Kruskal Wallis test

Table 11-19. Secondary efficacy parameter (Changes from screening of BCVA letters) by groups and visits (PP population)

	Group 1	Group 2	Group 3	p[1]
	Mean ± SD / Median (IQR)	Mean ± SD / Median (IQR)	Mean ± SD / Median (IQR)	
Month 3	-1.6 ± 10.1 / -1 (-9 / 1)	-3.4 ± 9.8 / -5 (-9 / -3)	-1 ± 6.5 / -0.5 (-7 / 5)	0.563
Month 6	1.6 ± 12 / 2 (-5 / 7)	2.1 ± 10.3 / 3 (-4 / 6)	0.2 ± 4.9 / 2 (-5 / 4)	0.751
Month 12	-0.6 ± 10.3 / -2 (-5 / 3)	-2.3 ± 7.3 / -3 (-5 / -2)	0.2 ± 5.8 / -1 (-4 / 6)	0.603

[1] Kruskal Wallis test

11.2.1.2.2 Central Macular Thickness (CMT)

Table 11-20 and Table 11-21 show the results for the progression of the CMT during the study, by group. No statistically significant differences were found between groups for the four study visits.

In Group 1 and Group 2, no significant differences were found between visits for the CMT. In Group 3, a statistical difference between visits was found (p = 0.021). Multiple comparisons (with Bonferroni correction) showed a statistical decrease of the CMT between screening and month-3 (p = 0.004 in ITT and p = 0.007 in PP).

Table 11-20. Secondary efficacy parameter: CMT by groups and visits (ITT population)

	Group 1	Group 2	Group 3	p[1]
	Mean ± SD / Median (IQR)	Mean ± SD / Median (IQR)	Mean ± SD / Median (IQR)	
Screening	329.3 ± 92.6 / 317 (275.5 - 351)	323.3 ± 62.1 / 319.5 (256 - 378)	377 ± 168 / 331 (290 - 408)	0.836
Month 3	351.6 ± 115.5 / 329 (268 - 423)	314 ± 107.3 / 274 (251 - 318)	288.5 ± 51.8 / 313 (223 - 330)	0.474
Month 6	360.8 ± 134.6 / 322 (264 - 431)	340.4 ± 118.3 / 311 (253 - 353)	336.4 ± 110.3 / 346 (300 - 362)	0.883
Month 12	334.6 ± 111.7 / 309 (266 - 339)	333.4 ± 129 / 290 (260 - 337)	328.2 ± 77.3 / 332 (302 - 356)	0.781
p[2]	0.413	0.273	0.021	

[1] Kruskal Wallis test (between groups); [2] Friedman test (within visits)

Table 11-21. Secondary efficacy parameter: CMT by groups and visits (PP population)

	Group 1	Group 2	Group 3	p[1]
	Mean ± SD / Median (IQR)	Mean ± SD / Median (IQR)	Mean ± SD / Median (IQR)	
Screening	334.3 ± 101.1 / 322.5 (268 - 355)	313.6 ± 57.2 / 300 (256 - 372)	345.5 ± 83 / 331 (310 - 357)	0.800
Month 3	351.6 ± 115.5 / 329 (268 - 423)	314 ± 107.3 / 274 (251 - 318)	296 ± 47.8 / 314 (284 - 330)	0.570
Month 6	360.8 ± 134.6 / 322 (264 - 431)	340.4 ± 118.3 / 311 (253 - 353)	336.4 ± 110.3 / 346 (300 - 362)	0.883
Month 12	334.6 ± 111.7 / 309 (266 - 339)	333.4 ± 129 / 290 (260 - 337)	312.6 ± 60.6 / 323.5 (302 - 336)	0.897
p[2]	0.413	0.284	0.029	

[1] Kruskal Wallis test (between groups); [2] Friedman test (within visits)

Figure 11-13, Figure 11-14 and Figure 11 15 show the CMT area by visits, by groups and by patients.

Figure 11-13. Secondary efficacy parameter: CMT by groups, by visits and by populations (ITT and PP populations) – mean value

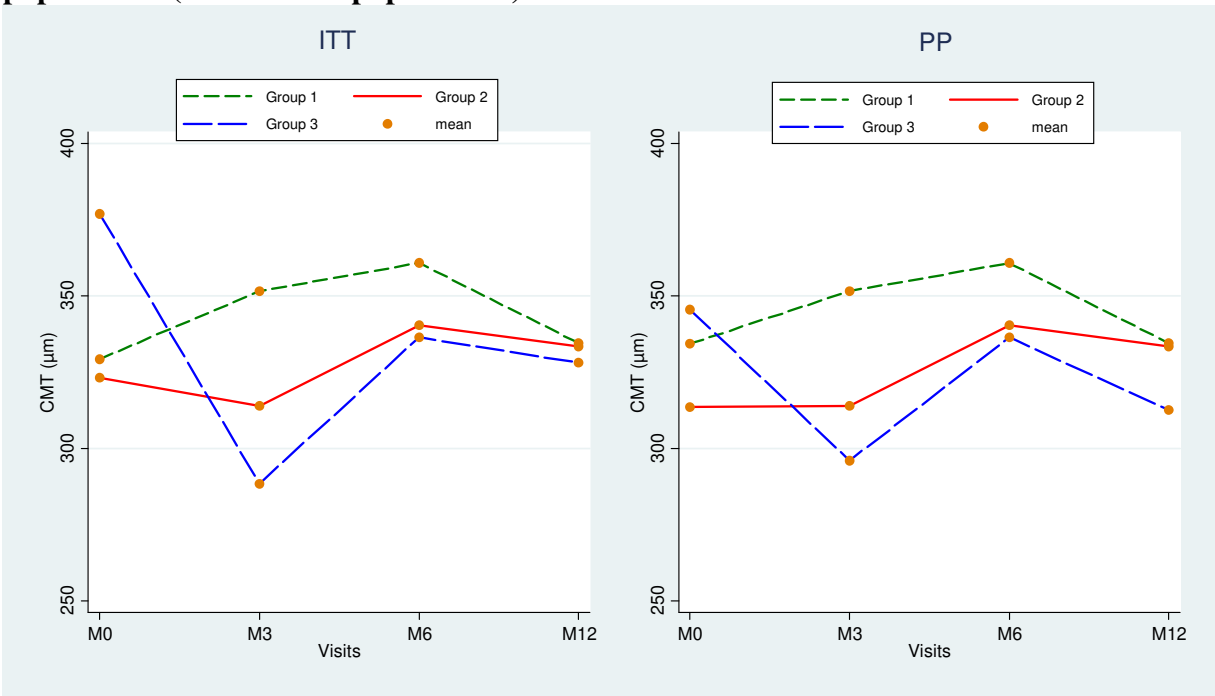


Figure 11-14. Secondary efficacy parameter: CMT by patients, groups, visits (ITT population)

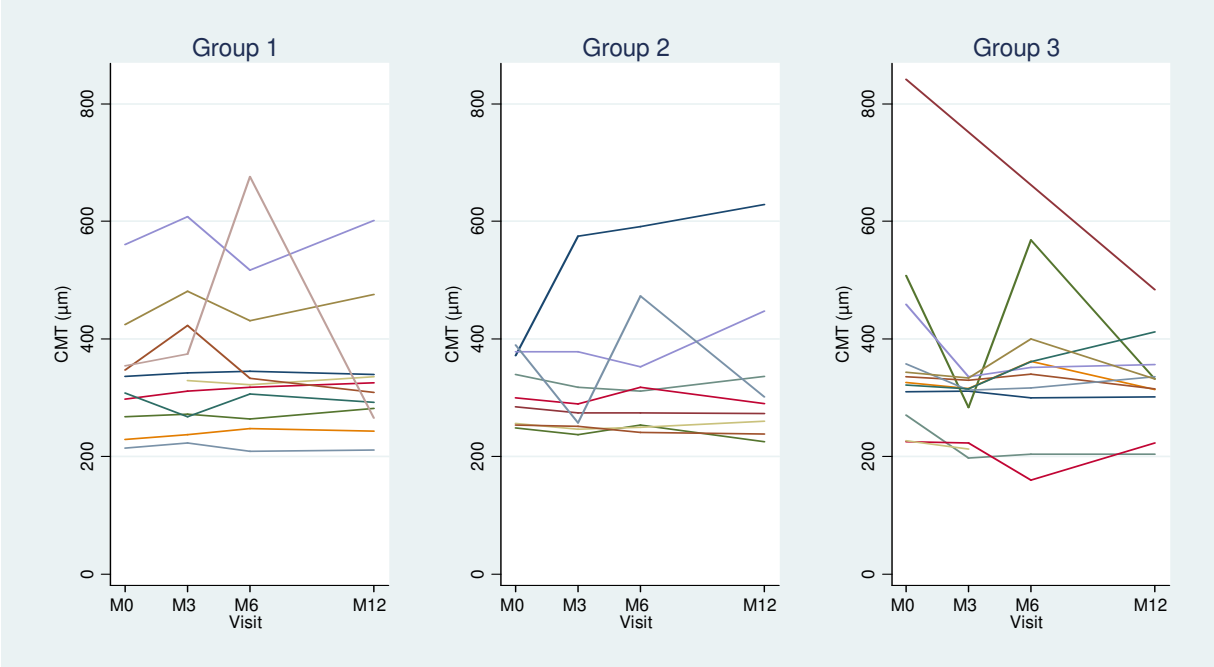
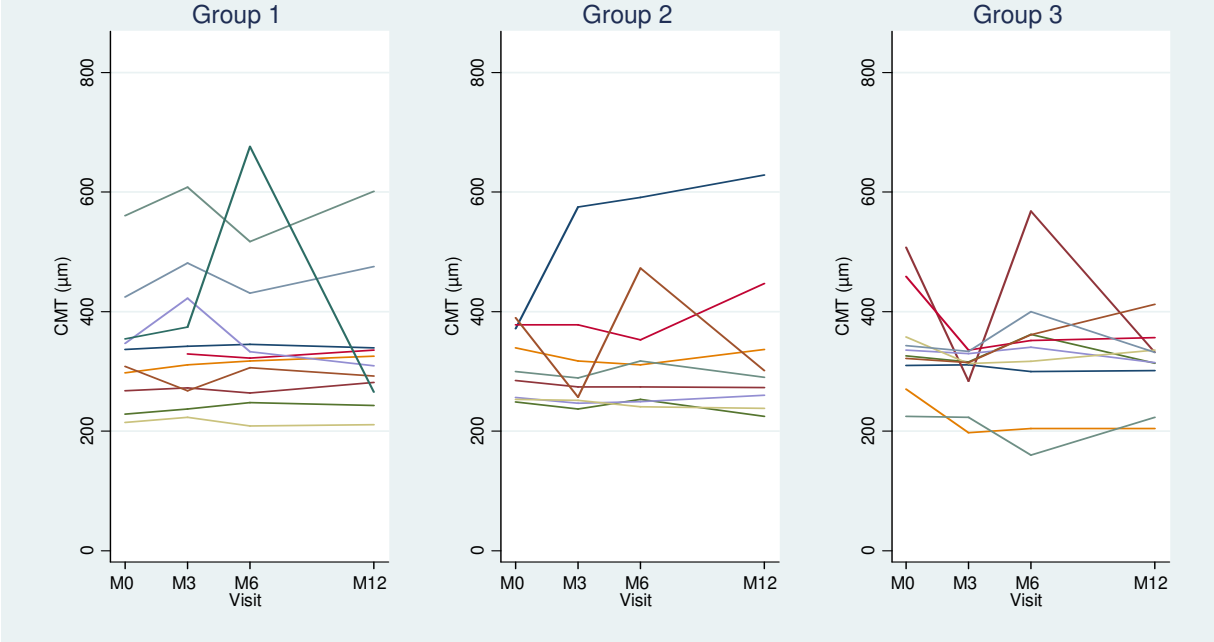


Figure 11-15. Secondary efficacy parameter: CMT by patients, groups, visits (PP population)



Analysing changes of the CMT from screening to the remainings visits (Table 11-22 and Table 11-23). There is no statistically significant differences between groups for the CMT changes at months 6 and 12. Statistical differences between groups were found for the CMT changes from screening to month-3 (p = 0.003). Multiple comparisons (with Bonferroni correction) showed a decrease of the CMT higher in Group 3 (p = 0.001 in ITT and PP population) than Group 1.

Table 11-22. Secondary efficacy parameter (Changes from screening of Macular Retinal Thickness) by groups and visits (ITT population)

	Group 1	Group 2	Group 3	p[1]
	Mean ± SD / Median (IQR)	Mean ± SD / Median (IQR)	Mean ± SD / Median (IQR)	
Month 3	19.6 ± 32.6 / 10.5 (5 / 47)	0.4 ± 86.5 / -11 (-12 / -2)	-46.3 ± 70.2 / -10 (-72 / -6)	0.003
Month 6	30.4 ± 103.7 / 2 (-6 / 19)	26.9 ± 79.4 / -6 (-12 / 18)	-9.1 ± 58.4 / -3 (-65 / 40)	0.791
Month 12	0.1 ± 40.8 / 8 (-16 / 27)	19.9 ± 97.5 / -10 (-15 / 4)	-62.5 ± 118.6 / -21 (-103 / -8)	0.137

[1] Kruskal Wallis test

Table 11-23. Secondary efficacy parameter (Changes from screening of Macular Retinal Thickness) by groups and visits (PP population)

	1- PRP	2- ITV	Group 3	p[1]
	Mean ± SD / Median (IQR)	Mean ± SD / Median (IQR)	Mean ± SD / Median (IQR)	
Month 3	19.6 ± 32.6 / 10.5 (5 / 47)	0.4 ± 86.5 / -11 (-12 / -2)	-49.5 ± 73.2 / -9.5 (-72 / -6)	0.004
Month 6	30.4 ± 103.7 / 2 (-6 / 19)	26.9 ± 79.4 / -6 (-12 / 18)	-9.1 ± 58.4 / -3 (-65 / 40)	0.791
Month 12	0.1 ± 40.8 / 8 (-16 / 27)	19.9 ± 97.5 / -10 (-15 / 4)	-32.9 ± 70.4 / -16.5 (-66 / -8)	0.237

[1] Kruskal Wallis test

11.2.1.2.3 NV – Complete remission

NV complete remission was defined as a decrease of the NV area to zero from baseline to months 3, 6 and 12.
Table 11-24 and Table 11-25 show complete remission of NV area by groups and visits. No statistical differences between groups were found.

Table 11-24. Secondary efficacy parameter: Complete remission of NV by groups and visits (ITT population) – cases with a NV area > 0 at baseline

			Group 1		Group 2		Group 3		p[1]
			No.	%	No.	%	No.	%	
NVE	Month 3	No	9	81.8	4	50.0	6	54.5	
		Yes	2	18.2	4	50.0	5	45.5	0.358
	Month 6	No	9	81.8	7	87.5	6	66.7	
		Yes	2	18.2	1	12.5	3	33.3	0.616
	Month 12	No	6	60.0	5	62.5	5	55.6	
		Yes	4	40.0	3	37.5	4	44.4	1.000
NVD	Month 3	No	5	83.3	2	50.0	2	25.0	
		Yes	1	16.7	2	50.0	6	75.0	0.138
	Month 6	No	4	66.7	1	25.0	3	42.9	
		Yes	2	33.3	3	75.0	4	57.1	0.582
	Month 12	No	4	80.0	2	50.0	4	57.1	
		Yes	1	20.0	2	50.0	3	42.9	0.668
NV Total	Month 3	No	10	83.3	5	55.6	7	58.3	
		Yes	2	16.7	4	44.4	5	41.7	0.379
	Month 6	No	10	83.3	7	77.8	7	70.0	
		Yes	2	16.7	2	22.2	3	30.0	0.864
	Month 12	No	8	72.7	7	77.8	8	80.0	
		Yes	3	27.3	2	22.2	2	20.0	1.000

[1] Exact Fisher's test

Table 11-25. Secondary efficacy parameter: Complete remission of NV by groups and visits (PP population) – cases with a NV area > 0 at baseline

			Group 1		Group 2		Group 3		p[1]
			No.	%	No.	%	No.	%	
NVE	Month 3	No	8	80.0	4	50.0	5	55.6	
		Yes	2	20.0	4	50.0	4	44.4	0.368
	Month 6	No	8	80.0	7	87.5	6	66.7	
		Yes	2	20.0	1	12.5	3	33.3	0.730
	Month 12	No	6	60.0	5	62.5	5	55.6	
		Yes	4	40.0	3	37.5	4	44.4	1.000
NVD	Month 3	No	4	50.0	2	50.0	2	28.6	
		Yes	1	20.0	2	50.0	5	71.4	0.217
	Month 6	No	3	60.0	1	25.0	3	42.9	
		Yes	2	40.0	3	75.0	4	57.1	0.816
	Month 12	No	4	80.0	2	50.0	4	57.1	
		Yes	1	20.0	2	50.0	3	42.9	0.668
NV Total	Month 3	No	9	81.8	5	55.6	6	60.0	
		Yes	2	18.2	4	44.4	4	40.0	0.390
	Month 6	No	9	81.8	7	77.8	7	70.0	
		Yes	2	18.2	2	22.2	3	30.0	0.869
	Month 12	No	8	72.7	7	77.8	8	80.0	
		Yes	3	27.3	2	22.2	2	20.0	1.000

[1] Exact Fisher's test

11.2.1.2.4 NV – Recurrence

NV recurrence was defined as a decrease of the NV area from baseline to months 3 or 6 followed by an increase of the NV area in months 6 or 12.

Only data from the PP population is presented since the NV recurrence requires data at months 3, 6 and 12.
Table 11-26 show NV recurrence by groups and visits. No statistically significant differences were found between groups in the proportion of subjects with NV recurrence.

Table 11-26. Secondary efficacy parameter: Recurrence of NV by groups (PP population)

		Group 1		Group 2		Group 3		p[1]
		No.	%	No.	%	No.	%	
NVE	No	5	45.5	1	11.1	5	50.0	
	Yes	6	54.5	8	88.9	5	50.0	0.176
NVD	No	10	90.9	7	77.8	6	60.0	
	Yes	1	9.1	2	22.2	4	40.0	0.265
NV Total	No	6	54.5	1	11.1	2	20.0	
	Yes	5	45.5	8	88.9	8	80.0	0.097

[1] Exact Fisher's test

11.2.1.2.5 NV – Relapse

NV relapse was defined as a decrease of the NV area to zero from baseline to months 3 or 6 followed by an increase of the NV area in months 6 or 12.

Only data from the PP population is presented since the NV recurrence requires data at months 3, 6 and 12.

Table 11 28 present relapse of NV area by groups. No significant differences were found between groups in the proportion of subjects with NV relapse.

Table 11-27. Secondary efficacy parameter: Relapse of NV by groups (PP population)

		Group 1		Group 2		Group 3		p[1]
		No.	%	No.	%	No.	%	
NVE	No	10	90.9	5	55.6	8	80.0	
	Yes	1	9.1	4	44.4	2	20.0	0.190
NVD	No	10	90.9	8	88.9	7	70.0	
	Yes	1	9.1	1	11.1	3	30.0	0.475
NV Total	No	10	99.9	5	55.6	6	60.0	
	Yes	1	9.1	4	44.4	4	40.0	0.149

[1] Exact Fisher's test

11.2.1.2.6 Need for vitrectomy

Other secondary parameters analysed were the need for vitrectomy regarding to the occurrence of vitreous haemorrhage and to the occurrence of vitreous haemorrhage or Vitreal haemorrhage density of 3+ or 4+ in some visit, the results are presented in Table 11-28. No statistically significant differences were found between groups in these two parameters.

Table 11-28. Secondary efficacy parameter: Occurrence of vitreous haemorrhage by groups

		Group 1		Group 2		Group 3		p[1]
		No.	%	No.	%	No.	%	
Vitrectomy	No	10	76.9	9	90.0	11	91.7	0.593
	Yes	3	23.1	1	10.0	1	8.3	
Vitrectomy or Vitreal haemorrhage density = 3+ or 4+	No	9	69.2	8	88.9	10	90.9	0.391
	Yes	4	30.8	1	11.1	1	9.1	

11.2.1.2.7 IOP

Table 11-29 and Table 11-30 show the results for the IOP at screening and final visits. No significant differences were found between groups in these visits for the ITT and PP populations. Analysing results for the three groups no significant differences between screening and final visits were found for groups 1 and 2. There was a significant IOP increase between screening and final visit for Group 3 (p = 0.020 in ITT population and p = 0.028 in PP population).

