



## Clinical trial results:

### Prophylactic effect of brimonidine on bleeding subconjunctival in 23G vitrectomy

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2012-002895-15   |
| Trial protocol           | ES               |
| Global end of trial date | 07 December 2016 |

#### Results information

|                                   |                                                          |
|-----------------------------------|----------------------------------------------------------|
| Result version number             | v1 (current)                                             |
| This version publication date     | 08 May 2022                                              |
| First version publication date    | 08 May 2022                                              |
| Summary attachment (see zip file) | Final Report EPROBRI (Informe final EPROBRI firmado.pdf) |

#### Trial information

##### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | EPROBRI-2011 |
|-----------------------|--------------|

##### Additional study identifiers

|                                    |   |
|------------------------------------|---|
| ISRCTN number                      | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN)   | - |

Notes:

#### Sponsors

|                              |                                                                                                                 |
|------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Fundación Oftalmológica del Mediterráneo                                                                        |
| Sponsor organisation address | Avenida Pío Baroja, 12, Valencia, Spain, 46015                                                                  |
| Public contact               | Departamento Ensayos Clínicos, Fundación Oftalmológica del Mediterráneo, +0034 96278 76 20, baron_margar@gva.es |
| Scientific contact           | Departamento Ensayos Clínicos, Fundación Oftalmológica del Mediterráneo, +0034 96278 76 20, baron_margar@gva.es |

Notes:

#### Paediatric regulatory details

|                                                                      |    |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

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**Results analysis stage**

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|                                                      |                  |
|------------------------------------------------------|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 16 November 2017 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 07 December 2016 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 07 December 2016 |
| Was the trial ended prematurely?                     | No               |

Notes:

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**General information about the trial**

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Main objective of the trial:

To determine if it can be prevented and in that percentage the appearance of subconjunctival haemorrhages after surgery of vitrectomía with 23G, by means of the use of brimonidina in collyrium in the preoperative medication.

Protection of trial subjects:

The medical personnel who will handle the medications as well as the patients have the necessary training for their participation in the clinical trial.

Serious adverse events are not expected to occur in patients. If so, the medical personnel are prepared to face them and the necessary measures will be taken corresponding to the nature and intensity of the event.

Background therapy: -

Evidence for comparator: -

|                                                           |               |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment                          | 21 March 2013 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |           |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Spain: 80 |
| Worldwide total number of subjects   | 80        |
| EEA total number of subjects         | 80        |

Notes:

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**Subjects enrolled per age group**

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|                                           |    |
|-------------------------------------------|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 19 |
| From 65 to 84 years                       | 59 |

|                   |   |
|-------------------|---|
| 85 years and over | 2 |
|-------------------|---|

## Subject disposition

### Recruitment

Recruitment details:

Patients who are going to undergo a 23G vitrectomy. Recruitment period: 3 years (2014-2016)  
Territories only in Spain. FISABIO OFTALMOLOGIA MEDICA

### Pre-assignment

Screening details:

Patients who are going to undergo a 23G vitrectomy (2014-2016).

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | OVERALL TRIAL (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Double blind                   |
| Roles blinded                | Subject, Investigator, Monitor |

### Arms

|                              |                                   |
|------------------------------|-----------------------------------|
| Are arms mutually exclusive? | Yes                               |
| <b>Arm title</b>             | Group 1: Alfadine treatment group |

Arm description:

Group 1, Alfadine treatment group: They will be administered 2 drops of the medication 15 minutes before surgery and another round 5 minutes before, in addition to the usual preoperative ones. Brimonidine eye drops have been supplied by Bausch & Lomb.

|                                        |                      |
|----------------------------------------|----------------------|
| Arm type                               | Experimental         |
| Investigational medicinal product name | Brimonidine tartrate |
| Investigational medicinal product code |                      |
| Other name                             |                      |
| Pharmaceutical forms                   | Eye drops            |
| Routes of administration               | Ophthalmic use       |

Dosage and administration details:

2 drops of the medication 15 minutes before surgery and another round 5 minutes before, in addition to the usual preoperative ones.

|                  |                        |
|------------------|------------------------|
| <b>Arm title</b> | Group 2: control group |
|------------------|------------------------|

Arm description:

Group 2, control group: Only the usual preoperative drops will be instilled.

|                                        |                |
|----------------------------------------|----------------|
| Arm type                               | Placebo        |
| Investigational medicinal product name | Placebo        |
| Investigational medicinal product code |                |
| Other name                             |                |
| Pharmaceutical forms                   | Eye drops      |
| Routes of administration               | Ophthalmic use |

Dosage and administration details:

study treatment drops are not instilled, only the usual preoperative drops will be instilled.

| <b>Number of subjects in period 1</b>        | Group 1: Alfadine treatment group | Group 2: control group |
|----------------------------------------------|-----------------------------------|------------------------|
| Started                                      | 42                                | 38                     |
| Completed                                    | 41                                | 36                     |
| Not completed                                | 1                                 | 2                      |
| Adverse event, non-fatal                     | -                                 | 1                      |
| bleeding is evidenced before surgery         | -                                 | 1                      |
| before surgery there is evidence of bleeding | 1                                 | -                      |

## Baseline characteristics

### Reporting groups

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | Group 1: Alfadine treatment group |
|-----------------------|-----------------------------------|

Reporting group description:

Group 1, Alfadine treatment group: They will be administered 2 drops of the medication 15 minutes before surgery and another round 5 minutes before, in addition to the usual preoperative ones. Brimonidine eye drops have been supplied by Bausch & Lomb.