Table 11-29. Secondary efficacy parameter: IOP by groups and visits (ITT population)

	Group 1	Group 2	Group 3	p[1]
	Mean ± SD / Median (IQR)	Mean ± SD / Median (IQR)	Mean ± SD / Median (IQR)	
Screening	16.0 ± 1.4 / 16 (16 - 17)	16.3 ± 2.1 / 16 (15 - 16)	15.2 ± 1.9 / 16 (14 - 16.5)	0.558
Month 12	15.8 ± 2.7 / 16 (14 - 17)	16.6 ± 2.9 / 16 (15 - 18)	18.0 ± 3.4 / 17 (16 - 19)	0.248
p[2]	0.972	0.795	0.020*	

[1] Kruskal Wallis test (between groups); [2] Wilcoxon test (within visits)

Table 11-30. Secondary efficacy parameter: IOP by groups and visits (PP population)

	Group 1	Group 2	Group 3	p[1]
	Mean ± SD / Median (IQR)	Mean ± SD / Median (IQR)	Mean ± SD / Median (IQR)	
Screening	15.9 ± 1.5 / 16 (15 - 17)	15.9 ± 1.7 / 16 (15 - 16)	15.1 ± 1.9 / 16 (14 - 16)	0.681
Month 12	16.0 ± 2.9 / 16 (14 - 18)	16.4 ± 3.0 / 16 (15 - 18)	18.2 ± 3.5 / 17.5 (16 - 19)	0.277
p[2]	0.718	0.584	0.028*	

[1] Kruskal Wallis test (between groups); [2] Wilcoxon test (within visits)

11.2.1.2.8 Additional focal or grid laser for DME

Table 11-31 and Table 11-32 shows the efficacy results regarding to additional focal or grid laser for DME by groups. No significant differences were found in the proportion of subjects which needed additional focal or grid laser for DME between treatments.

Table 11-31. Secondary efficacy parameter: additional focal or grid laser for DME by groups (ITT population)

	Group 1		Group 2		Group 3		p[1]
	No.	%	No.	%	No.	%	
No	11	84.6	10	100.0	9	75.0	0.283
Yes	2	15.4	0	0.0	3	25.0	

[1] Exact Fisher's test

Table 11-32. Secondary efficacy parameter: additional focal or grid laser for DME by groups (PP population)

	Group 1		Group 2		Group 3		p[1]
	No.	%	No.	%	No.	%	
No	9	81.8	9	100.0	7	70.0	0.212
Yes	2	18.2	0	0.0	3	30.0	

11.2.1.2.9 Number of treatments

In Table 11 36, Table 11 38, Table 11 38 and Table 11 39 are presented the results regarding to the number of PRP treatments and the number of ITV treatments. No statistically significant differences were found between groups 1 and 3 for the number of PRP treatments, and between groups 2 and 3 for the number of ITV treatments.

Table 11-33. Secondary efficacy parameter: Number of PRP treatments by group (ITT population)

	Group 1		Group 3		p[1]
	No.	%	No.	%	
0	0	0.0	1	8.3	0.378
1	4	30.8	1	8.3	
2	2	15.4	0	0.0	
3	1	7.7	2	16.7	
4	2	15.4	4	33.3	
5	3	23.1	1	8.3	
6	0	0.0	1	8.3	
7	0	0.0	1	8.3	
8	1	7.7	1	8.3	
Mean ± SD / Median (IQR)	3.2 ± 2.2 / 3 (1-5)		4.1 ± 2.3 / 4 (3-5.5)		

[1] Mann-Whitney test

Table 11-34. Secondary efficacy parameter: Number of PRP treatments by group (PP population)

	Group 1		Group 3		p[1]
	No.	%	No.	%	
0	0	0.0	0	0.0	0.089
1	2	18.2	0	0.0	
2	2	18.2	0	0.0	
3	1	9.1	2	20.0	
4	2	18.2	4	40.0	
5	3	27.3	1	10.0	
6	0	0.0	1	10.0	
7	0	0.0	1	10.0	
8	1	9.1	1	10.0	
Mean ± SD / Median (IQR)	3.6 ± 2.1 / 4 (2-5)		4.8 ± 1.7 / 4 (4-6)		

[1] Mann-Whitney test

Table 11-35. Secondary efficacy parameter: Number of ITV treatment by groups (ITT population)

	Group 2		Group 3		p[1]
	No.	%	No.	%	
0	0	0.0	0	0.0	0.616
1	1	10.0	0	0.0	
2	0	0.0	1	8.3	
3	1	10.0	1	8.3	
4	4	40.0	1	8.3	
5	0	0.0	3	25.0	
6	1	0.0	4	33.3	
7	2	20.0	1	8.3	
8	0	0.0	1	8.3	
9	1	0.0	0	0.0	
Mean ± SD / Median (IQR)	4.9 ± 2.3 / 4 (4-7)		5.3 ± 1.7 / 5.5 (4.5-6)		

[1] Mann-Whitney test

Table 11-36. Secondary efficacy parameter: Number of ITV treatment by groups (PP population)

	Group 2		Group 3		p[1]
	No.	**%**	**No.**	**%**	
0	0	0.0	0	0.0	0.404
1	0	0.0	0	0.0	
2	0	0.0	0	0.0	
3	1	11.1	0	0.0	
4	4	44.4	1	10.0	
5	0	0.0	3	30.0	
6	1	11.1	4	40.0	
7	2	22.2	1	10.0	
8	0	0.0	1	10.0	
9	1	10.0	0	0.0	
Mean ± SD / Median (IQR)	5.3 ± 2.0 / 4 (4-7)		5.8 ± 1.1 / 6 (5-6)		

[1] Mann-Whitney test

11.2.2 Statistical / Analytical Issues

Due to the small number of cases (recruitment below 65% of the planned and drop-out rate of 14.3%), the distribution of data doesn't follow a normal distribution and therefore non-parametric tests (Mann-Whitney test, Wilcoxon test, Kruskal-Wallis test and Friedman test) were used. The Exact Fisher test was used for nominal and/or categorical variables.

Considering the primary efficacy results at month-12 for the PP population, the small number of cases included in this study only provides 40.3% power to detect a statistically significant difference between groups, therefore the primary efficacy results of this study cannot be considered conclusive.

11.2.2.1 Adjustments for Covariates

Adjustments for Covariates was not performed.

11.2.2.2 Handling of Dropouts or Missing Data

The PP population was used without missing data imputation due to the small number of drop-outs, the small sample size and due to the similar results found between the ITT and the PP populations.

11.2.2.3 Interim Analyses and Data Monitoring

No interim analyses were performed.
Three on-site monitoring visits were performed in each clinical centre.

11.2.2.4 Multicenter 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 except for the CMT.
A correction was applied to correct measures obtained for the CMT, because centres could used either the Cirrus HD-OCT or the Spectralis HRA+OCT. The Cirrus HD-OCT measures were considered as reference, correcting measures obtained by Spectralis HRA+OCT subtracting 15 µm.

11.2.2.5 Multiple Comparisons/Multiplicity

The Bonferroni adjustment for multiple comparisons was used for the Fisher Exact test, Kruskall-Wallis test and Friedman test.

11.2.3 Tabulation of individual response data

Individual data is provided in appendix.

11.2.4 By-patient displays

By-patient displays are included in the efficacy analysis.

11.2.5 Efficacy conclusions

Of the 54 eyes required in the sample size calculation, it was possible to randomize only 35 eyes/patients: 13 to PRP group, 10 to ITV group and the remaining 12 to the combined treatment group (PRP+ITV). Of these, 32 completed the study and 3 withdraw (2 removed informed consent and one subject from PRP+ITV group withdraw due to coronary heart ischemia).

At baseline, the 3 study groups were well balanced, presenting similar clinical and demographic characteristics ($p \geq 0.060$). All included subjects were type 2 diabetics.

Twelve months after the initial visit, subjects treated with PRP+ITV presented higher proportions both for NVD and NVE regression.
This good response in all study groups is more clear when considering NVE regression which was 100.0% (9 out of 9 subjects), 75.0% (6 out of 8 subjects) and 69.2% (9 out of 13 subjects) respectively for PRP+ITV, ITV alone and PRP alone. Regarding NVD the respective values were 87.5% (7 out of 8 subjects), 60.0% (3 out of 5 subjects) and 55.6% (5 out of 9 subjects).

When considering the main aim of the study, which is complete regression of NV, this was found to occur, for the NVE, in the same range for the three study groups whereas for NVD, there was a better response when ITV was used, both alone or in association with PRP (PRP+ITV).
It is to be noted that regression for both NVE and NVD occurred earlier at 3 months in the groups treated with ITV, both alone or in association with PRP.

It is worth noting that there was no need for laser recue treatment in the group receiving ITV alone and that the occurrence of PDR-related complications, such as severe vitreous haemorrhage and/or other PDR complications requiring vitrectomy was superior in eyes assigned to PRP alone (30.8%, 4 out of 13 subjects) than in eyes treated with ITV alone (11.1%, 1 out of 9 subjects) or in association, PRP+ITV (9.0%, 1 out of 10 subjects) ($p=0.391$).
Regarding BCVA, there were no significant variations during the study follow-up and was comparable between all the study groups ($p \geq 0.477$). All study groups maintained comparable values at 3, 6 and 12 months visits ($p \geq 0.173$) and there were also no significant changes within each group ($p \geq 0.207$).

Regarding CMT, CMT also remained comparable between all the study groups during all the follow-up visits. Decrease CMT variations during the study were not statistically significant among the study groups except at 3 months, where the CMT decrease was significant in the PRP+ITV group ($p=0.004$).
The median (IQR) number of PRP treatments performed in the PRP group was 3 (1-5) and 4 (3-5) in the PRP+ITV group ($p=0.378$).
In the PRP group, 1 out of the 3 patients that showed reactivation of the neovascularization at month-3 or month-6 was retreated. In the PRP+ITV group, all patients showed reactivation (6) and were retreated.

The number of ITV injections administered in the ITV group and in the combined treatment group was also comparable (p=0.239), with a median (IQR) of 5 (5-7) and 6 (5-7), respectively.

12 Safety evaluation

12.1 Extent of exposure

The maximum exposure duration was 12 months with a minimum of 4 weeks interval between the ranibizumab intravitreal injections, the Study Drug. Only the first three injections were mandatory. Afterwards, in each visit the investigator decided whether the subject needed to receive additional ranibizumab intravitreal injections. Visits were scheduled monthly. According to the Protocol, subjects allocated in Group 2 and in Group 3 received ranibizumab intravitreal injections *pro re nata*, whereas subjects allocated in Group 1 did not receive ranibizumab intravitreal injections.

The dose and concentration of the ranibizumab intravitreal injections corresponded to the values in the Summary of the Product Characteristics (dose of 0.5mg that corresponds to an injection volume of 0.05ml).

A total of 44 subjects signed the Informed Consent Form and attended the Screening Visit. 35 subjects were enrolled in the study (13 subjects in Group 1, 10 subjects in Group 2 and 12 subjects in Group 3) and 9 subjects were Screening Failures. Moreover, 30 subjects completed the clinical trial and 5 subjects were drop-outs. In Group 2 and Group 3 the number of ranibizumab intravitreal injections received varied between 2 and 9. Further information is presented in Table Table 12-1 and Table 12-2.

Table 12-1. Number of subjects per treatment arm.

Treatment arm	Number of Subjects
Group 1 (PRP)	13
Group 2 (Lucentis®)	10
Group 3 (Lucentis® + PRP)	12

Table 12-2. Cumulative Subject Exposure

Subject Number	Treatment Group	Ranobizumab Intravitreal Injection	Date of the first Injection	Total of Injections	Final Status
0301	1	No	-	-	Completed
0302	Screening Failure	-	-	-	-
0303	3	Yes	26/01/2011	5	Completed
0304	Screening Failure	-	-	-	-
0305	Screening Failure	-	-	-	-
0306	2	Yes	11/04/2011	4	Completed
0307	1	No	-	-	Drop-out
0308	3	Yes	11/05/2011	2	Discontinues due to disease worsening
0309	1	No	-	-	Completed
0310	2	Yes	22/06/2011	6	Completed
0311	3	Yes	27/10/2011	5	Completed
0312	2	Yes	04/01/2012	4	Completed
0313	3	Yes	08/02/2012	8	Completed
0314	1	No	-	-	Completed
0315	2	Yes	29/02/2012	1	Drop-out
0316	3	Yes	14/06/2012	6	Completed
0317	1	No	-	-	Discontinues due to disease worsening
0318	Screening Failure	-	-	-	-
0319	2	Yes	20/06/2012	7	Completed
0320	1	No	-	-	Completed
0321	3	Yes	01/08/2012	6	Completed
0322	1	No	-	-	Completed

Table 12-2. Cumulative Subject Exposure (continuation)

Subject Number	Treatment Group	Ranobizumab Intravitreal Injection	Date of the first Injection	Total of Injections	Status
0323	2	Yes	11/10/2012	4	Completed
0324	3	Yes	31/10/2012	5	Completed
0325	3	Yes	17/10/2012	3	Drop-out
0326	Screening Failure	-	-	-	-
0327	1	No	-	-	Completed
0401	2	Yes	02/03/2011	3	Completed
0402	1	No	-	-	Completed
0403	Screening Failure	-	-	-	-
0404	3	Yes	07/09/2012	7	Completed
0405	3	Yes	22/09/2012	4	Completed
0406	1	No	-	-	Completed
0601	1	No	-	-	Completed
0602	Screening Failure	-	-	-	-
0603	2	Yes	14/01/2011	4	Completed
0604	3	Yes	14/01/2011	6	Completed
0605	1	No	-	-	Completed
0606	2	Yes	14/01/2011	7	Completed
0607	3	Yes	15/06/2011	6	Completed
0608	1	No	-	-	Completed
0701	2	Yes	29/11/2011	9	Completed
0702	Screening Failure	-	-	-	-

12.2 Adverse events (AEs)

12.2.1 Brief summary of adverse events

36 adverse events were reported in this study from 20 subjects.
17 of the adverse events correspond to eye disorders.
Further, 1 adverse event (angina unstable) may be related to the Study Drug, 1 adverse event (ulcerative keratitis) is likely to be related to the injection procedure and 1 adverse event (eye pain) is likely to be related to the laser procedure.
4 adverse events were considered serious adverse events and one of them was considered a serious adverse reaction (expected).

12.2.2 Display of adverse events

Table 12-3 presents the list of the frequency of the adverse events per Group (1, 2 and 3) considering the preferred terms and the corresponding System Organ Class and Table 12-4 presents the list of the frequency of the System Organ Class per Group (1, 2 and 3).

Table 12-3. Adverse events overall (n=36) and frequency of events

AEs with onset after the start of treatment	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	Total n (%)	System organ class	SAE
Patients with AEs	8 (42.1%)	5 (26.3%)	7 (36.8%)	19 (100.0%)		
Preferred term						
Angina Unstable	0	1 (2.8%)	0	1 (2.8%)	Cardiac disorders	**Yes**
Anxiety	0	0	1 (2.8%)	1 (2.8%)	Psychiatric disorders	No
Benign Prostatic Hyperplasia	0	0	1 (2.8%)	1 (2.8%)	Reproductive system and breast disorders	**Yes**
Benign Neoplasm of Adrenal Gland	0	1 (2.8%)	0	1 (2.8%)	Neoplasm benign, malignant and unspecified	**Yes**
Cardiac Valve Disease	0	0	1 (2.8%)	1 (2.8%)	Cardiac disorders	No
Cystitis	0	0	1 (2.8%)	1 (2.8%)	Infections and infestations	No
Conjunctivitis (Bilateral)	0	0	1 (2.8%)	1 (2.8%)	Eye disorders	No
Cough	0	0	1 (2.8%)	1 (2.8%)	Respiratory, thoracic abd mediastinal disorders	No
Depression	1 (2.8%)	0	0	1 (2.8%)	Psychiatric disorders	No
Diabetic Retinopathy	1 (2.8%)	0	0	1 (2.8%)	Eye disorders	No
Eye Pain	1 (2.8%)	0	0	1 (2.8%)	Eye disorders	No
Erysipelas	0	0	1 (2.8%)	1 (2.8%)	Skin and subcutaneous tissue disorders	**Yes**
Hypertension	0	0	1 (2.8%)	1 (2.8%)	Vascular disorders	No
Hyperuricaemia	1 (2.8%)	0	0	1 (2.8%)	Metabolism and nutrition disorders	No
Hypoglycaemia	0	0	1 (2.8%)	1 (2.8%)	Metabolism and nutrition disorders	No
Influenza	0	0	1 (2.8%)	1 (2.8%)	Infections and infestations	No
Ischaemic Cardiomyopathy	0	0	1 (2.8%)	1 (2.8%)	Cardiac disorders	No
Ocular Hypertension	0	0	1 (2.8%)	1 (2.8%)	Eye disorders	No
Oral Mucosal Blistering	0	0	1 (2.8%)	1 (2.8%)	Gastrointestinal disorders	No
Preauricular Cyst	1 (2.8%)	0	0	1 (2.8%)	Ear and 63abyrinth disorders	No
Renal Impairment	1 (2.8%)	0	0	1 (2.8%)	Renal and urinary disorders	No
Retinal Detachment	0	1 (2.8%)	0	1 (2.8%)	Eye disorders	No
Retinal Neovascularisation	1 (2.8%)	0	0	1 (2.8%)	Eye disorders	No
Rhinitis	0	0	1 (2.8%)	1 (2.8%)	Infections and infestations	No
Ulcerative Keratitis	0	0	1 (2.8%)	1 (2.8%)	Eye disorders	No
Vitrectomy	0	1 (2.8%)	0	1 (2.8%)	Surgical and medical procedure	No
Vitreous Haemorrhage	7 (19.4%)	2 (5.7%)	1 (2.8%)	10 (28.6%)	Eye disorders	No
Total	14 (40.0%)	6 (16.6%)	16 (45.7%)	36 (100%)		

Table 12-4 System organ classes

AEs with onset after the start of treatment	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	Total n (%)
Total number of AEs	14 (40.0%)	5 (14.3%)	16 (45.7%)	35 (100%)
System organ class				
Cardiac disorders	0	1(2.8%)	2(5.7%)	2(5.7%)
Ear and labyrinth disorders	1(2.8%)	0	0	1(2.8%)
Eye disorders	10	3(8.6%)	4(11.4%)	17(48.6%)
Gastrointestinal disorders	0	0	1(2.8%)	1(2.8%)
Infections and infestations	0	0	3(8.6%)	3(8.6%)
Metabolism and nutrition disorders	1(2.8%)	0	1(2.8%)	2(5.7%)
Neoplasm benign, malignant and unspecified (incl cysts and polyps)	0	1(2.8%)	0	1(2.8%)
Psychiatric disorders	1(2.8%)	0	1(2.8%)	1(2.8%)
Renal and urinary disorders	1(2.8%)	0	0	1(2.8%)
Reproductive system and breast disorders	0	0	1(2.8%)	1(2.8%)
Respiratory, thoracic and and mediastinal disorders	0	0	1(2.8%)	1(2.8%)
Skin and subcutaneous tissue disorders	0	0	1(2.8%)	1(2.8%)
Surgical and medical procedure	0	1 (2.8%)	0	1 (2.8%)
Vascular disorders	0	0	1(2.8%)	1(2.8%)

12.2.3 Analysis of adverse events

36 AEs were reported during the Study, 14 in Group 1, 6 in Group 2 and 16 in Group 3.
Vitreous haemorrhage was the most frequent AE, being reported 10 times (7 in Group 1, 2 in Group 2 and 1 in Group 3). All the remaing AEs were reported only once.
Adverse events in higher proportion are included in the eye disorders class (n=17, 48.6%). Of those AEs, 10 are in Group 1, 3 in Group 2 and 4 in Group 3).

12.2.4 Listing of adverse events by patient

Table 12-5 presents the list of all adverse events per patient.

Table 12-5. Listing of adverse events by patient.

Subject number	Treatment group	AE Preferred Term	Severity	SAE	Visit number	Site	Study eye	Related to Procedure	Related to Study Drug
0303	3	Oral Mucosal Blistering	Mild	No	7	Non-ocular	NA	No	No
0307	1	Vitreous Haemorrhage	Moderate	No	2	Right Eye	Yes	No	No
0308	3	Benign Prostatic Hyperplasia	Severe	Yes	4	Non-ocular	NA	No	No
0308	3	Ischaemic Cardiomyopathy	Severe	No	4	Non-ocular	NA	No	No
0308	3	Cardiac Valve Disease	Severe	No	4	Non-ocular	NA	No	No
0309	1	Depression	Moderate	No	12	Non-ocular	NA	No	No
0310	2	Vitreous Haemorrhage	Moderate	No	6	Right Eye	No	No	No
0311	3	Conjunctivitis	Mild	No	8	Both Eyes	Yes	No	No
0313	3	Hypoglycaemia	Mild	No	10	Non-ocular	NA	No	No
0314	1	Preauricular Cyst	Mild	No	11	Non-ocular	NA	No	No
0317	1	Retinal Neovascularisation	Severe	No	4	Left Eye	Yes	No	No
0317	1	Diabetic Retinopathy	Severe	No	4	Left Eye	Yes	No	No
0319	2	Retinal Detachment	Moderate	No	3	Right Eye	No	No	No
0319	2	Vitrectomy	Moderate	No	5	Right Eye	No	No	No
0320	1	Vitreous Haemorrhage	Moderate	No	2	Right Eye	No	No	No
0320	1	Vitreous Haemorrhage	Moderate	No	2	Left Eye	Yes	No	No
0320	1	Vitreous Haemorrhage	Moderate	No	5	Left Eye	Yes	No	No
0320	1	Vitreous Haemorrhage	Moderate	No	8	Left Eye	Yes	No	No
0320	1	Vitreous Haemorrhage	Moderate	No	11	Right Eye	No	No	No
0320	1	Hyperuricaemia	Mild	No	10	Non-ocular	NA	No	No
0321	3	Ulcerative keratitis	Mild	No	6	Right Eye	Yes	Yes	No
0321	3	Vitreous Haemorrhage	Moderate	No	8	Right Eye	Yes	No	No
0321	3	Cystitis	Mild	No	8	Non-ocular	NA	No	No
0321	3	Hypertension	Mild	No	8	Non-ocular	NA	No	No
0321	3	Erysipelas	Severe	Yes	9	Non-ocular	NA	No	No
0322	1	Vitreous Haemorrhage	Mild	No	9	Left Eye	Yes	No	No
0323	2	Vitreous Haemorrhage	Moderate	No	4	Right Eye	No	No	No
0324	3	Influenza	Moderate	No	1	Non-ocular	NA	No	No
0601	1	Eye Pain	Mild	No	2	Right Eye	Yes	Yes	No
0603	2	Angina Unstable	Moderate	Yes	12	Non-ocular	NA	No	Yes
0604	3	Anxiety	Mild	No	1	Non-ocular	NA	No	No
0604	3	Rhinitis	Mild	No	1	Non-ocular	NA	No	No
0604	3	Ocular Hypertension	Mild	No	6	Left Eye	Yes	No	No
0604	3	Cough	Mild	No	6	Non-ocular	NA	No	No
0605	1	Renal Impairment	Mild	No	5	Non-ocular	NA	No	No
0701	2	Benign Neoplasm of Adrenal Gland	Moderate	Yes	6	Non-ocular	NA	No	No

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

There were no deaths during the Study.
4 serious adverse events were reported during the Study. Three of them were considered not related to the Study Drug and one of them was considered a serious adverse reaction (expected).

There were 3 drop-outs during the Study and 2 patients that discontinued the study due to disease worsening:

- Patient 0315 (Group 2) and Patient 0325 (Group 3) discontinued the Study due to personal issues (patients could not attend the visits).

- Patient 0308 (Group 3) discontinued due to surgery to Benign Prostatic Hyperplasia. This adverse event was considered a serious adverse event not related to Study Drug. Due to the surgery, patient could not attend visits.

- Patient 0307 (Group 1) discontinued due worsening of the Proliferative Diabetic Retinopathy and need vitrectomy in the Study Eye (Vitreous Haemorrhage). Patient was allocated in Group 1, so he/she was not receiving Study Drug.

- Patient 0317 (Group 1) discontinued due worsening of the Proliferative Diabetic Retinopathy and need of surgery in the Study Eye. Patient was allocated in Group 1, so he/she was not receiving Study Drug.

Table 12-6 presents number of deaths, serious adverse events, clinically significant adverse events, patients discontinued due to SAEs and patients discontinued due to clinically significant adverse events, per Group (1, 2 and 3).

Table 12-6. Deaths, other serious or clinically significant adverse events or related discontinuations.

	Group 1	Group 2	Group 3	Total
	No.	No.	No.	No.
Patients with SAE(s)	0	2	2	4
Serious or other significant events				
Death	0	0	0	0
SAE(s)	0	2	2	4
Clinically significant AE(s) (Moderate or severe AE)	9	6	6	21
Discontinued due to SAE(s)	0	0	1	1
Discontinued due to clin. sign. AE(s)	2	0	0	2

12.3.1 Listing of deaths, other serious adverse events, and other significant adverse events

Table 12-7 presents the list of serious adverse events.

Table 12-7. List of the serious adverse events.

SAE Number	Serious Adverse Event System Organ Class Preferred Term	Patient Number	Group
SAE Number 1	**Neoplasms benign, malignant and unspecified (incl cysts and polyps)** Benign neoplasm of adrenal gland	0701	Group 2 (Lucentis®)
SAE Number 2	**Reproductive system and breast disorders** Benign prostatic hyperplasia	0308	Group 3 (Lucentis® + PRP)
SAE Number 3	**Cardiac disorders** Angina unstable	0603	Group 2 (Lucentis®)
SAE Number 4	**Skin and subcutaneous tissue disorders** Erysipelas	0321	Group 3 (Lucentis® + PRP)

12.3.2 Narratives of deaths, other serious adverse events, and certain other significant adverse events

Table 12-8 presents the list of the narratives of the serious adverse events.

Table 12-8. List of the narratives of the serious adverse events.

Preferred Term	Subejct Group	Narrative
SAE Number 1 Benign neoplasm of adrenal gland	**0701** Group 2 (Lucentis®)	Female patient, date of birth: 14/03/1955. Relevant medical history: diabetes mellitus, hypertension and depression. Surgery of a benign neoplasm of adrenal gland. Patient was hospitalized between 15/03/2011 and 19/03/2011 and she recovered without sequealae. Patient continued participating in the Study. Serious adverse event was not related to the Study Drug.
SAE Number 2 Benign prostatic hyperplasia	**0308** Group 3 (Lucentis® + PRP)	Male patient, date of birth: 16/11/1944. Relevant medical history: diabetes mellitus type 2, hypertension and veneous vascular insufficiency. Surgery of a benign prostatic hyperplasia. Patient was hospitalized between 26/07/2011 and 01/08/2011 and she recovered without sequealae. Patient discontinued participating in the Study as could not attend the visits. Serious adverse event not related to the Study Drug.
SAE Number 3 Angina unstable	**0603** Group 2 (Lucentis®)	68 years-old male, was hospitalized to undergo a coronary angioplasty with stent on 13th November 2012 due to angina unstable. Last time the subject received an intravitreal injection of ranibizumab was 6 months before (13th May 2012). Subject recovered without sequelae. Relevant medical history included hypertension, diabetes mellitus and obesity. Before this event, the medication of the subject was Risidon (metformin, films-coated tablet, oral administration), Xelevia 100 (sitagliptin, films-coated tablet, oral administration) and Olsar Plus 20/12.5(olmesartan and hydrochlorothiazide, films-coated tablet, oral administration). After this event, Olsar Plus 20/12.5 was stopped and subject started the following medications: ramipril 5 (oral administration), bisoprolol 5 (oral administration), clopidogrel (films-coated tablet, oral administration) and Crestor (rosuvastatin, films-coated tablet, oral administration). The investigator considers unlikely to be related with ranibizumab. This event was not reported in expedited fashion as angina unstable is mentioned in the Investigator Brochure as a serious adverse event potentially related with ranibizumab. This event was also reported to the Marketing Authorization Holder of ranibizumab.
SAE Number 4 Erysipelas	**0321** Group 3 (Lucentis® + PRP)	Female patient, date of birth: 14/05/1974. Relevant medical history: diabetes mellitus type 1. Patient was hospitalized between 02/03/2013 and 15/03/2013 due to Erysipelas and she recovered without sequealae. Patient continued participating in the Study. Serious adverse event was not related to the Study Drug.

12.3.3 Analysis and discussion of deaths, other serious adverse events, and other significant adverse events

There were no deaths during the Study.
4 serious adverse events were reported during the Study.
SAEs Number 1, 2 and 4 were considered not related to the Study Drug.
SAE number 3 was considered a serious adverse reaction (expected). Nevertheless, the investigator considers unlikely to be related with ranibizumab because the last intravitreal injection of ranibizumab was 6 months before the serious adverse event.

12.4 Clinical laboratory evaluation

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

Descriptive statistics of HbA1C values by groups are shown in Table12-8.

Table 12-9 Descriptive statistics of HbA1C at screening visit by group

	Group 1	Group 2	Group 3
Mean ± SD (Range)	8.08 ± 1.47 (6.2 - 11)	7.83 ± 1.2 (6.4 - 9.7)	7.94 ± 1.31 (6.6 - 10.3)
Median (IQR)	8 (6.8 - 8.7)	7.55 (7 - 8.9)	7.2 (6.7 – 9.0)

Table 12-9 presents the list of individual laboratory measurements of HbA1C by patient.

Table 12-10. Individual laboratory measurements of HbA1C by patient

Patient number	Treatment	HbA1C
0301	1	7.5 (Normal)
0303	3	7.2 (Normal)
0306	2	**7.7 (Abnormal)**
0309	1	**11 (Abnormal)**
0310	2	6.4 (Normal)
0311	3	**9.7 (Abnormal)**
0312	2	**9.7 (Abnormal)**
0313	3	6.7 (Normal)
0314	1	**8.7 (Abnormal)**
0316	3	7.1 (Normal)
0319	2	**9.7 (Abnormal)**
0320	1	**8.6 (Abnormal)**
0321	3	**10.3 (Abnormal)**
0322	1	6.8 (Normal)
0323	2	6.6 (Normal)
0324	3	6.7 (Normal)
0327	1	**8 (Abnormal)**
0401	2	7 (Normal)
0402	1	6.2 (Normal)
0404	3	6.6 (Normal)
0405	3	**8.5 (Abnormal)**
0406	1	**8.6 (Abnormal)**
0601	1	6.2 (Normal)
0603	2	7.2 (Normal)
0604	3	**9 (Abnormal)**
0605	1	**9.6 (Abnormal)**
0606	2	**7.7 (Abnormal)**
0607	3	7.1 (Normal)
0608	1	**9.6 (Abnormal)**
0701	2	7.4 (Normal)

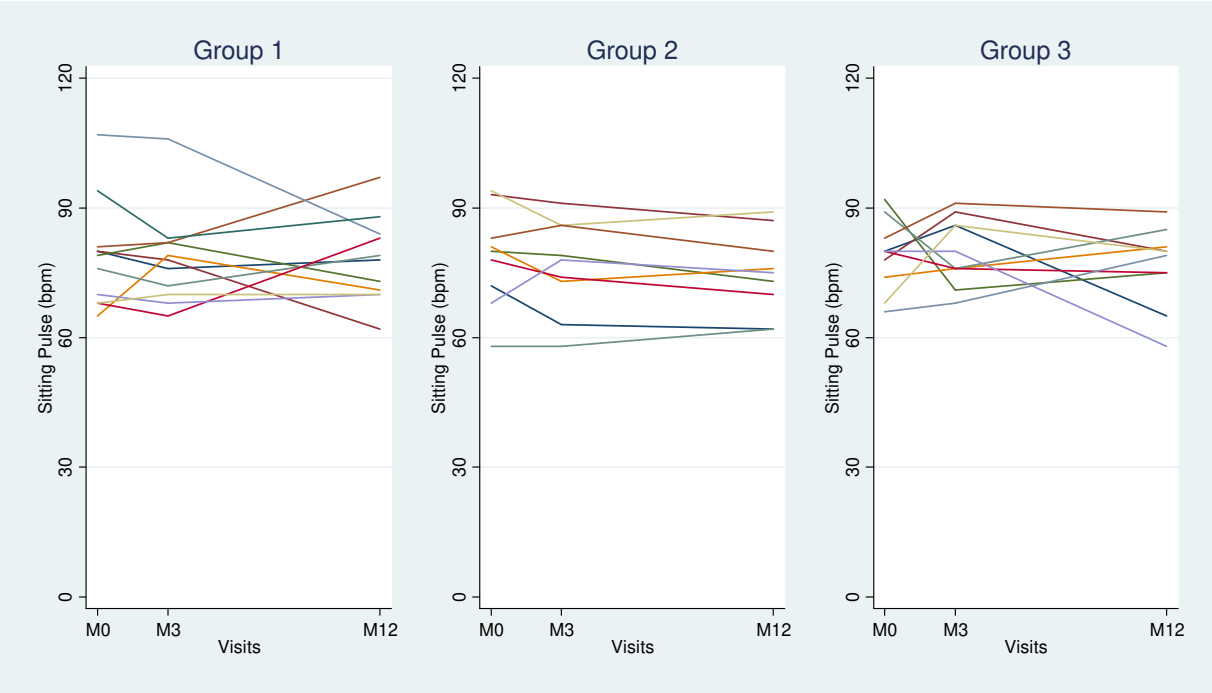
12.5 Vital signs, physical findings, and other observations related to safety

Sitting pulse by groups are summarized in Table 12- and presented in Figure 12-1.

Table 12-11. Descriptive statistics of Sitting Pulse by group and visit

		Group 1	Group 2	Group 3
SCR	Mean ± SD (Range)	78.91 ± 12.42 (65 - 107)	78.56 ± 11.47 (58 - 94)	79.00 ± 8.19 (66 - 92)
	Median (IQR)	79 (68 - 81)	80 (72 - 83)	80 (74 - 83)
M3	Mean ± SD (Range)	78.27 ± 11.02 (65 - 106)	76.44 ± 10.85 (58 - 91)	79.90 ± 7.8 (68 - 91)
	Median (IQR)	78 (70 - 82)	78 (73 - 86)	78 (76 - 86)
M12	Mean ± SD (Range)	77.73 ± 9.9 (62 - 97)	74.89 ± 9.57 (62 - 89)	76.70 ± 9.18 (58 - 89)
	Median (IQR)	78 (70 - 84)	75 (70 - 80)	79.5 (75 - 81)

Figure 12-1. Sitting Pulse by patients, groups, visits

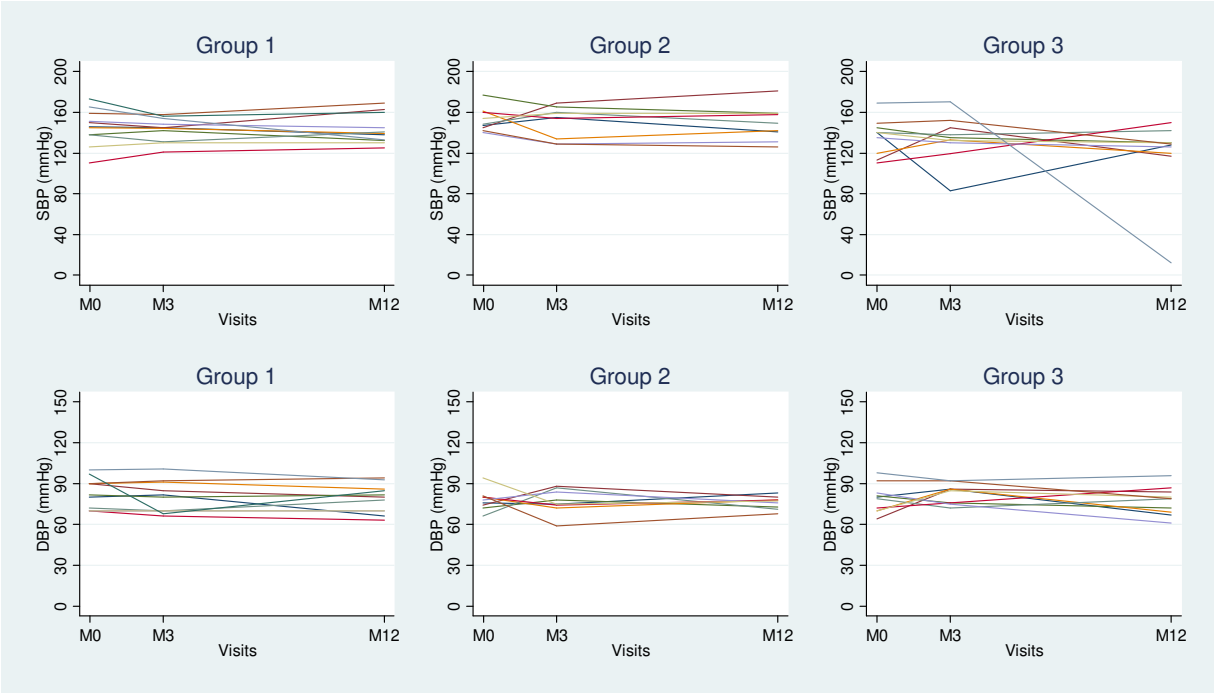


Systolic blood pressure (SBP) and diastolic blood pressure (DBP) by groups are summarized in Table 12 12 and presented in Figure 12 2.

Table 12-12. Descriptive statistics of Blood Pressure by group and visit

			Group 1	Group 2	Group 3
SCR	Systolic	Mean ± SD (Range)	145.55 ± 17.67 (110 - 173)	152.67 ± 11.75 (140 - 177)	136.1 ± 17.79 (110 - 169)
		Median (IQR)	146 (138 - 159)	148 (145 - 160)	140 (120 - 145)
	Diastolic	Mean ± SD (Range)	82.82 ± 11.27 (70 - 100)	77.89 ± 7.69 (66 - 94)	78.9 ± 10.47 (64 - 98)
		Median (IQR)	82 (70 - 90)	78 (74 - 80)	79.5 (70 - 83)
M3	Systolic	Mean ± SD (Range)	143.09 ± 11.61 (121 - 158)	150.44 ± 15.59 (129 - 169)	133.7 ± 22.62 (83 - 170)
		Median (IQR)	145 (131 - 154)	155 (134 - 160)	134 (130 - 145)
	Diastolic	Mean ± SD (Range)	79.55 ± 11.72 (66 - 101)	76.89 ± 8.92 (59 - 88)	82.6 ± 7.26 (72 - 92)
		Median (IQR)	80 (70 - 91)	75 (74 - 84)	85.5 (76 - 86)
M12	Systolic	Mean ± SD (Range)	143.18 ± 14.59 (125 - 169)	149.56 ± 16.84 (126 - 181)	118.4 ± 38.6 (12 - 150)
		Median (IQR)	139 (132 - 160)	149 (141 - 159)	128.5 (120 - 130)
	Diastolic	Mean ± SD (Range)	78.82 ± 10.51 (63 - 94)	76 ± 4.64 (68 - 83)	77.4 ± 10.38 (61 - 96)
		Median (IQR)	80 (70 - 86)	77 (73 - 78)	79 (69 - 84)

Figure 12-2. Blood Pressure by patients, groups, visits



Intraocular pressure by groups are summarized in Table 12-, Table 12- and Table 12-5 and presented in Figure 12-3 and in

Figure 12-4.

Table 12-13. Descriptive statistics of Intraocular Pressure by group and visit (PP population)

		Group 1	Group 2	Group 3
SCR	Mean ± SD (Range)	15.91 ± 1.51 (13 - 18)	15.89 ± 1.69 (14 - 20)	15.10 ± 1.91 (11 - 17)
	Median (IQR)	16 (15 - 17)	16 (15 - 16)	16 (14 - 16)
M12	Mean ± SD (Range)	16.00 ± 2.93 (12 - 22)	16.44 ± 3.00 (13 - 21)	18.20 ± 3.52 (14 - 27)
	Median (IQR)	16 (14 - 18)	16 (15 - 18)	17.5 (16 - 19)

Figure 12-3. Intraocular pressure according to arm of treatment, by patient.

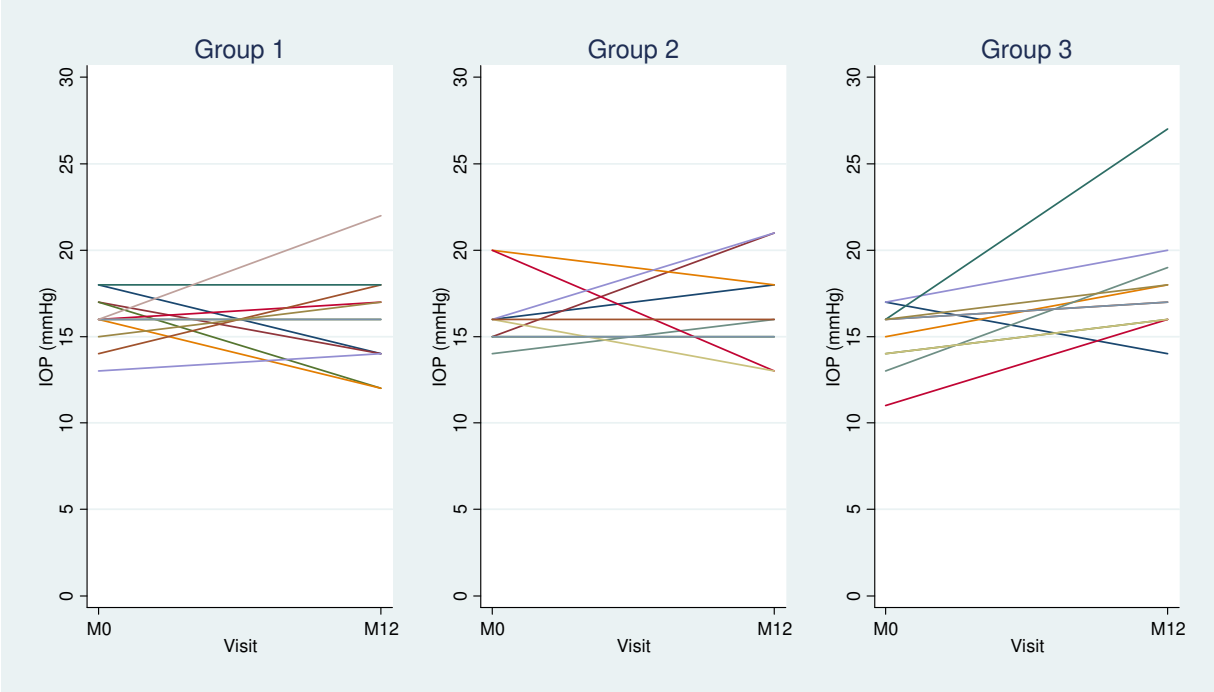


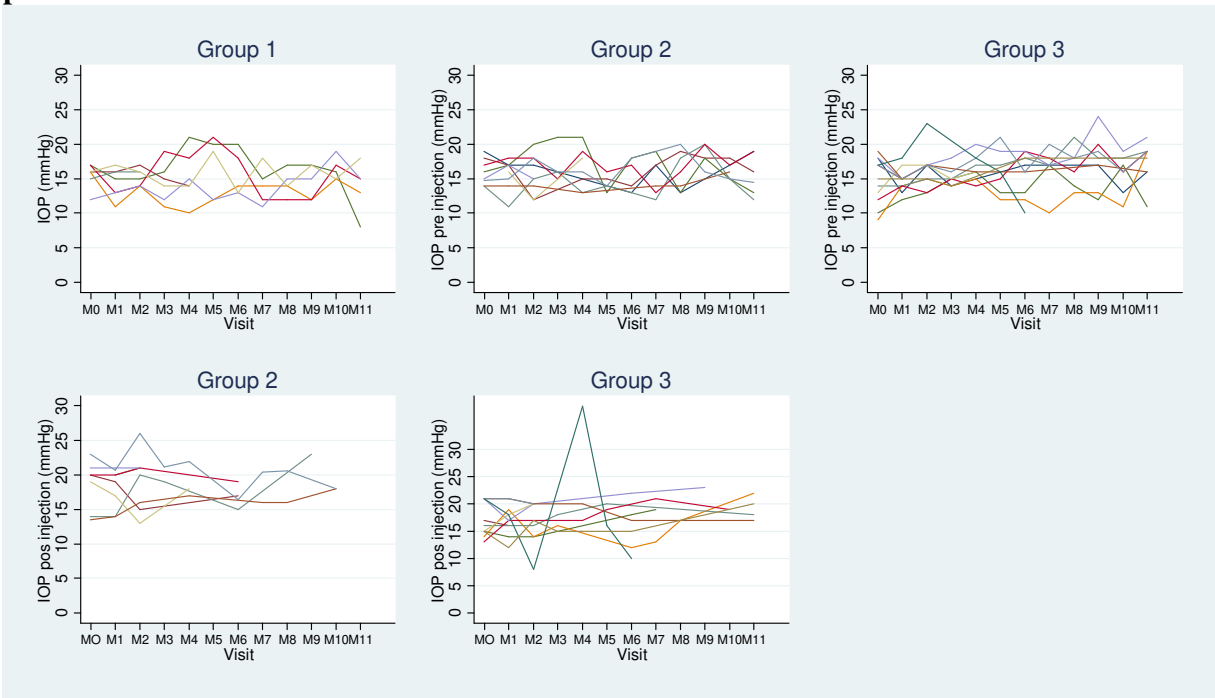
Table 12-14. Descriptive statistics of Intraocular Pressure pre treatment by group and visit

		Group 1	Group 2	Group 3
M0	Mean ± SD (Range)	15.6 ± 2.07 (12 - 17)	15.96 ± 1.88 (14 - 19)	14.9 ± 3.54 (9 - 19)
	Median (IQR)	16 (16 - 17)	15.5 (14.35 - 17.5)	16 (12 - 18)
M1	Mean ± SD (Range)	13.8 ± 2.28 (11 - 17)	15.78 ± 2.17 (11 - 18)	14.5 ± 1.58 (12 - 18)
	Median (IQR)	13 (13 - 15)	17 (15 - 17)	14.5 (14 - 15)
M2	Mean ± SD (Range)	14.6 ± 0.89 (14 - 16)	15.67 ± 2.78 (12 - 20)	16.2 ± 2.86 (13 - 23)
	Median (IQR)	14 (14 - 15)	15 (14 - 18)	16 (15 - 17)
M3	Mean ± SD (Range)	14.4 ± 3.21 (11 - 19)	17 ± 2.71 (15 - 21)	15.13 ± 1.36 (14 - 18)
	Median (IQR)	14 (12 - 16)	16 (15.5 - 18.5)	15 (14 - 15.5)
M4	Mean ± SD (Range)	15.6 ± 4.16 (10 - 21)	16.43 ± 3.05 (13 - 21)	16.75 ± 1.91 (14 - 20)
	Median (IQR)	15 (14 - 18)	16 (13 - 19)	16.5 (15.5 - 18)
M5	Mean ± SD (Range)	16.8 ± 4.44 (12 - 21)	14.4 ± 1.14 (13 - 16)	16.14 ± 3.18 (12 - 21)
	Median (IQR)	19 (12 - 20)	14 (14 - 15)	16 (13 - 19)
M6	Mean ± SD (Range)	15.6 ± 3.21 (13 - 20)	15.5 ± 2.43 (13 - 18)	15.8 ± 3.12 (10 - 19)
	Median (IQR)	14 (13 - 18)	15.5 (13 - 18)	16.5 (13 - 18)
M7	Mean ± SD (Range)	14 ± 2.74 (11 - 18)	15.86 ± 2.85 (12 - 19)	16.5 ± 3.39 (10 - 20)
	Median (IQR)	14 (12 - 15)	17 (13 - 19)	17 (17 - 18)
M8	Mean ± SD (Range)	14.4 ± 1.82 (12 - 17)	16.14 ± 2.91 (13 - 20)	16.67 ± 2.94 (13 - 21)
	Median (IQR)	14 (14 - 15)	16 (13 - 19)	17 (14 - 18)
M9	Mean ± SD (Range)	14.6 ± 2.51 (12 - 17)	17.83 ± 2.04 (15 - 20)	17.5 ± 3.82 (12 - 24)
	Median (IQR)	15 (12 - 17)	18 (16 - 20)	17.5 (15 - 19.5)
M10	Mean ± SD (Range)	16.4 ± 1.67 (15 - 19)	16.14 ± 1.21 (15 - 18)	15.71 ± 2.81 (11 - 19)
	Median (IQR)	16 (15 - 17)	16 (15 - 17)	16 (13 - 18)
M11	Mean ± SD (Range)	13.8 ± 3.7 (8 - 18)	15.58 ± 2.97 (12 - 19)	17.56 ± 2.92 (11 - 21)
	Median (IQR)	15 (13 - 15)	15.25 (13 - 19)	19 (16 - 19)

Table 12-5. Descriptive statistics of Intraocular Pressure for Groups 2 and 3 pos injection, by group and visit

		Group 2	Group 3
M0	Mean ± SD (Range)	18.64 ± 3.57 (13.5 - 23)	17.44 ± 3.47 (13 - 21)
	Median (IQR)	20 (14 - 21)	16 (15 - 21)
M1	Mean ± SD (Range)	18.21 ± 2.88 (14 - 21)	17.22 ± 2.99 (12 - 21)
	Median (IQR)	19.5 (15.5 - 20.35)	17 (16 - 19)
M2	Mean ± SD (Range)	19.13 ± 4.19 (13 - 26)	16.13 ± 4.16 (8 - 20)
	Median (IQR)	20.5 (15.5 - 21)	16.5 (14 - 20)
M3	Mean ± SD (Range)	20.1 ± 1.56 (19 - 21.2)	16.33 ± 1.53 (15 - 18)
	Median (IQR)	20.1 (19 - 21.2)	16 (15 - 18)
M4	Mean ± SD (Range)	18.97 ± 2.59 (17 - 21.9)	25 ± 11.36 (17 - 38)
	Median (IQR)	18 (17 - 21.9)	20 (17 - 38)
M5	Mean ± SD (Range)	14.0 (1 patient)	18.33 ± 2.08 (16 - 20)
	Median (IQR)		19 (16 - 20)
M6	Mean ± SD (Range)	16.85 ± 1.66 (15 - 19)	15.67 ± 4.32 (10 - 22)
	Median (IQR)	16.7 (15.7 - 18)	16 (12 - 18)
M7	Mean ± SD (Range)	18.2 ± 3.11 (16 - 20.4)	17.67 ± 4.16 (13 - 21)
	Median (IQR)	18.2 (16 - 20.4)	19 (13 - 21)
M8	Mean ± SD (Range)	18.3 ± 3.25 (16 - 20.6)	17 ±0.0 (17 - 17)
	Median (IQR)	18.3 (16 - 20.6)	17 (17 - 17)
M9	Mean ± SD (Range)	23.0 ±0.0 (23 - 23)	20 ± 4.24 (17 - 23)
	Median (IQR)	23 (23 - 23)	20 (17 - 23)
M10	Mean ± SD (Range)	18 ± 0.0 (18 - 18)	19.0 ±0.0 (19 - 19)
	Median (IQR)	18 (18 - 18)	19 (19 - 19)
M11	Mean ± SD (Range)	18.0 (1 patient)	19.25 ± 2.22 (17 - 22)
	Median (IQR)		19 (17.5 - 21)

Figure 12-4. Intraocular pressure pre/pos injection according to treatment arm, by patient.



Inflammation Assessment results are presented in Table 12-6, Table 12-, Table 12- and Table 12-.

Table 12-6. Inflammation Assessment: Anterior chamber flare (Level scale: 0, Trace, 1 +, 2 +, 3 +, 4 +)

		Group 1		Group 2		Group 3	
		No.	%	No.	%	No.	%
SCR	0	11	100	9	100	10	100
M0	0	11	100	9	100	10	100
M1	0	11	100	9	100	10	100
M2	0	11	100	9	100	10	100
M3	0	11	100	9	100	10	100
M4	0	11	100	9	100	10	100
M5	0	11	100	9	100	10	100
M6	0	11	100	9	100	10	100
M7	0	11	100	9	100	10	100
M8	0	11	100	9	100	10	100
M9	0	11	100	9	100	10	100
M10	0	11	100	9	100	10	100
M11	0	11	100	9	100	10	100
M12	0	11	100	9	100	10	100

Table 12-7. Inflammation Assessment: Anterior chamber cells Level scale: 0, Trace, 1 +, 2 +, 3 +, 4 +)

		Group 1		Group 2		Group 3	
		No.	%	No.	%	No.	%
SCR	0	11	100	9	100	10	100
M0	0	11	100	9	100	10	100
M1	0	11	100	9	100	10	100
M2	0	11	100	9	100	10	100
M3	0	11	100	9	100	10	100
M4	0	11	100	9	100	10	100
M5	0	11	100	9	100	10	100
M6	0	11	100	9	100	10	100
M7	0	11	100	9	100	10	100
M8	0	11	100	9	100	10	100
M9	0	11	100	9	100	10	100
M10	0	11	100	9	100	10	100
M11	0	11	100	9	100	10	100
M12	0	11	100	9	100	10	100

Table 12-8. Inflammation Assessment: Vitreous cells Level scale: 0, Trace, 1 +, 2 +, 3 +, 4 +)

		Group 1		Group 2		Group 3	
		No.	%	No.	%	No.	%
SCR	0	11	100.0	9	100.0	10	100.0
M0	0	10	90.9	9	100.0	10	100.0
	Trace	0	0.0	0	0.0	0	0.0
	1 +	1	9.1	0	0.0	0	0.0
M1	0	10	90.9	8	88.9	10	100.0
	Trace	0	0.0	1	11.1	0	0.0
	2 +	1	9.1	0	0.0	0	0.0
M2	0	11	100.0	9	100.0	10	100.0
M3	0	11	100.0	9	100.0	10	100.0
M4	0	11	100.0	9	100.0	10	100.0
M5	0	11	100.0	9	100.0	10	100.0
M6	0	11	100.0	9	100.0	10	100.0
M7	0	11	100.0	9	100.0	10	100.0
M8	0	11	100.0	9	100.0	10	100.0
M9	0	11	100.0	9	100.0	10	100.0
M10	0	11	100.0	9	100.0	10	100.0
M11	0	11	100.0	9	100.0	10	100.0
M12	0	11	100.0	9	100.0	10	100.0

Table 12-9. Inflammation Assessment: Vitreal haemorrhage density (Level scale: 0, Trace, 1 +, 2 +, 3 +, 4 +)

		Group 1		Group 2		Group 3	
		No.	%	No.	%	No.	%
SCR	0	10	90.9	8	88.9	7	70.0
	Trace	0	0.0	1	11.1	0	0.0
	1 +	0	0.0	0	0.0	2	20.0
	2 +	0	0.0	0	0.0	0	0.0
	3 +	0	0.0	0	0.0	0	0.0
	4 +	1	9.1	0	0.0	1	10.0
M0	0	9	81.8	8	88.9	10	100.0
	Trace	0	0.0	1	11.1	0	0.0
	1 +	0	0.0	0	0.0	0	0.0
	2 +	1	9.1	0	0.0	0	0.0
	3 +	1	9.1	0	0.0	0	0.0
M1	0	9	81.8	9	100.0	10	100.0
	Trace	1	9.1	0	0.0	0	0.0
	1 +	0	0.0	0	0.0	0	0.0
	2 +	0	0.0	0	0.0	0	0.0
	3 +	1	9.1	0	0.0	0	0.0
M2	0	11	100.0	9	100.0	10	100.0
M3	0	11	100.0	9	100.0	10	100.0
M4	0	11	100.0	9	100.0	10	100.0
M5	0	11	100.0	9	100.0	10	100.0
M6	0	11	100.0	9	100.0	10	100.0
M7	0	11	100.0	9	100.0	10	100.0
M8	0	11	100.0	9	100.0	10	100.0
M9	0	11	100.0	9	100.0	10	100.0
M10	0	11	100.0	9	100.0	10	100.0
M11	0	11	100.0	9	100.0	10	100.0
M12	0	11	100.0	9	100.0	10	100.0

Results of Slit Lamp Exam are presented in Table 12-2, Table 12-3, Table 12-4, Table 12-5, Table 12-6 and Table 12-7.

Table 12-2. Slit Lamp Exam: Lids (Level scale: Normal, Clinically insignificant abnormality, Clinically significant abnormality)

		Group 1		Group 2		Group 3	
		No.	%	No.	%	No.	%
SCR	Normal	11	100	9	100	10.0	100
M0	Normal	11	100	9	100	10.0	100
M1	Normal	11	100	9	100	10.0	100
M2	Normal	11	100	9	100	10.0	100
M3	Normal	11	100	9	100	10.0	100
M4	Normal	11	100	9	100	10.0	100
M5	Normal	11	100	9	100	10.0	100
M6	Normal	11	100	9	100	9.0	90
	Clinically insignificant abnormality	0	0	0	0	0.0	0
	Clinically significant abnormality	0	0	0	0	1.0	10
M7	Normal	11	100	9	100	10.0	100
M8	Normal	11	100	9	100	10.0	100
M9	Normal	11	100	9	100	10.0	100
M10	Normal	11	100	9	100	10.0	100
M11	Normal	11	100	9	100	10.0	100
M12	Normal	11	100	9	100	10.0	100

Table 12-3. Slit Lamp Exam: Cornea (Level scale: Normal, Clinically insignificant abnormality, Clinically significant abnormality)

		Group 1		Group 2		Group 3	
		No.	%	No.	%	No.	%
SCR	Normal	11	100	9	100	9	90
	Clinically insignificant abnormality	0	0	0	0	1	10
M0	Normal	11	100	9	100	9	90
	Clinically insignificant abnormality	0	0	0	0	1	10
M1	Normal	11	100	9	100	9	90
	Clinically insignificant abnormality	0	0	0	0	1	10
M2	Normal	11	100	9	100	10	100
M3	Normal	11	100	9	100	10	100
M4	Normal	11	100	9	100	9	90
	Clinically insignificant abnormality	0	0	0	0	1	10
M5	Normal	11	100	9	100	9	90
	Clinically insignificant abnormality	0	0	0	0	1	10
M6	Normal	11	100	9	100	9	90
	Clinically insignificant abnormality	0	0	0	0	1	10
M7	Normal	11	100	9	100	9	90
	Clinically insignificant abnormality	0	0	0	0	1	10
M8	Normal	11	100	9	100	9	90
	Clinically insignificant abnormality	0	0	0	0	1	10
M9	Normal	11	100	9	100	9	90
	Clinically insignificant abnormality	0	0	0	0	1	10
M10	Normal	11	100	9	100	9	90
	Clinically insignificant abnormality	0	0	0	0	1	10
M11	Normal	11	100	9	100	9	90
	Clinically insignificant abnormality	0	0	0	0	1	10
M12	Normal	11	100	9	100	9	90
	Clinically insignificant abnormality	0	0	0	0	1	10

Table 12-4. Slit Lamp Exam: Conjunctiva (Level scale: Normal, Clinically insignificant abnormality, Clinically significant abnormality)

		Group 1		Group 2		Group 3	
		No.	%	No.	%	No.	%
SCR	Normal	11	100	9	100	10	100
M0	Normal	11	100	9	100	10	100
M1	Normal	11	100	9	100	10	100
M2	Normal	11	100	9	100	9	90
	Clinically insignificant abnormality	0	0	0	0	1	10
M3	Normal	11	100	9	100	10	100
M4	Normal	11	100	9	100	10	100
M5	Normal	11	100	9	100	10	100
M6	Normal	11	100	1	100	9	90
	Clinically insignificant abnormality	0	0	0	0	0	0
	Clinically significant abnormality	0	0	0	0	1	10
M7	Normal	11	100	9	100	10	100
M8	Normal	11	100	9	100	10	100
M9	Normal	11	100	9	100	10	100
M10	Normal	11	100	9	100	10	100
M11	Normal	11	100	8	88.9	10	100
	Clinically insignificant abnormality	0	0	0	0	0	0
	Clinically significant abnormality	0	0	1	11.11	0	0
M12	Normal	11	100	9	100	10	100

Table 12-5. Slit Lamp Exam: Iris (Level scale: Normal, Clinically insignificant abnormality, Clinically significant abnormality)

		Group 1		Group 2		Group 3	
		No.	%	No.	%	No.	%
SCR	Normal	11	100	9	100	10.0	100
M0	Normal	11	100	9	100	10.0	100
M1	Normal	11	100	9	100	10.0	100
M2	Normal	11	100	9	100	10.0	100
M3	Normal	11	100	9	100	10.0	100
M4	Normal	11	100	9	100	10.0	100
M5	Normal	11	100	9	100	10.0	100
M6	Normal	11	100	9	100	10.0	100
M7	Normal	11	100	9	100	10.0	100
M8	Normal	11	100	9	100	10.0	100
M9	Normal	11	100	9	100	10.0	100
M10	Normal	11	100	9	100	9.0	90
	Clinically insignificant abnormality	0	0	0	0	1.0	10
M11	Normal	11	100	9	100	10.0	100
M12	Normal	11	100	9	100	10.0	100

Table 12-6. Slit Lamp Exam: Lens (Level scale: Normal, Clinically insignificant abnormality, Clinically significant abnormality)

		Group 1		Group 2		Group 3	
		No.	%	No.	%	No.	%
SCR	Normal	9	81.8	6	66.7	6	60.0
	Clinically insignificant abnormality	2	18.2	2	22.2	4	40.0
	Clinically significant abnormality	0	0.0	1	11.1	0	0.0
M0	Normal	8	80.0	6	66.7	7	70.0
	Clinically insignificant abnormality	2	20.0	2	22.2	3	30.0
	Clinically significant abnormality	0	0.0	1	11.1	0	0.0
M1	Normal	9	81.8	8	88.9	7	70.0
	Clinically insignificant abnormality	2	18.2	1	11.1	3	30.0
M2	Normal	9	81.8	7	77.8	6	60.0
	Clinically insignificant abnormality	2	18.2	1	11.1	4	40.0
	Clinically significant abnormality	0	0.0	1	11.1	0	0.0
M3	Normal	10	90.9	4	50.0	7	70.0
	Clinically insignificant abnormality	1	9.1	3	37.5	3	30.0
	Clinically significant abnormality	0	0.0	1	12.5	0	0.0
M4	Normal	10	90.9	4	50.0	7	70.0
	Clinically insignificant abnormality	1	9.1	2	25.0	3	30.0
	Clinically significant abnormality	0	0.0	2	25.0	0	0.0
M5	Normal	10	90.9	4	50.0	7	70.0
	Clinically insignificant abnormality	1	9.1	3	37.5	3	30.0
	Clinically significant abnormality	0	0.0	1	12.5	0	0.0
M6	Normal	9	81.8	6	75.0	7	70.0
	Clinically insignificant abnormality	2	18.2	1	12.5	3	30.0
	Clinically significant abnormality	0	0.0	1	12.5	0	0.0
M7	Normal	9	81.8	7	77.8	6	60.0
	Clinically insignificant abnormality	2	18.2	1	11.1	4	40.0
	Clinically significant abnormality	0	0.0	1	11.1	0	0.0
M8	Normal	10	90.9	6	66.7	8	80.0
	Clinically insignificant abnormality	1	9.1	2	22.2	2	20.0
	Clinically significant abnormality	0	0.0	1	11.1	0	0.0
M9	Normal	10	90.9	7	77.8	7	70.0
	Clinically insignificant abnormality	1	9.1	1	11.1	3	30.0
	Clinically significant abnormality	0	0.0	1	11.1	0	0.0
M10	Normal	10	90.9	7	77.8	7	70.0
	Clinically insignificant abnormality	1	9.1	2	22.2	3	30.0
M11	Normal	10	90.9	6	66.7	6	60.0
	Clinically insignificant abnormality	1	9.1	2	22.2	4	40.0
	Clinically significant abnormality	0	0.0	1	11.1	0	0.0
M12	Normal	10	90.9	6	66.7	7	70.0
	Clinically insignificant abnormality	1	9.1	2	22.2	3	30.0
	Clinically significant abnormality	0	0.0	1	11.1	0	0.0

Table 12-7. Slit Lamp Exam: Anterior chamber (Level scale: Normal, Clinically insignificant abnormality, Clinically significant abnormality)

		Group 1		Group 2		Group 3	
		No.	%	No.	%	No.	%
SCR	Normal	11	100	9	100	10	100
M0	Normal	11	100	9	100	10	100
M1	Normal	11	100	9	100	10	100
M2	Normal	11	100	9	100	10	100
M3	Normal	11	100	9	100	10	100
M4	Normal	11	100	9	100	9	90
	Clinically insignificant abnormality	0	0	0	0	1	10
M5	Normal	11	100	9	100	10	100
M6	Normal	11	100	9	100	10	100
M7	Normal	11	100	9	100	10	100
M8	Normal	11	100	9	100	10	100
M9	Normal	11	100	9	100	10	100
M10	Normal	11	100	8	88.89	10	100
	Clinically insignificant abnormality	0	0	0	0	0	0
	Clinically significant abnormality	0	0	1	11.11	0	0
M11	Normal	11	100	9	100	10	100
M12	Normal	11	100	9	100	10	100

Ophthalmoscopy results are presented in Table 12-8, Table 12-9, Table 12-10, Table 12-12, Table 12-13 and Table 12-1412-15.

Table 12-8. Ophthalmoscopy: Vitreous (Level scale: Normal, Clinically insignificant abnormality, Clinically significant abnormality)

		Group 1		Group 2		Group 3	
		No.	%	No.	%	No.	%
SCR	Normal	9	81.8	9	100.0	5	55.6
	Clinically insignificant abnormality	0	0.0	0	0.0	2	22.2
	Clinically significant abnormality	2	18.2	0	0.0	2	22.2
M0	Normal	9	81.8	9	100.0	6	60.0
	Clinically insignificant abnormality	1	9.1	0	0.0	2	20.0
	Clinically significant abnormality	1	9.1	0	0.0	2	20.0
M1	Normal	8	72.7	9	100.0	9	90.0
	Clinically insignificant abnormality	2	18.2	0	0.0	1	10.0
	Clinically significant abnormality	1	9.1	0	0.0	0	0.0
M2	Normal	11	100.0	8	88.9	9	90.0
	Clinically insignificant abnormality	0	0.0	1	11.1	1	10.0
M3	Normal	10	90.9	9	100.0	9	90.0
	Clinically insignificant abnormality	0	0.0	0	0.0	1	10.0
	Clinically significant abnormality	1	9.1	0	0.0	0	0.0
M4	Normal	9	81.8	9	100.0	9	90.0
	Clinically insignificant abnormality	0	0.0	0	0.0	1	10.0
	Clinically significant abnormality	2	18.2	0	0.0	0	0.0
M5	Normal	11	100.0	9	100.0	10	100.0
M6	Normal	8	72.7	9	100.0	10	100.0
	Clinically insignificant abnormality	1	9.1	0	0.0	0	0.0
	Clinically significant abnormality	2	18.2	0	0.0	0	0.0
M7	Normal	9	81.8	7	77.8	9	90.0
	Clinically insignificant abnormality	1	9.1	0	0.0	0	0.0
	Clinically significant abnormality	1	9.1	2	22.2	1	10.0
M8	Normal	10	90.9	9	100.0	10	100.0
	Clinically insignificant abnormality	0	0.0	0	0.0	0	0.0
	Clinically significant abnormality	1	9.1	0	0.0	0	0.0
M9	Normal	11	100.0	9	100.0	10	100.0
M10	Normal	11	100.0	7	77.8	10	100.0
	Clinically insignificant abnormality	0	0.0	0	0.0	0	0.0
	Clinically significant abnormality	0	0.0	2	22.2	0	0.0
M11	Normal	11	100.0	9	100.0	10	100.0
M12	Normal	11	100.0	9	100.0	10	100.0

Table 12-9. Ophthalmoscopy: Retina (Level scale: Normal, Clinically insignificant abnormality, Clinically significant abnormality)

		Group 1		Group 2		Group 3	
		No.	%	No.	%	No.	%
SCR	Normal	0	0.0	0	0.0	2	22.2
	Clinically insignificant abnormality	0	0.0	0	0.0	0	0.0
	Clinically significant abnormality	11	100.0	9	100.0	7	77.8
M0	Normal	0	0.0	0	0.0	1	10.0
	Clinically insignificant abnormality	1	9.1	1	11.1	0	0.0
	Clinically significant abnormality	10	90.9	8	88.9	9	90.0
M1	Normal	0	0.0	1	11.1	1	10.0
	Clinically insignificant abnormality	2	18.2	2	22.2	0	0.0
	Clinically significant abnormality	9	81.8	6	66.7	9	90.0
M2	Normal	3	27.3	3	33.3	2	20.0
	Clinically insignificant abnormality	2	18.2	1	11.1	3	30.0
	Clinically significant abnormality	6	54.6	5	55.6	5	50.0
M3	Normal	2	18.2	3	33.3	3	30.0
	Clinically insignificant abnormality	1	9.1	2	22.2	4	40.0
	Clinically significant abnormality	8	72.7	4	44.4	3	30.0
M4	Normal	2	18.2	3	33.3	4	40.0
	Clinically insignificant abnormality	1	9.1	2	22.2	2	20.0
	Clinically significant abnormality	8	72.7	4	44.4	4	40.0
M5	Normal	2	18.2	2	22.2	5	50.0
	Clinically insignificant abnormality	1	9.1	1	11.1	3	30.0
	Clinically significant abnormality	8	72.7	6	66.7	2	20.0
M6	Normal	2	18.2	1	11.1	3	30.0
	Clinically insignificant abnormality	1	9.1	1	11.1	3	30.0
	Clinically significant abnormality	8	72.7	7	77.8	4	40.0
M7	Normal	3	27.3	3	33.3	3	30.0
	Clinically insignificant abnormality	0	0.0	3	33.3	2	20.0
	Clinically significant abnormality	8	72.7	3	33.3	5	50.0
M8	Normal	2	18.2	3	33.3	6	60.0
	Clinically insignificant abnormality	2	18.2	3	33.3	2	20.0
	Clinically significant abnormality	7	63.6	3	33.3	2	20.0
M9	Normal	2	18.2	1	11.1	7	70.0
	Clinically insignificant abnormality	1	9.1	3	33.3	2	20.0
	Clinically significant abnormality	8	72.7	5	55.6	1	10.0
M10	Normal	3	27.3	5	55.6	5	50.0
	Clinically insignificant abnormality	2	18.2	2	22.2	1	10.0
	Clinically significant abnormality	6	54.6	2	22.2	4	40.0
M11	Normal	4	36.4	3	33.3	4	40.0
	Clinically insignificant abnormality	1	9.1	3	33.3	2	20.0
	Clinically significant abnormality	6	54.6	3	33.3	4	40.0
M12	Normal	3	27.3	2	22.2	5	50.0
	Clinically insignificant abnormality	1	9.1	3	33.3	2	20.0
	Clinically significant abnormality	7	63.6	4	44.4	3	30.0

Table 12-10. Ophthalmoscopy: Macula (Level scale: Normal, Clinically insignificant abnormality, Clinically significant abnormality)

		Group 1		Group 2		Group 3	
		No.	%	No.	%	No.	%
SCR	Normal	3	27.3	5	55.6	4	44.4
	Clinically insignificant abnormality	1	9.1	1	11.1	0	0.0
	Clinically significant abnormality	7	63.6	3	33.3	5	55.6
M0	Normal	3	27.3	5	55.6	4	40.0
	Clinically insignificant abnormality	2	18.2	0	0.0	0	0.0
	Clinically significant abnormality	6	54.6	4	44.4	6	60.0
M1	Normal	4	40.0	4	44.4	5	50.0
	Clinically insignificant abnormality	1	10.0	1	11.1	0	0.0
	Clinically significant abnormality	5	50.0	4	44.4	5	50.0
M2	Normal	5	45.5	4	44.4	5	50.0
	Clinically insignificant abnormality	1	9.1	2	22.2	1	10.0
	Clinically significant abnormality	5	45.5	3	33.3	4	40.0
M3	Normal	2	18.2	5	55.6	6	60.0
	Clinically insignificant abnormality	4	36.4	1	11.1	1	10.0
	Clinically significant abnormality	5	45.5	3	33.3	3	30.0
M4	Normal	5	45.5	5	55.6	6	60.0
	Clinically insignificant abnormality	2	18.2	0	0.0	0	0.0
	Clinically significant abnormality	4	36.4	4	44.4	4	40.0
M5	Normal	6	54.6	6	66.7	7	70.0
	Clinically insignificant abnormality	2	18.2	0	0.0	1	10.0
	Clinically significant abnormality	3	27.3	3	33.3	2	20.0
M6	Normal	6	54.6	5	55.6	7	70.0
	Clinically insignificant abnormality	1	9.1	2	22.2	0	0.0
	Clinically significant abnormality	4	36.4	2	22.2	3	30.0
M7	Normal	3	27.3	6	66.7	6	60.0
	Clinically insignificant abnormality	3	27.3	2	22.2	2	20.0
	Clinically significant abnormality	5	45.5	1	11.1	2	20.0
M8	Normal	5	45.5	7	77.8	5	50.0
	Clinically insignificant abnormality	1	9.1	0	0.0	2	20.0
	Clinically significant abnormality	5	45.5	2	22.2	3	30.0
M9	Normal	5	45.5	5	55.6	5	50.0
	Clinically insignificant abnormality	1	9.1	2	22.2	2	20.0
	Clinically significant abnormality	5	45.5	2	22.2	3	30.0
M10	Normal	6	54.6	7	77.8	7	70.0
	Clinically insignificant abnormality	2	18.2	1	11.1	1	10.0
	Clinically significant abnormality	3	27.3	1	11.1	2	20.0
M11	Normal	6	54.6	6	66.7	5	50.0
	Clinically insignificant abnormality	1	9.1	2	22.2	2	20.0
	Clinically significant abnormality	4	36.4	1	11.1	3	30.0
M12	Normal	6	54.6	6	66.7	5	50.0
	Clinically insignificant abnormality	2	18.2	1	11.1	3	30.0
	Clinically significant abnormality	3	27.3	2	22.2	2	20.0

Table 12-11. Ophthalmoscopy: Choroid (Level scale: Normal, Clinically insignificant abnormality, Clinically significant abnormality)

		Group 1		Group 2		Group 3	
		No.	**%**	**No.**	**%**	**No.**	**%**
SCR	Normal	11	100.0	9	100.0	8	88.9
	Clinically insignificant abnormality	0	0.0	0	0.0	0	0.0
	Clinically significant abnormality	0	0.0	0	0.0	1	11.1
M0	Normal	11	100.0	9	100.0	10	100.0
M1	Normal	10	90.9	9	100.0	10	100.0
	Clinically insignificant abnormality	0	0.0	0	0.0	0	0.0
	Clinically significant abnormality	1	9.1	0	0.0	0	0.0
M2	Normal	11	100.0	9	100.0	10	100.0
M3	Normal	11	100.0	9	100.0	10	100.0
M4	Normal	11	100.0	9	100.0	10	100.0
M5	Normal	11	100.0	9	100.0	10	100.0
M6	Normal	9	81.8	9	100.0	9	90.0
	Clinically insignificant abnormality	1	9.1	0	0.0	0	0.0
	Clinically significant abnormality	1	9.1	0	0.0	1	10.0
M7	Normal	11	100.0	9	100.0	10	100.0
M8	Normal	11	100.0	9	100.0	10	100.0
M9	Normal	11	100.0	9	100.0	10	100.0
M10	Normal	11	100.0	9	100.0	10	100.0
M11	Normal	11	100.0	9	100.0	10	100.0
M12	Normal	11	100.0	9	100.0	10	100.0

Table 12-12. Ophthalmoscopy: Optic nerve (Level scale: Normal, Clinically insignificant abnormality, Clinically significant abnormality)

		Group 1		Group 2		Group 3	
		No.	%	No.	%	No.	%
SCR	Normal	5	45.5	8	88.9	6	60.0
	Clinically insignificant abnormality	0	0.0	0	0.0	0	0.0
	Clinically significant abnormality	6	54.6	1	11.1	4	40.0
M0	Normal	7	63.6	5	55.6	7	70.0
	Clinically insignificant abnormality	0	0.0	0	0.0	0	0.0
	Clinically significant abnormality	4	36.4	4	44.4	3	30.0
M1	Normal	8	72.7	7	77.8	8	80.0
	Clinically insignificant abnormality	0	0.0	1	11.1	0	0.0
	Clinically significant abnormality	3	27.3	1	11.1	2	20.0
M2	Normal	6	54.6	8	88.9	9	90.0
	Clinically insignificant abnormality	1	9.1	1	11.1	0	0.0
	Clinically significant abnormality	4	36.4	0	0.0	1	10.0
M3	Normal	9	81.8	9	100.0	10	100.0
	Clinically insignificant abnormality	0	0.0	0	0.0	0	0.0
	Clinically significant abnormality	2	18.2	0	0.0	0	0.0
M4	Normal	8	72.7	7	77.8	10	100.0
	Clinically insignificant abnormality	0	0.0	0	0.0	0	0.0
	Clinically significant abnormality	3	27.3	2	22.2	0	0.0
M5	Normal	8	72.7	9	100.0	9	90.0
	Clinically insignificant abnormality	1	9.1	0	0.0	0	0.0
	Clinically significant abnormality	2	18.2	0	0.0	1	10.0
M6	Normal	9	81.8	9	100.0	8	80.0
	Clinically insignificant abnormality	0	0.0	0	0.0	0	0.0
	Clinically significant abnormality	2	18.2	0	0.0	2	20.0
M7	Normal	8	72.7	9	100.0	10	100.0
	Clinically insignificant abnormality	0	0.0	0	0.0	0	0.0
	Clinically significant abnormality	3	27.3	0	0.0	0	0.0
M8	Normal	8	72.7	9	100.0	10	100.0
	Clinically insignificant abnormality	0	0.0	0	0.0	0	0.0
	Clinically significant abnormality	3	27.3	0	0.0	0	0.0
M9	Normal	8	72.7	9	100.0	9	90.0
	Clinically insignificant abnormality	0	0.0	0	0.0	0	0.0
	Clinically significant abnormality	3	27.3	0	0.0	1	10.0
M10	Normal	8	72.7	8	88.9	10	100.0
	Clinically insignificant abnormality	0	0.0	1	11.1	0	0.0
	Clinically significant abnormality	3	27.3	0	0.0	0	0.0
M11	Normal	8	72.7	8	88.9	9	90.0
	Clinically insignificant abnormality	0	0.0	1	11.1	0	0.0
	Clinically significant abnormality	3	27.3	0	0.0	1	10.0
M12	Normal	9	81.8	8	88.9	9	90.0
	Clinically insignificant abnormality	0	0.0	1	11.1	0	0.0
	Clinically significant abnormality	2	18.2	0	0.0	1	10.0

Table 12-13. Ophthalmoscopy: Optic nerve pallor (Level scale: Normal, Clinically insignificant abnormality, Clinically significant abnormality)

		Group 1		Group 2		Group 3	
		No.	%	No.	%	No.	%
SCR	Normal	11	100.0	8	88.9	10	100.0
	Clinically insignificant abnormality	0	0.0	0	0.0	0	0.0
	Clinically significant abnormality	0	0.0	1	11.1	0	0.0
M0	Normal	10	90.9	9	100.0	10	100.0
	Clinically insignificant abnormality	0	0.0	0	0.0	0	0.0
	Clinically significant abnormality	1	9.1	0	0.0	0	0.0
M1	Normal	10	90.9	9	100.0	9	90.0
	Clinically insignificant abnormality	0	0.0	0	0.0	0	0.0
	Clinically significant abnormality	1	9.1	0	0.0	1	10.0
M2	Normal	11	100.0	9	100.0	10	100.0
M3	Normal	11	100.0	9	100.0	10	100.0
M4	Normal	11	100.0	9	100.0	10	100.0
M5	Normal	11	100.0	9	100.0	10	100.0
M6	Normal	11	100.0	9	100.0	10	100.0
M7	Normal	11	100.0	9	100.0	10	100.0
M8	Normal	11	100.0	9	100.0	10	100.0
M9	Normal	11	100.0	9	100.0	10	100.0
M10	Normal	11	100.0	9	100.0	10	100.0
M11	Normal	11	100.0	9	100.0	10	100.0
M12	Normal	11	100.0	9	100.0	10	100.0

Table 12-1412-15. Ophthalmoscopy: Other

		Group 1		Group 2		Group 3	
		No.	%	No.	%	No.	%
SCR	Normal	11	100.0	8	100.0	10	100.0
M0	Normal	11	100.0	8	100.0	10	100.0
M1	Normal	11	100.0	8	100.0	10	100.0
M2	Normal	11	100.0	8	100.0	10	100.0
M3	Normal	11	100.0	9	100.0	10	100.0
M4	Normal	11	100.0	9	100.0	10	100.0
M5	Normal	11	100.0	9	100.0	10	100.0
M6	Normal	11	100.0	9	100.0	10	100.0
M7	Normal	11	100.0	9	100.0	10	100.0
M8	Normal	11	100.0	9	100.0	10	100.0
M9	Normal	11	100.0	9	100.0	10	100.0
M10	Normal	11	100.0	9	100.0	10	100.0
M11	Normal	11	100.0	9	100.0	10	100.0
M12	Normal	11	100.0	9	100.0	10	100.0

Table 12-16 shows results about intraretinal edema with center involvement.

Table 12-16. Intraretinal edema with center involvement

		Group 1		Group 2		Group 3	
		No.	**%**	**No.**	**%**	**No.**	**%**
SCR	Absent	3	27.3	5	55.6	3	30.0
	Present	8	72.7	4	44.4	7	70.0
M3	Absent	2	18.2	3	33.3	2	20.0
	Present	9	81.8	6	66.7	8	80.0
M6	Absent	3	30.0	4	44.4	2	20.0
	Present	7	70.0	5	55.6	8	80.0
M12	Absent	3	30.0	2	22.2	2	20.0
	Present	7	70.0	7	77.8	8	80.0

12.6 Safety conclusions

35 adverse events were reported in this study.
17 of the adverse events correspond to eye disorders.
Further, 1 adverse event (angina unstable) may be related to the Study Drug, 1 adverse event (ulcerative keratitis) is likely to be related to the injection procedure and 1 adverse event (eye pain) is likely to be related to the laser procedure.
4 adverse events were considered serious adverse events and one of them was considered a serious adverse reaction (expected).

13 Discussion and overall conclusions

This study showed that combined therapy (PRP+ITV group) resulted in a higher proportions of eyes with NV regression one year after the beginning of the trial but this effect was not significantly different from the remaining treatment arms which may be due to the small number of patients enrolled in the study. The occurrence of severe vitreous haemorrhage or PDR-related complications requiring vitrectomy was more frequent in eyes assigned to PRP monotherapy (30.8%). Finally, the eyes with high-risk NV assigned to ITV monotherapy did not need any laser rescue treatment during the twelve month period of follow-up.
Altogether these results suggest that ranibizumab may have a place in the treatment of NV by itself or as an adjuvant to PRP at least in diabetic type 2 patients.

Data from NVE and NVD regression was analyzed separately. We believe that the clinical implications and prognosis of these two types of NV are quite different (Rand et al., 1985) (Duh, 2008). The percentage of regression achieved was higher for NVE than NVD.
There is only another study (Ferraz et al., 2014) that has assessed ITV efficacy for high-risk PDR in a clinical trial setting. The authors included two treatment arms in their trial: PRP alone and PRP+ITV. In both groups, a significant within-group reduction of the total area of fluorescein leakage was observed, with more reduction in eyes receiving combined therapy. In our study, the results were similar with combined therapy showing a better response particularly in terms of NVE area reduction. The observed differences between the two studies are probably linked with the different study designs. First of all, we included three and not two treatment arms. Additionally, as briefly stated in the introduction of this manuscript, the trial reported by Ferraz et al. presented a combined treatment arm in which PRP and ITV were performed at baseline, but retreatment included only ITV injections.
Regarding the occurrence of severe vitreous haemorrhage and/or PDR-related complications it was higher in PRP monotherapy group with a higher frequency of VH of any severity grade in the same eyes.
It is of major relevance that none of the eyes in the ITV monotherapy group needed rescue pan-retinal photocoagulation treatment. ITV showed efficacy in controlling the NV by itself during the twelve month period of the study. Considering the side effects on vision of pan-retinal photocoagulation, ITV monotherapy appears as an interesting alternative, at least for the initial period of twelve months.
Most of the ITV eyes required 5 injections (50%), but the median number did not differ significantly for eyes with combined therapy. Regarding the number of PRP performed sessions, it did not also vary significantly between eyes treated with PRP alone and PRP+ITV.
We also looked at other secondary outcomes in our trial. One of them was the evolution of BCVA, which did not differ among the study groups and remained stable within each group.
All our treatment groups presented comparable CMT results. The only differences were found at 3 months, when eyes assigned to ITV therapy showed a significantly higher reduction of CMT than eyes treated with PRP alone.

Vitreous haemorrhage was the most frequently observed AE. Besides this, all the remaining were always observed with a frequency of 2.8% (1 case for all AE) and were similar in all the three groups.

The main limitations of this trial are the follow-up period and the reduced number of patients included in the study, clearly short of the needed calculated sample size. It is to be noticed that this is an exploratory study of one year duration and after the end of the study the patients were followed according to the usual clinical practice and any potential treatment after the study was performed at the research center at the discretion of their ophthalmologist. Regarding the number of included patients, even with an extension of the recruitment period, we were not able to include the initially planned number of patients. Moreover, it should be noticed that many patients had already received photocoagulation before entering the study, and therefore due to the variability that this data may have, it was impossible to analyze influence of the total number of laser spots in this study. To overcome this limitation it was ensured that the DRS Protocol recommendation of a complete PRP with 800 to 1.600 laser burns of 500 µm (ETDRS, 1987) was followed in the study and that this treatment was equally provided to every patient that were randomized to both PRP groups.
Future multicenter studies with a larger sample size are needed to achieve definite conclusions about the potential advantages of adding ITV to the standard PRP therapy. Our group is already conducting a multicenter trial with this aim (NCT01941329), with the collaboration of several European centers.

In conclusion, this exploratory randomized controlled trial suggests that intravitreal ranibizumab is safe and may be considered as a therapy for high-risk proliferative diabetic retinopathy eyes. The results obtained using ITV alone or in combined therapy are comparable or better than PRP alone. It remains to be demonstrated if this beneficial effect can be sustained for periods longer than twelve months.

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

All results referred in text are presented.

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16 Appendices

16.1 Study information

16.1.1 Protocol and protocol amendments

16.1.2 Sample case report form (unique pages only)

16.1.3 IECs and CA approval - representative written information for patient and sample consent forms

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

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

16.1.6 Publication based on the study

The manuscript entitled: "Ranibizumab for high-risk proliferative diabetic retinopathy. An exploratory randomized controlled trial", João Figueira, Rufino Silva, José Henriques, Paulo Caldeira Rosa, Inês Laíns, Pedro Melo, Sandrina Gonçalves Nunes, José Cunha-Vaz, was accepted for publication in the Journal Ophthalmologica on 2015, October 28th.

Ranibizumab for high-risk proliferative diabetic retinopathy. An exploratory randomized controlled trial

Short running title: Ranibizumab for proliferative diabetic retinopathy

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Abstract

Purpose: To compare efficacy and safety of Intravitreal Ranibizumab (IVR) in monotherapy or associated with Panretinal Photocoagulation (PRP) versus conventional PRP, for high-risk Proliferative Diabetic Retinopathy (PDR) without vitreoretinal traction.

Procedures: Multicenter randomized trial, with three treatment arms: PRP vs IVR alone and PRP+IVR combined treatment. Follow-up was performed at months 3, 6 and 12.

Results: Thirty-five subjects were randomized and 32 used for analysis. Complete regression of neovessels elsewhere (NVE) occurred in 100% (PRP+IVR); 75% (IVR) and 69.2% (PRP) and for neovessels of the disk (NVD) in 44.4% (PRP+IVR), 37.5% (IVR) and 30.8% (PRP). During the one year duration of treatment, there was no need for laser rescue treatment in IVR treated eyes.

Conclusions: This trial suggests that the use of IVR is safe and may have a beneficial effect in the treatment of eyes with high-risk PDR.

Message of paper: Ranibizumab appears to have a place in the treatment of PDR.

Key-words: proliferative diabetic retinopathy; anti-VEGF, laser treatment.

Introduction

Diabetic retinopathy (DR) remains a leading cause of blindness in working-age populations [1]. The proliferative form of the disease, characterized by the growth of new abnormal leaky vessels, is one of the most significantly linked with vision impairment [2]. Among the underlying mechanisms of proliferative DR (PDR) stands out retinal hypoxia, a major inducer of vascular endothelial growth factor (VEGF) transcription [3]. Studies revealed that VEGF is a main mediator of ocular neovascularization (NV) [4] and its levels are elevated in the ocular fluids of patients with PDR [5], thus emphasizing that VEGF might play a role in PDR pathogenesis.

Currently, the only proven treatment for PDR is panretinal photocoagulation (PRP) [6]. PRP is remarkably effective and has saved vision in many patients over the past several decades [7,8]. Nevertheless, in up to 5% of the cases, neovessels continue to grow and vitrectomy is required, despite an appropriate initial treatment [9]. In these cases, vitreous hemorrhage is common and frequently precludes laser completion [3]. Furthermore, PRP adverse effects are now widely recognized, such as worsening of DME and decline in peripheral and night vision function [10].

Considering the current evidence that VEGF takes part in the pathogenesis of PDR and the limitations of PRP, antiangiogenic agents have been recently admitted as new therapeutic options. Surprisingly, most of the available studies reported observational short-term data [11,12] and focused on intravitreal injections of bevacizumab (IVB) [11–15], a full-length anti-VEGF antibody that remains off-label for intraocular use [6]. Scarce data is available for ranibizumab, an approved agent for intravitreal use, with activity against all isoforms of VEGF and widely administered throughout the world [1]. To our knowledge, there are only two published randomized studies in this field, one focusing on non-high risk [16] and the other on high-risk [17] PDR eyes. In this last trial [17], a control group was assigned to PRP and the study group received two sessions of PRP plus a single intravitreal ranibizumab (IVR) injection. Retreatment was performed with IVR in monotherapy. There are however in this reported trial confounding factors. For instance, all the eyes received PRP at baseline, making it impossible to evaluate the effect of IVR

alone. Therefore, the safety and efficacy of IVR as an adjunctive or alternative therapy for high risk PDR remains to be established.

This manuscript reports the one year results of a randomized, multicenter, controlled trial which aimed to assess the efficacy and safety of IVR for the treatment of patients with high-risk PDR (HR-PDR). Three study arms were compared: standard monotherapy with PRP, IVR monotherapy and PRP plus IVR.

Methods

This randomized, open label, phase II, controlled trial (NCT01280929) recruited patients from November 2010 to November 2012 in four Centers from Portugal. It was designed and implemented in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, and based on the ethical principles of the Declaration of Helsinki. The National Regulatory Authorities reviewed and approved the study protocol and its procedures. Informed consent was obtained for all subjects before randomization and after explanation of the nature and possible consequences of their participation in the trial.

Study population

Type 2 diabetic patients with HR-PDR, aged 18 years or older, with best-corrected visual acuity (BCVA) at screening > 20/320 (25 letters in the ETDRS Chart) in the study eye were considered eligible for this study. HR-PDR was defined according to the ETDRS criteria [18]. Vitreous hemorrhages and/or pre-retinal hemorrhages were allowed if not compromising NV assessment.

Exclusion criteria included: 1) Treatment with panretinal or macular photocoagulation, YAG laser, cryoablation or laser retinopexy within the 6 months prior to inclusion; 2) Treatment with any investigational agents for DR, anti-VEGF agents or corticosteroids in the 90 days prior to inclusion; 3) Presence of fibrovascular proliferation with associated retinal traction; 4) Presence of atrophy, scarring, fibrosis or hard exudates involving the center of the macula; 5) History of previous vitrectomy; 6) HbA1c equal or superior to 11% or systemic uncontrolled diabetes; 7) Underlying significant systemic diseases (such as severe cardiac disease and significantly impaired renal function, among others) 8) Significant media opacities, which might interfere with visual acuity, assessment of toxicity or fundus photography.

Randomization and treatment arms

Randomization was performed by an automated system at a 1:1:1 ratio to one of three treatment arms:

- PRP group: at study inclusion, these eyes received standard of care PRP, according to the ETDRS protocol [18]. After the first 3 months, PRP could be repeated if necessary.
- IVR group: eyes assigned to IVR in monotherapy received 3 loading-dose injections of ranibizumab 0.5 mg (month 0, 1 and 2). During the remaining follow-up, if NV persisted or recurred, subjects could receive additional IVR with a minimum of 4 weeks interval. Rescue treatment with PRP could be performed after 3 months of follow-up (6 months after the initial injection) if considered necessary.
- PRP+IVR group: eyes in this group received a combined treatment of IVR plus PRP (2 weeks ± 1 week after each injection), at months 0, 1 and 2. Afterwards, they could receive additional combined treatments, with at least 4 weeks of interval, if the NV persisted and/or if recurrence was verified.

For all study groups, in the occurrence of diabetic macular edema (DME), the standard of care treatment at the time of this trial was allowed: focal and/or grid macular laser, according to the ETDRS protocol [19]. Administration of any intravitreal corticosteroids or other anti-antiangiogenic drugs besides the study drug were not allowed, even for the non-study eye.

Study protocol and follow-up

Included patients were followed during 12 months on a monthly basis. At baseline, the study protocol included: a complete ophthalmological examination, with BCVA evaluated with ETDRS charts at 4 meters distance, slit-lamp biomicroscopy, Goldmann tonometry and dilated fundus evaluation; 7 ETDRS fields digital fundus photographs (30 degrees); digital fluorescein angiography (FA); and optical coherence tomography (OCT) using Cirrus™ HD-OCT (Carl Zeiss Meditec, USA) or Spectralis™ HRA+OCT (Heidelberg Engineering, Germany), according to which device was available in the study centers. The Macular Cube 512*128* protocol and the volume scan protocol were used for the Cirrus™ and the Spectralis™ OCT devices, respectively.

The entire baseline procedures were repeated at months 3, 6 and 12. In the remaining monthly evaluations, only the complete ophthalmological exam and

the evaluation of adverse events were performed. At baseline and last visit (month-12), blood biochemistry analysis, including HbA1c, were additionally obtained.

All the performed color fundus photographs and fluorescein angiograms were evaluated and graded in a centralized reading center (Coimbra Ophthalmologic Reading Centre - CORC), by certified graders. The area of NV was measured in disc area (DA) decimal units, based on color fundus photographs and FA. The area of neovessels of the disc (NVD), neovessels elsewhere (NVE) and the total area of NV were considered for analysis.

Central macular thickness (CMT) was automatically obtained from the OCT devices, as the average macular thickness of the 1 mm diameter circle centered on the fovea. Considering that some of the centers performed OCT with Cirrus™ and the remaining with Spectralis™ OCT, 15 µm were subtracted to the measurements obtained with the last device in order to pool the data [20].

Sample size

A total of 54 subjects (18 per treatment arm) was estimated for this study. The sample size calculation was based on the rate of NV regression at month-12 (primary outcome), assuming a 25% rate for the PRP group and a 90% rate for the IVR and the PRP+IVR groups [21,22], with a 10% dropout rate, a two-sided significance of 0.01 and a power of 0.9.

Statistical analysis

An intention-to-treat (ITT) analysis was performed. By definition, ITT includes all the subjects initially randomly assigned to one of the treatment arms regardless of potential withdrawal from treatment or deviations from the protocol, thus avoiding overoptimistic estimates of the efficacy of an intervention. If noncompliant subjects and dropouts are excluded from the final analysis, it might create important prognostic differences among treatment groups [9]. To deal with missing outcome data of patients who withdraw from the study, we used the last-observation carried forward method.

Due to the small number of patients included in the study non-parametric test were used.

Traditional descriptive statistics were performed, namely the nominal variables were summarized with frequencies and percentages and the continuous variables with median and interquartile range. Univariate analyses were

performed to analyze the differences between the 3 study groups. The Exact Fisher test was used for categorical variables and the Man-Whitney test for the continuous. To compare the evolution between visits for the NV area, the BCVA and the CMT the Wilcoxon and the Friedman tests were used. Bonferroni corrections for multiple testing were performed.
All statistical analyses were performed with STATA version 12.1 (StataCorp LP, College Station, TX, USA) and p-values less or equal than 0.05 were considered statistically significant results.

Results

Of the 54 eyes required in the sample size calculation, it was possible to randomize only 35 eyes/patients: 13 to PRP group, 10 to IVR group and the remaining 12 to the combined treatment group (PRP+IVR). Of these, 32 completed the study and 3 withdraw (2 removed informed consent and one subject from PRP+IVR group withdraw due to coronary heart ischemia) (Figure 1).

At baseline, the 3 study groups were well balanced, presenting similar clinical and demographic characteristics, as detailed in Table 1 ($p \geq 0.060$). All included subjects were type 2 diabetics.

Twelve months after the initial visit, subjects treated with PRP+IVR presented higher proportions both for NVD and NVE regression (Table 2).
This good response in all study groups is more clear when considering NVE regression which was 100.0% (9 out of 9 subjects), 75.0% (6 out of 8 subjects) and 69.2% (9 out of 13 subjects) respectively for PRP+IVR, IVR alone and PRP alone. Regarding NVD the respective values were 87.5% (7 out of 8 subjects), 60.0% (3 out of 5 subjects) and 55.6% (5 out of 9 subjects).

When considering the main aim of the study, which is complete regression of NV, this was found to occur, for the NVE, in the same range for the three study groups whereas for NVD, there was a better response when IVR was used, both alone or in association with PRP (PRP+IVR) (Table 3).

It is to be noted that regression for both NVE and NVD occurred earlier at 3 months in the groups treated with IVR, both alone or in association with PRP.

It is worth noting that there was no need for laser recue treatment in the group receiving IVR alone and that the occurrence of PDR-related complications, such as severe vitreous hemorrhage and/or other PDR complications requiring vitrectomy was superior in eyes assigned to PRP alone (30.8%, 4 out of 13 subjects) than in eyes treated with IVR alone (11.1%, 1 out of 9 subjects) or in association, PRP+IVR (9.0%, 1 out of 10 subjects) (p=0.391).
Regarding BCVA, there were no significant variations during the study follow-up and was comparable between all the study groups ($p \geq 0.477$). All study groups maintained comparable values at 3, 6 and 12 months visits ($p \geq 0.173$) and there were also no significant changes within each group (Table 4, $p \geq 0.207$).

Regarding CMT, CMT also remained comparable between all the study groups during all the follow-up visits (Table 4). Decrease CMT variations during the study were not statistically significant among the study groups except at 3 months, where the CMT decrease was significant in the PRP+IVR group (p=0.004).
The median (IQR) number of PRP treatments performed in the PRP group was 3 (1-5) and 4 (3-5) in the PRP+IVR group (p=0.378).
In the PRP group, 1 out of the 3 patients that showed reactivation of the neovascularization at month-3 or month-6 was retreated. In the PRP+IVR group, all patients showed reactivation (6) and were retreated.
The number of IVR injections administered in the IVR group and in the combined treatment group was also comparable (p=0.239), with a median (IQR) of 5 (5-7) and 6 (5-7), respectively.
Regarding systemic safety, one subject from IVR group presented a potentially related serious adverse event: need for coronary angioplasty due to unstable angina. One patient from PRP+IVR group developed Erysipelas.

Discussion

We report the 12 months results of an exploratory randomized clinical trial designed to compare the efficacy of PRP, the standard treatment for high-risk PDR, with IVR in monotherapy or combined with PRP in the treatment of high-risk PDR without vitreoretinal traction. Our results showed that combined therapy (PRP+IVR group) resulted in a higher proportions of eyes with NV regression one year after the beginning of the trial but this effect was not significantly different from the remaining treatment arms which may be due to the small number of patients enrolled in the study. The occurrence of severe vitreous hemorrhage or PDR-related complications requiring vitrectomy was more frequent in eyes assigned to PRP monotherapy (30.8%). Finally, the eyes with high-risk NV assigned to IVR monotherapy did not need any laser rescue treatment during the twelve month period of follow-up.

Altogether these results suggest that ranibizumab may have a place in the treatment of NV by itself or as an adjuvant to PRP at least in diabetic type 2 patients.

We have analyzed the data looking at NVE and NVD regression separately. We believe that the clinical implications and prognosis of these two types of NV are quite different [23,24]. The percentage of regression achieved was higher for NVE than NVD.

There is only another study [17] that has assessed IVR efficacy for high-risk PDR in a clinical trial setting. The authors included two treatment arms in their trial: PRP alone and PRP+IVR. In both groups, a significant within-group reduction of the total area of fluorescein leakage was observed, with more reduction in eyes receiving combined therapy. In our study, the results were similar with combined therapy showing a better response particularly in terms of NVE area reduction. The observed differences between the two studies are probably linked with the different study designs. First of all, we included three and not two treatment arms. Additionally, as briefly stated in the introduction of this manuscript, the trial reported by Ferraz et al. [17] presented a combined treatment arm in which PRP and IVR were performed at baseline, but retreatment included only IVR injections.

Regarding the occurrence of severe vitreous hemorrhage and/or PDR-related complications it was higher in PRP monotherapy group with a higher frequency of VH of any severity grade in the same eyes.

It is of major relevance that none of the eyes in the IVR monotherapy group needed rescue pan-retinal photocoagulation treatment. IVR showed efficacy in controlling the NV by itself during the twelve month period of the study. Considering the side effects on vision of pan-retinal photocoagulation, IVR monotherapy appears as an interesting alternative, at least for the initial period of twelve months.

Most of the IVR eyes required 5 injections (50%), but the median number did not differ significantly for eyes with combined therapy. Regarding the number of PRP performed sessions, it did not also vary significantly between eyes treated with PRP alone and PRP+IVR.

We also looked at other secondary outcomes in our trial. One of them was the evolution of BCVA, which did not differ among the study groups and remained stable within each group. All our treatment groups presented comparable CMT results. The only differences were found at 3 months, when eyes assigned to IVR therapy showed a significantly higher reduction of CMT than eyes treated with PRP alone.

The main limitations of this trial are the follow-up period and the reduced number of patients included in the study, clearly short of the needed calculated sample size. It is to be noticed that this is an exploratory study of one year duration and after the end of the study the patients were followed according to the usual clinical practice and any potential treatment after the study was performed at the research center at the discretion of their ophthalmologist. Regarding the number of included patients, even with an extension of the recruitment period, we were not able to include the initially planned number of patients. Moreover, it should be noticed that many patients had already received photocoagulation before entering the study, and therefore due to the variability that this data may have, it was impossible to analyze influence of the total number of laser spots in this study. To overcome this limitation it was ensured that the DRS Protocol recommendation of a complete PRP with 800 to 1.600 laser burns of 500 µm [25] was followed in the study and that this treatment was equally provided to every patient that were randomized to both PRP groups.

Future multicenter studies with a larger sample size are needed to achieve definite conclusions about the potential advantages of adding IVR to the

standard PRP therapy. Our group is already conducting a multicenter trial with this aim (NCT01941329), with the collaboration of several European centers.

In conclusion, this exploratory randomized controlled trial suggests that intravitreal ranibizumab is safe and may be considered as a therapy for high-risk proliferative diabetic retinopathy eyes. The results obtained using IVR alone or in combined therapy are comparable or better than PRP alone. It remains to be demonstrated if this beneficial effect can be sustained for periods longer than twelve months.

Conflict of Interest

José Cunha-Vaz is consultant for Alimera Sciences, Allergan, Bayer, Fovea Pharmaceuticals, GeneSignal, Novartis, OM Pharma, Pfizer, Roche and Zeiss.
João Figueira is consultant for Allergan, Bayer, Novartis, Alcon and Kemin Pharma.
Paulo Caldeira Rosa is consultant for Bayer and Novartis.
José Henriques is consultant for Alimera Sciences, Bayer, Novartis and Pfizer.
Rufino Silva is member of Advisory Board of Allergan, Alimera, Novartis, Bayer, Alcon and Thea.
Inês Laíns, Pedro Melo and Sandrina Nunes have no other conflict of interest to declare.

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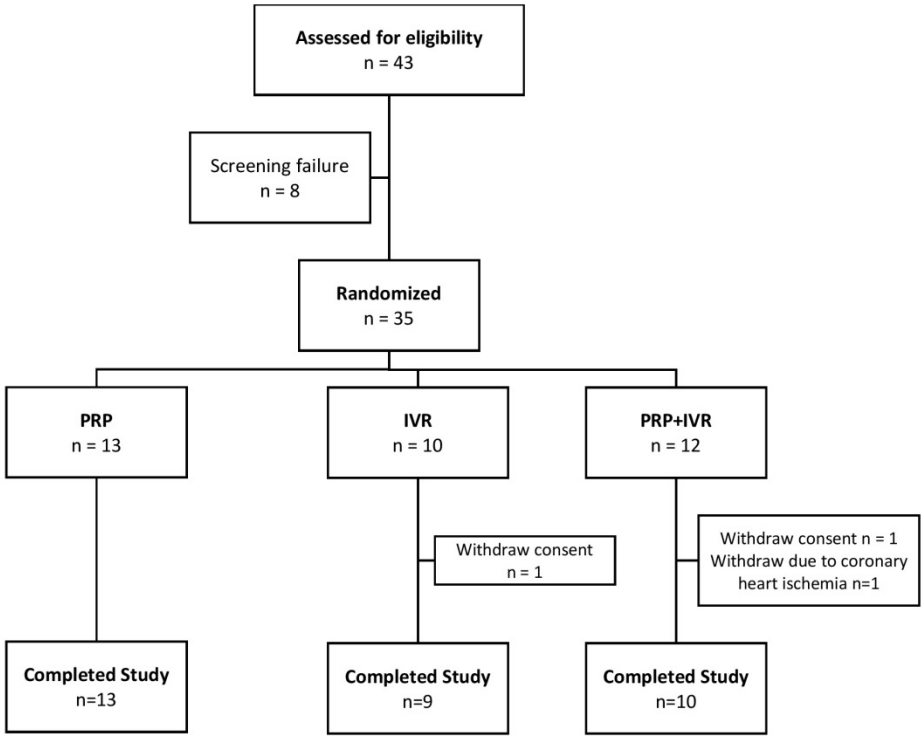

Fig. 1. CONSORT flowchart of the trial (PRP – panretinal photocoagulation; IVR – intravitreal ranibizumab).

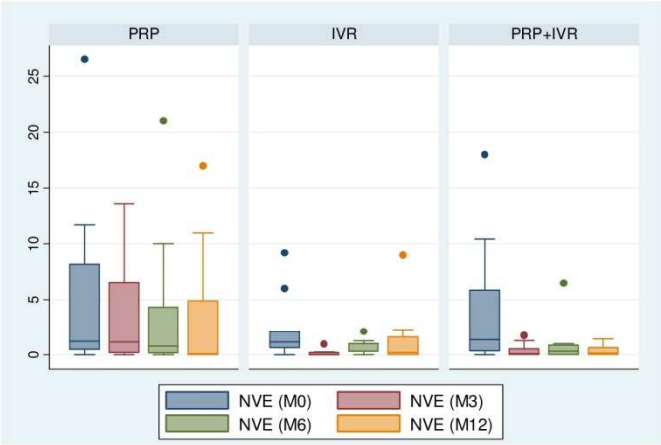

Fig. 2. Area of NVE in decimal DA units by study group.

1

Table 1. Clinical and demographic characteristics of the intention-to-treat population (n=35).

	PRP	IVR	PRP+IVR	p-value
Sex n(%)				
Female	3 (23.1)	4 (40.0)	2 (16.7)	0.557
Male	10 (76.9)	6 (60.0)	10 (83.3)	
Age years, median (IQR)	54 (44 - 59)	61 (52 - 65)	57 (49.5 - 61.5)	0.382
BMI kg/m^2, median (IQR)	28.6 (27.3 - 31.8)	31.5 (27.1 - 36.2)	28.9 (27- 33.1)	0.457
HbA1C %, median (IQR)	8 (6.8 - 8.7)	7.55 (7 - 8.9)	7.2 (6.7 - 9)	0.975
Heart rate bpm, median (IQR)	79 (68 - 81)	79 (68 - 83)	80 (76 - 85.5)	0.824
SBP mm/Hg, median (IQR)	151 (145 - 161)	140 (127.5 - 146.5)	146 (138 - 159)	0.060
DBP mm/Hg, median (IQR)	80 (70 - 90)	79 (74 - 81)	79.5 (70 - 86)	0.930
IOP mm/Hg, Median (IQR)	16 (16 - 17)	16 (15 - 16)	16 (14 - 16.5)	0.588
NVE DA, median (IQR)	1.2 (0.5 - 8.2)	1.1 (0.6 - 2.1)	1.4 (0.3 - 5.8)	0.988
NVD DA, median (IQR)	0.3 (0.0 - 0.8)	0.1 (0.0 - 0.5)	0.4 (0.0 - 1.3)	0.624
BCVA letters n, median (IQR)	76 (71 - 78)	76.5 (73 - 79)	76 (64 - 79)	0.777
CMT µm,median (IQR)	317 (275.5 - 351)	319.5 (256 - 378)	331 (290 - 408)	0.836

Legend: n- number; IQR – interquartile range; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; IOP – intra-ocular pressure; NVE – neovessels elsewhere; NVD – neovessels of the disc; NV – neovessels; BCVA – best corrected visual acuity; CMT – central macular retinal thickness; PRP – panretinal photocoagulation; IVR – intravitreal ranibizumab.

Table 2. Proportion of eyes with or without NV regression from baseline to the 12 month visit.

		PRP	IVR	PRP+IVR	p-value
NVE	With regression	9/13 (69.2%)	6/8 (75.0%)	9/9 (100.0%)	0.190
	Without regression	4/13 (30.8%)	2/8 (25.0%)	0/9 (0.0%)	
NVD	With regression	5/9 (55.6%)	3/5 (60.0%)	7/8 (87.5%)	0.334
	Without regression	4/9 (44.4%)	2/5 (40.0%)	1/8 (12.5%)	

Legend: NVD – neovessels of the disc; NVE – neovessels elsewhere; NV – neovessels; PRP – panretinal photocoagulation; IVR – intravitreal ranibizumab.

1

Table 3. Proportion of eyes with complete NV regression from baseline to the 12-month visit (eyes presenting no area of NV at baseline and at the 12-month visit are not considered).

		PRP	IVR	PRP+IVR
NVE	Complete regression	4/13 (30.8%)	3/8 (37.5%)	4/9 (44.4%)
NVD	Complete regression	2/9 (22.2%)	2/5 (40.0%)	3/8 (37.5%)

Legend: NVD – neovessels of the disc; NVE – neovessels elsewhere; NV – neovessels; PRP – panretinal photocoagulation; IVR – intravitreal ranibizumab.

Table 4. BCVA and CMT during the study according to each study group.

		PRP	IVR	PRP + IVR	p-value*
		Median (IQR)	Median (IQR)	Median (IQR)	
BCVA	Baseline	76 (71 - 78)	76.5 (73 - 79)	76 (64 - 79)	0.777
	Month 3	67 (60 - 77)	73 (69 - 74)	78 (63 - 81)	0.173
	Month 6	74 (64 - 82)	75 (71 - 79)	77 (63 - 82)	0.924
	Month 12	69 (60 - 78)	68 (67 - 77)	74 (59 - 80)	0.841
CMT	Baseline	317 (275 - 351)	319 (256 - 378)	331 (290 - 408)	0.836
	Month 3	329 (268 - 423)	274 (251 - 318)	313 (223 - 330)	0.474
	Month 6	322 (264 - 431)	311 (253 - 353)	346 (346 - 362)	0.883
	Month 12	309 (266 - 339)	290 (260 - 337)	332 (302 - 356)	0.781

Legend: BCVA – best corrected visual acuity; CMT – central macular thickness; NVD – neovessels of the disc; NVE – neovessels elsewhere; NV – neovessels; PRP – panretinal photocoagulation; IVR – intravitreal ranibizumab; IQR – intraquartil range. * p-value for the comparison among the groups; ** p-value for the comparison within group.

16.2 Patient data listings

Concomitant medication by patient.

Patient Number	Treatment	Medication / Non-Drug Therapy	INN	Therapeutic class
0301	1	Crestor 5	Rosuvastatina	Aparelho cardiovascular/ Antidislipidémicos/ Estatinas
0301	1	Dilbloc 25	Carvedilol	Aparelho cardiovascular/ Anti-hipertensores/ Depressores da actividade adrenérgica/ Bloqueadores beta/ Bloqueadores beta e alfa
0301	1	Flindix Retard	Dinitrato de isossorbida	Aparelho cardiovascular/ Vasodilatadores/ Antianginosos
0301	1	Insuline	Insulina aspártico	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Insulinas De acção intermédia
0301	1	Janumet 50/100	Metformina + Sitagliptina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Outros antidiabéticos orais
0301	1	Lasix 40 mg	Furosemida	Aparelho cardiovascular/ Anti-hipertensores/ Diuréticos/ Diuréticos da ansa
0301	1	Pritor 80 mg	Telmisartan	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Antagonistas dos receptores da angiotensina
0301	1	Tacirel	Trimetazidina	Aparelho cardiovascular/ Vasodilatadores/ Antianginosos
0303	3	Bezacor (Dezacor)	Deflazacorte	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Corticosteróides/ Glucocorticóides
0303	3	Brufen 400	Ibuprofeno	Aparelho locomotor/ Anti-inflamatórios não esteróides/ Derivados do ácido propiónico
0303	3	Coversil	Coversyl	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Inibidores da enzima de conversão da angiotensina
0303	3	Fludox (Flodex)	Indapamida	Aparelho cardiovascular/ Anti-hipertensores/ Diuréticos/ Tiazidas e análogos /
0303	3	Insuline (Novonix)	Insulina asparte	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Insulinas De acção intermédia
0306	2	Diamicron	Gliclazida	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e

Concomitant medication by patient.

				glucagom/ Sulfonilureias
0306	2	Janumet 50/100	Metformina + Sitagliptina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Outros antidiabéticos orais
0306	2	Risidon	Metformina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Antidiabéticos orais/ Biguanidas
0307	1	Diltiem	Diltiazem	Aparelho cardiovascular / Antiarrítmicos/ Bloqueadores da entrada do cálcio (Classe IV)
0307	1	Enalapril	Enalapril	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Inibidores da enzima de conversão da angiotensina
0307	1	Insuline	Insulina aspártico	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Insulinas De acção intermédia
0307	1	Stagid	Metformina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Antidiabéticos orais/ Biguanidas
0308	3	Eucreas	Metformina + Vildagliptina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Outros antidiabéticos orais
0308	3	Insulin	Insulina aspártico	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Insulinas De acção intermédia
0308	3	Plavix	Clopidogrel	Sangue/ Anticoagulantes e antitrombóticos/ Anticoagulantes/ Antiagregantes plaquetários
0308	3	Procoralan 5	Ivabradina	Aparelho cardiovascular/ Vasodilatadores/ Antianginosos
0308	3	Ramipril	Ramipril	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Inibidores da enzima de conversão da angiotensina
0308	3	Visacor	Loflazepato de etilo	Sistema Nervoso Central/ Psicofármacos/ Ansiolíticos, sedativos e hipnóticos/ Benzodiazepinas
0309	1	Amlodipine 5	Amlodipina	Sistema Nervoso Central/ Psicofármacos/ Ansiolíticos, sedativos e hipnóticos/ Benzodiazepinas

Concomitant medication by patient.

0309	1	Eucreas	Metformina + Vildagliptina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Outros antidiabéticos orais
0309	1	Insulin	Insulina aspártico	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Insulinas De acção intermédia
0309	1	Insulin	Insulina humana (isofânica)	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Insulinas De acção intermédia
0309	1	Janumet 1000/500	Metformina + Sitagliptina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Outros antidiabéticos orais
0309	1	Losartan + Hipoclortiazide	Losartan + Hipoclortiazide	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Antagonistas dos receptores da angiotensina
0309	1	Losartan 50	Losartan	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Antagonistas dos receptores da angiotensina
0309	1	Pravastatin	Pravastatina	Aparelho cardiovascular/ Antidislipidémicos/ Estatinas
0309	1	Sinvastatine 40	Sinvastatina	Aparelho cardiovascular/ Antidislipidémicos/ Estatinas
0309	1	Victan 2 mg	Loflazepato de etilo	Sistema Nervoso Central/ Psicofármacos/ Ansiolíticos, sedativos e hipnóticos/ Benzodiazepinas
0310	2	Co-Aprovel	Irbesartan + Hidroclorotiazida	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Antagonistas dos receptores da angiotensina
0310	2	Diamicron	Gliclazida	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Sulfonilureias
0310	2	Herbesser	Diltiazem	Aparelho cardiovascular/ Antiarrítmicos/ Bloqueadores da entrada do cálcio (Classe IV)
0310	2	Janumet 50/1000	Metformina + Sitagliptina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Outros antidiabéticos orais
0310	2	Sinvastatina	Sinvastatina	Aparelho cardiovascular/ Antidislipidémicos/ Estatinas
0311	3	Crestor	Rosuvastatina	Aparelho cardiovascular/ Antidislipidémicos/ Estatinas

Concomitant medication by patient.

0311	3	Diamicron	Gliclazida	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Sulfonilureias
0311	3	Eucreas	Metformina + Vildagliptina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Outros antidiabéticos orais
0311	3	Floxdol (Floxedol)	Ofloxacina	Medicamentos usados em afecções oculares/ Anti-infecciosos tópicos/ Antibacterianos
0311	3	Metformina	Metformina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Antidiabéticos orais/ Outros antidiabéticos orais
0311	3	Oftacilox	Ciprofloxacina	Medicamentos usados em afecções oculares/ Anti-infecciosos tópicos/ Antibacterianos
0312	2	Actrapid	Insulina humana (solúvel)	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Insulinas De acção curta
0312	2	Amlodipina	Amlodipina	Sistema Nervoso Central/ Psicofármacos/ Ansiolíticos, sedativos e hipnóticos/ Benzodiazepinas
0312	2	Atacand	Candesartan	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Antagonistas dos receptores da angiotensina
0312	2	Janumet	Metformina + Sitagliptina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Outros antidiabéticos orais
0312	2	Lercanipina (Lercanidipina)	Enalapril + Lercanidipina	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Inibidores da enzima de conversão da angiotensina
0312	2	Neurobion	Cianocobalamina + Piridoxina + Tiamina	Nutrição /Vitaminas e sais minerais/ Vitaminas/ Associações de vitaminas
0312	2	Preterax	Perindopril + Indapamida	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Inibidores da enzima de conversão da angiotensina
0312	2	Tromalyt	Ácido acetilsalicílico	Sangue/ Anticoagulantes e antitrombóticos/ Anticoagulantes/ Antiagregantes plaquetários
0313	3	ACTOS	Pioglitazona	Antidiabéticos orais
0313	3	Diamicron 30 LM	Gliclazida	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Sulfonilureias

Concomitant medication by patient.

0313	3	Diamicron 60	Gliclazida	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Sulfonilureias
0313	3	Janumet	Metformina + Sitagliptina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Outros antidiabéticos orais
0313	3	Lercanidipina	Enalapril + Lercanidipina	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Inibidores da enzima de conversão da angiotensina
0313	3	Losartan + Hidroclorotiazida	Losartan + HCT2	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Antagonistas dos receptores da angiotensina
0314	1	Brufen 400	Ibuprofeno	Aparelho locomotor/ Anti-inflamatórios não esteróides/ Derivados do ácido propiónico
0314	1	Clavamox DT	Amoxicilina + Ácido clavulânico	Medicamentos anti-infecciosos/ Antibacterianos/ Associações de penicilinas com inibidores das lactamases beta
0314	1	Insulin	Insulina aspártico	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Insulinas De acção intermédia
0315	2	Diamicron	Gliclazida	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Sulfonilureias
0315	2	Doxi-OM	Dobesilato de cálcio	Aparelho cardiovascular/ 3.6. Venotrópicos
0315	2	Flindix	Dinitrato de isossorbida	Aparelho cardiovascular/ Vasodilatadores/ Antianginosos
0315	2	Insulatard	Insulina humana (isofânica)	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Insulinas De acção intermédia
0315	2	Ramipril	Ramipril	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Inibidores da enzima de conversão da angiotensina
0315	2	Risidon	Metformina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Antidiabéticos orais/ Biguanidas
0315	2	Sinvastatina	Sinvastatina	Aparelho cardiovascular/ Antidislipidémicos/ Estatinas
0315	2	Starlix	Nateglinida	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e

Concomitant medication by patient.

				glucagom/ Antidiabéticos orais
0315	2	Ticlopidina	Ticlopidina	Sangue/ Anticoagulantes e antitrombóticos/ Anticoagulantes/ Antiagregantes plaquetários
0316	3	Velmetia	Metformina + Sitagliptina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Outros antidiabéticos orais
0317	1	Coversyl	Coversyl	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Inibidores da enzima de conversão da angiotensina
0317	1	Crestor	Rosuvastatina	Aparelho cardiovascular/ Antidislipidémicos/ Estatinas
0317	1	Mixtard 30	Insulina humana (solúvel + isofânica)	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Insulinas De acção curta/ Insulina humana
0319	2	Copalia 5/160	Amlodipina + Valsartan	Aparelho cardiovascular/ Anti-hipertensores/ Bloqueadores da entrada do cálcio
0319	2	Risidon 1000	Metformina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Antidiabéticos orais/ Biguanidas
0320	1	Adalat Orl 30	Nifedipina	Aparelho cardiovascular/ Anti-hipertensores/ Bloqueadores da entrada do cálcio
0320	1	Blopress 32	Candesartan	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Antagonistas dos receptores da angiotensina
0320	1	Carvediol (Carvedilol)	Carvedilol	Medicamentos anti-infecciosos/ Antibacterianos/ Cefalosporinas/ Cefalosporinas de 3ª. Geração
0320	1	Humalog	Insulina lispro (solúvel)	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Insulinas De acção intermédia
0320	1	Idapamida 2,5	Indapamida	Aparelho cardiovascular/ Anti-hipertensores/ Diuréticos/ Tiazidas e análogos
0320	1	Lantus	Insulina glargina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Insulinas De acção prolongada
0320	1	Sinvastatina	Sinvastatina	Aparelho cardiovascular/ Antidislipidémicos/ Estatinas

Concomitant medication by patient.

0320	1	Supralip	Fenofibrato	Aparelho cardiovascular/ Antidislipidémicos/ Fibratos
0320	1	Telmisertan 80	Telmisartan	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Antagonistas dos receptores da angiotensina
0320	1	Zyloric	Alopurinol	Aparelho locomotor/ Medicamentos usados para o tratamento da gota
0321	3	Aspirina GR 100mg	Ácido acetilsalicílico	Sangue/ Anticoagulantes e antitrombóticos/ Anticoagulantes/ Antiagregantes plaquetários
0321	3	Azitromicina	Azitromicina	Medicamentos anti-infecciosos/ Antibacterianos/ Macrólidos
0321	3	Clindamicina	Clindamicina	Medicamentos anti-infecciosos/ Antibacterianos/ Outros antibacterianos
0321	3	Dictem (Diltiem)	Diltiazem	Aparelho cardiovascular/ Antiarrítmicos/ Bloqueadores da entrada do cálcio (Classe IV)
0321	3	Esomeprazol	Esomeprazol	Aparelho digestivo/ Antiácidos e anti-ulcerosos/ Modificadores da secreção gástrica/ Inibidores da bomba de protões
0321	3	Insulina Humalog	Insulina lispro (solúvel + protamina)	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Insulinas De acção intermédia
0321	3	Insulina Levemir 26U	Insulina detemir	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Insulinas De acção intermédia
0321	3	Meropenem	Meropenem	Medicamentos anti-infecciosos/ Antibacteriano/ Carbapenemes
0321	3	Norfloxacina	Norfloxacina	Medicamentos usados em afecções oculares/ Anti-infecciosos tópicos/ Antibacterianos
0321	3	Ramipril	Ramipril	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Inibidores da enzima de conversão da angiotensina
0321	3	Urispas	Flavoxato	Aparelho geniturinário/ Outros medicamentos usados em disfunções geniturinárias/ nas perturbações da micção/ na incontinência urinária
0321	3	Visacor	Loflazepato de etilo	Sistema Nervoso Central/ Psicofármacos/ Ansiolíticos, sedativos e hipnóticos/ Benzodiazepinas
0322	1	Aspirina GR 100mg	Ácido acetilsalicílico	Sangue/ Anticoagulantes e antitrombóticos/ Anticoagulantes/ Antiagregantes plaquetários
0322	1	Eucreas	Metformina + Vildagliptina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e

Concomitant medication by patient.

				glucagom/ Outros antidiabéticos orais
0322	1	Furosemida	Furosemida	Aparelho cardiovascular/ Anti-hipertensores/ Diuréticos/ Diuréticos da ansa
0322	1	Humalog Mix	Insulina lispro (solúvel + protamina)	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Insulinas De acção intermédia
0322	1	Pentoxifilina	Pentoxifilina	Aparelho cardiovascular/ Vasodilatadores/ Outros vasodilatadores
0322	1	Triatec	Ramipril	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Inibidores da enzima de conversão da angiotensina
0323	2	Atorvastatina	Amlodipina + Atorvastatina	Aparelho cardiovascular/ Antidislipidémicos/ Estatinas
0323	2	Enalapril	Enalapril	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Inibidores da enzima de conversão da angiotensina
0323	2	Eucreas	Metformina + Vildagliptina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Outros antidiabéticos orais
0323	2	Losartan	Losartan	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Antagonistas dos receptores da angiotensina
0324	3	Insulin	Insulina aspártico	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Insulinas De acção intermédia
0325	3	Adalat CR30	Nifedipina	Aparelho cardiovascular/ Anti-hipertensores/ Bloqueadores da entrada do cálcio
0325	3	Insulin Mixtard 30	Insulina humana (isofânica)	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Insulinas De acção intermédia
0325	3	Ledertrexato	Metotrexato	Aparelho cardiovascular/ Anti-hipertensores/ Diuréticos/ Diuréticos da ansa
0325	3	Lepicortinolo	Prednisolona	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Corticosteróides/ Glucocorticóides
0325	3	Losartan + HCT2	Losartan + Hidroclorotiazida	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Antagonistas dos receptores da angiotensina

Concomitant medication by patient.

0325	3	Ramipril	Ramipril	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Inibidores da enzima de conversão da angiotensina
0325	3	Sinvastatina	Sinvastatina	Aparelho cardiovascular/ Antidislipidémicos/ Estatinas
0327	1	Neomix	Prednisolona	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Corticosteróides/ Glucocorticóides
0327	1	Risidon	Metformina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Antidiabéticos orais/ Biguanidas
0327	1	Visacor	Loflazepato de etilo	Sistema Nervoso Central/ Psicofármacos/ Ansiolíticos, sedativos e hipnóticos/ Benzodiazepinas
0401	2	Acarbose	Acarbose	Antidiabéticos orais/ Inibidores da glucosidase intestinal alfa
0401	2	Diazepam	Diazepam	Sistema Nervoso Central/ Psicofármacos/ Ansiolíticos, sedativos e hipnóticos/ Benzodiazepinas
0401	2	Focal Laser		
0401	2	Gliclazide	Gliclazida	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Antidiabéticos orais/ Sulfonilureias
0401	2	Lucentis	Ranibizumab	Tratamento da degenerescência macular relacionada com a idade (DMI) neovascular (húmida).
0401	2	Metformin	Metformina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Antidiabéticos orais/ Outros antidiabéticos orais
0401	2	Nitroderm TTs	Nitroglicerina	Aparelho cardiovascular/ Vasodilatadores/ Antianginosos
0401	2	Trimetazidine	Trimetazidina	Aparelho cardiovascular/ Vasodilatadores/ Antianginosos
0401	2	Xelevia	Sitagliptina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Outros antidiabéticos orais
0401	2	Zolnor	Amlodipina + Olmesartan medoxomilo	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Antagonistas dos receptores da angiotensina
0402	1	Concor	Bisoprolol	Aparelho cardiovascular/ Anti-hipertensores/ Depressores da actividade adrenérgica/ Bloqueadores beta/ Selectivos cardíacos

Concomitant medication by patient.

0402	1	Digassin (Digesan)	Bromoprida	Aparelho digestivo/ Suplementos enzimáticos, bacilos lácteos e análogos
0402	1	Flindix	Dinitrato de isossorbida	Aparelho cardiovascular/ Vasodilatadores/ Antianginosos
0402	1	Ibustrin	Indobufeno	Sangue/ Anticoagulantes e antitrombóticos/ Anticoagulantes/ Antiagregantes plaquetários
0402	1	Novo Mix 30 Penfill	Insulina humana	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Insulinas/ De acção curta
0402	1	Risidon	Metformina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Antidiabéticos orais/ Biguanidas
0402	1	Sedoxil	Mexazolam	Sistema Nervoso Central/ Psicofármacos/ Ansiolíticos, sedativos e hipnóticos/ Benzodiazepinas
0402	1	Triticum AC	Trazodona	Sistema Nervoso Central/ Psicofármacos/ Antidepressores/ Tricíclicos e afins
0402	1	Viartril S	Glucosamina	Aparelho locomotor/ Medicamentos para tratamento da artrose
0402	1	Zaldior	Tramadol + Paracetamol	Sistema Nervoso Central/ Analgésicos estupefacientes
0402	1	Zarator	Atorvastatina	Aparelho cardiovascular/ Antidislipidémicos/ Estatinas
0404	3	Adalat CR	Nifedipina	Aparelho cardiovascular/ Anti-hipertensores/ Bloqueadores da entrada do cálcio
0404	3	Aprovel	Irbesartan	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Antagonistas dos receptores da angiotensina
0404	3	Fludex	Indapamida	Aparelho cardiovascular/ Anti-hipertensores/ Diuréticos/ Tiazidas e análogos
0404	3	Vasiflex	Ácido ascórbico	Nutrição/ Vitaminas e sais minerais/ Vitaminas/ Vitaminas hidrossolúveis/ Vitamina C
0405	3	Diamicron	Gliclazida	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Sulfonilureias
0405	3	Eucreas	Metformina + Vildagliptina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Outros antidiabéticos orais
0405	3	Ramipril	Ramipril	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Inibidores da enzima de conversão da angiotensina

Concomitant medication by patient.

0405	3	Sinvastatine	Sinvastatina	Aparelho cardiovascular/ Antidislipidémicos/ Estatinas
0406	1	Amlodipine	Amlodipina	Sistema Nervoso Central/ Psicofármacos/ Ansiolíticos, sedativos e hipnóticos/ Benzodiazepinas
0406	1	Crestor	Rosuvastatina	Aparelho cardiovascular/ Antidislipidémicos/ Estatinas
0406	1	Lasix	Furosemida	Aparelho cardiovascular/ Anti-hipertensores/ Diuréticos/ Diuréticos da ansa
0406	1	Renitec	Enalapril	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Inibidores da enzima de conversão da angiotensina
0406	1	Sedoxil	Mexazolam	Sistema Nervoso Central/ Psicofármacos/ Ansiolíticos, sedativos e hipnóticos/ Benzodiazepinas
0406	1	Venosmil	Hidrosmina	Aparelho cardiovascular/ Venotrópicos
0601	1	Diamicron LM	Gliclazida	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Sulfonilureias
0601	1	Loidocaina Subtenon	Lidocaína	Sistema Nervoso Central/ Anestésicos locais
0601	1	Risidon	Metformina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Antidiabéticos orais/ Biguanidas
0601	1	Tiaprin 2,5	Felodipina + Ramipril	Aparelho cardiovascular/ Anti-hipertensores/ Bloqueadores da entrada do cálcio
0601	1	Trental 400	Pentoxifilina	Aparelho cardiovascular/ Vasodilatadores/ Outros vasodilatadores
0603	2	Bisoprolol	Bisoprolol	Aparelho cardiovascular/ Anti-hipertensores/ Depressores da actividade adrenérgica/ Bloqueadores beta/ Selectivos cardíacos
0603	2	Clopidogrel	Clopidogrel	Sangue/ Anticoagulantes e antitrombóticos/ Anticoagulantes/ Antiagregantes plaquetários
0603	2	Coronarioplasty with stent		
0603	2	Crestor 20 mg	Rosuvastatina	Aparelho cardiovascular/ Antidislipidémicos/ Estatinas
0603	2	Olsar Plus	Olmesartan medoxomilo + Hidroclorotiazida	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Antagonistas dos receptores da angiotensina

Concomitant medication by patient.

0603	2	Ramipril 5 mg	Ramipril	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Inibidores da enzima de conversão da angiotensina
0603	2	Risidon	Metformina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Antidiabéticos orais/ Biguanidas
0603	2	Xelevia 100 mg	Sitagliptina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Outros antidiabéticos orais
0604	3	Alprazolam 0,25 mg	Alprazolam	Sistema Nervoso Central/ Psicofármacos/ Ansiolíticos, sedativos e hipnóticos/ Benzodiazepinas
0604	3	Atacand	Candesartan	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Antagonistas dos receptores da angiotensina
0604	3	Captopril	Captopril	Aparelho cardiovascular / Anti-hipertensores / Depressores da actividade adrenérgica / Bloqueadores beta /Bloqueadores beta e alfa /
0604	3	Ceftriaxone (Ceftriaxona)	Ceftriaxona	Medicamentos anti-infecciosos/ Antibacterianos/ Cefalosporinas/ Cefalosporinas de 3ª. Geração
0604	3	Cipralex 10 mg	Escitalopram	Sistema Nervoso Central/ Psicofármacos/ Antidepressores/ Inibidores selectivos de recaptação da serotonina (ISRS)
0604	3	Co-Aprovel	Irbesartan + Hidroclorotiazida	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Antagonistas dos receptores da angiotensina
0604	3	Dalacin	Clindamicina	Medicamentos anti-infecciosos/ Antibacterianos/ Outros antibacterianos
0604	3	Insulin	Insulina aspártico	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Insulinas De acção intermédia
0604	3	Xyzal 5 mg	Levocetirizina	Medicação antialérgica/ Anti-histamínicos/ Anti-histamínicos não sedativos
0605	1	ADT	Amitriptilina	Sistema Nervoso Central/ Psicofármacos/ Antidepressores/ Tricíclicos e afins
0605	1	Anafranil 75 mg	Clomipramina	Sistema Nervoso Central/ Psicofármacos/ Antidepressores/ Tricíclicos e afins

Concomitant medication by patient.

0605	1	Captopril	Captopril	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Inibidores da enzima de conversão da angiotensina
0605	1	Folifer	Ácido fólico + Ferro	Sangue/ Antianémicos/ Compostos de ferro/ Ferro por via oral
0605	1	Insulin	Insulina aspártico	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Insulinas De acção intermédia
0605	1	Unisedil	Diazepam	Sistema Nervoso Central/ Psicofármacos/ Ansiolíticos, sedativos e hipnóticos/ Benzodiazepinas
0605	1	Venlafaxina	Venlafaxina	Sistema Nervoso Central/ Psicofármacos/ Antidepressores/ Inibidores selectivos da recaptação da serotonina e da noradrenalina (ISRSN)
0606	2	AAS 150 mg	Ácido acetilsalicílico	Sangue/ Anticoagulantes e antitrombóticos/ Antiagregantes plaquetários
0606	2	Actos 30 mg	Pioglitazona	Antidiabéticos orais
0606	2	Conversyl 10 mg (Coversyl)	Coversyl	Aparelho cardiovascular/Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Inibidores da enzima de conversão da angiotensina
0606	2	Daonil 5mg	Glibenclamida	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Sulfonilureias
0606	2	Ferrograd Folico	Sulfato ferroso + Ácido fólico	Sangue/ Antianémicos/ Compostos de ferro/ Ferro por via oral
0606	2	Furosemida 40 mg	Furosemida	Aparelho cardiovascular/ Anti-hipertensores/ Diuréticos/ Diuréticos da ansa
0606	2	Glucobay 100mg	Acarbose	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Inibidores da glucosidase intestinal alfa
0606	2	Januvia 100 mg	Sitagliptina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Outros antidiabéticos orais
0606	2	Olsar 40 mg	Olmesartan medoxomilo	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Antagonistas dos receptores da angiotensina
0606	2	Risidon 1000 mg	Metformina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Antidiabéticos orais/ Biguanidas

Concomitant medication by patient.

0606	2	Triticum AC	Trazodona	Sistema Nervoso Central/ Psicofármacos/ Antidepressores/ Tricíclicos e afins
0606	2	Victan 2 mg	Loflazepato de etilo	Sistema Nervoso Central/ Psicofármacos/ Ansiolíticos, sedativos e hipnóticos/ Benzodiazepinas
0606	2	Zanicor 10 mg	Lercanidipina	Aparelho cardiovascular/ Anti-hipertensores/ Bloqueadores da entrada do cálcio
0606	2	Zarator 20 mg	Atorvastatina	Aparelho cardiovascular/ Antidislipidémicos/ Estatinas
0607	3	Diamicron LM 30	Gliclazida	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Sulfonilureias
0607	3	Dilbloc 25	Carvedilol	Aparelho cardiovascular / Anti-hipertensores/ Depressores da actividade adrenérgica/ Bloqueadores beta/ Bloqueadores beta e alfa
0607	3	Janumet 50/1000	Metformina + Sitagliptina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Outros antidiabéticos orais
0607	3	Lasix 40 mg	Furosemida	Aparelho cardiovascular/ Anti-hipertensores/ Diuréticos/ Diuréticos da ansa
0607	3	Lisinopril 20	Lisinopril	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Inibidores da enzima de conversão da angiotensina
0607	3	Procoralan 5	Ivabradina	Aparelho cardiovascular/ Vasodilatadores/ Antianginosos
0607	3	Tromalyt	Ácido acetilsalicílico	Sangue/ Anticoagulantes e antitrombóticos/ Anticoagulantes/ Antiagregantes plaquetários
0608	1	Azarga	Brinzolamida + Timolol	Medicamentos usados em afecções oculares/ Medicamentos usados no tratamento do glaucoma
0608	1	Esomeprazol	Esomeprazol	Aparelho digestivo/ Antiácidos e anti-ulcerosos/ Modificadores da secreção gástrica/ Inibidores da bomba de protões
0608	1	Insuline	Insulina aspártico	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Insulinas De acção intermédia
0701	2	AAS	Ácido acetilsalicílico	Sangue/ Anticoagulantes e antitrombóticos/ Anticoagulantes/ Antiagregantes plaquetários
0701	2	Inalapril (Enalapril)	Enalapril	Aparelho cardiovascular/ Anti-hipertensores/ Modificadores do eixo renina angiotensina/ Inibidores da enzima de conversão da angiotensina

Concomitant medication by patient.

0701	2	Iron	Altizida + Espironolactona	Aparelho cardiovascular/ Anti-hipertensores/ Diuréticos/ Associações de diuréticos
0701	2	Long Insuline	Insulina humana (isofânica)	Hormonas e medicamentos usados no tratamento das doenças endócrinas / Insulinas, antidiabéticos orais e glucagom / Insulinas De acção intermédia
0701	2	sitagliptina	sitagliptina	Hormonas e medicamentos usados no tratamento das doenças endócrinas/ Insulinas, antidiabéticos orais e glucagom/ Antidiabéticos orais/ Outros antidiabéticos orais
0701	2	Trazodona	trazodona	Sistema Nervoso Central/ Psicofármaco/ Antidepressores/ Tricíclicos e afins
0701	2	Venlafaxina	Venlafaxina	Sistema Nervoso Central/ Psicofármacos/ Antidepressores/ Inibidores selectivos da recaptação da serotonina e da noradrenalina (ISRSN)

16.3 Case Report Forms