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | Group 2: control group |
|-----------------------|------------------------|

Reporting group description:

Group 2, control group: Only the usual preoperative drops will be instilled.

| Reporting group values                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Group 1: Alfadine treatment group | Group 2: control group | Total |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|------------------------|-------|
| Number of subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 42                                | 38                     | 80    |
| Age categorical                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                   |                        |       |
| The sample is finally made up of 77 patients who underwent 23G vitrectomy surgery in PHYSABIO-OPHTHALMOLOGY by the team of surgeons from the vitreo-retina unit. A total of 39 men (50.6%) and 38 women (49.4%) participated in the study, with a mean age of $68.4 \pm 10.7$ years and a range between 28 and 86 years. The trial period was from February 2013 to December 2016. The patients were divided into 2 treated groups and controls, according to the treatment with brimonidine ( $n = 41$ ) or not ( $n = 36$ ). This work is a prospective controlled study with a 2-week follow-up and data recording at baseline |                                   |                        |       |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                   |                        |       |
| Adults (18-64 years)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 12                                | 7                      | 19    |
| From 65-84 years                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 29                                | 29                     | 58    |
| 85 years and over                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 1                                 | 2                      | 3     |
| Gender categorical                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                   |                        |       |
| The secondary variables are: age, sex, if the patient is hypertensive, if he is diabetic, takes anticoagulants or antiaggregants. This same model will be used to evaluate the influence of other demographic and clinical factors.                                                                                                                                                                                                                                                                                                                                                                                               |                                   |                        |       |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                   |                        |       |
| Female                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 20                                | 18                     | 38    |
| Male                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 22                                | 20                     | 42    |
| Number of bleeding quadrants                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                   |                        |       |
| Evolution of the incidence of bleeding<br>After surgery and the first 3 days, the rate of patients with subconjunctival hemorrhage is similar, there is only a statistical trend, with the percentage of bleeding being higher in the group of untreated patients. It is in the last visit where certain statistically significant differences are appreciated: 7.3% of eyes in the drug group presented subconjunctival hemorrhage, compared to 28.6% among the controls. Brimonidine treatment reduces the risk of bleeding by 80.3% compared to a control at the end of follow-up.<br>The following conclusions are draw       |                                   |                        |       |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                   |                        |       |
| bleeding quadrants                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 42                                | 38                     | 80    |
| Evolution of the number of affected quadrants                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                   |                        |       |
| More than the incidence of bleeding, the number of quadrants affected is the main answer to evaluate the effect of brimonidine; since it adds to the first, the nuance of the scope of the alteration. Table 3 describes in detail the observed distribution, which is graphically summarized in Figure 2:<br>In terms of the number of quadrants, it is noted (descriptively) that the control subjects have a greater predisposition to a greater number of quadrants affected by subconjunctival hemorrhage, than in the group treated with brimonidine.<br>It is accepted that in T2 the distributions of the number of       |                                   |                        |       |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                   |                        |       |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |    |    |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|----|----|
| affected quadrants                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 42 | 38 | 80 |
| Antiplatelet                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |    |    |    |
| We will present the results of this subgroup of patients, taking into account that the n is low: 6 patients with antiplatelet agents in the control group and 7 patients in the group treated with brimonidine. According to the protocols of the anesthetists at the center, low-dose antiplatelet agents (eg, ADIRO 100) are not withdrawn before surgery, they are only withdrawn when the dose is higher (eg ADIRO 300, TROMALYT). Treatment with brimonidine does not specifically improve in an added way in patients who are antiaggregated, because they do not bleed more after 23G vitreoretinal surgery. |    |    |    |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |    |    |
| Antiplatelet                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 42 | 38 | 80 |
| Anticoagulants                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |    |    |    |
| In this group, the n is very low: 4 patients in the control group and 3 patients in the brimonidine treatment group, so the results are not conclusive. We will still expose them. According to the protocols of the anesthetists of the center, the anticoagulants are withdrawn before surgery and are replaced by low molecular weight heparins. Most outstanding is the significant triple interaction ( $p = 0.033$ ). In this case, it is the slight worsening of the response in the controls taking anticoagulants that causes statistical significance. Treatment with brimonidine specifically improves   |    |    |    |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |    |    |
| Anticoagulants                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 42 | 38 | 80 |
| Arterial hypertension                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |    |    |    |
| Of the total sample size, 49.4% (n 38) of the patients did not have HT, compared to 50.9% (n 39) who did suffer from this disease. The Brunner-Langer model shows that there is no relevant effect attributable to the arterial hypertension diagnosis in terms of subconjunctival hemorrhage after 23G vitrectomy.                                                                                                                                                                                                                                                                                                 |    |    |    |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |    |    |
| Arterial hypertension                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 42 | 38 | 80 |
| Diabetes Mellitus (DM)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |    |    |    |
| Of the total of patients included in this study (n = 77), only 26 were diabetic, 6 were type I and 20 were type II. The Brunner-Langer model shows that there is no relevant effect attributable to the diagnosis of diabetes in terms of subconjunctival hemorrhage after 23G vitrectomy. If we do the analysis by type of diabetes, type I or type II, we also do not find any statistically significant results.                                                                                                                                                                                                 |    |    |    |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |    |    |
| Diabetes Mellitus                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 42 | 38 | 80 |
| Conjunctival rupture after vitrectomy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |    |    |    |
| When analyzing these variables on the effect of subconjunctival hemorrhage and the prophylactic effect of brimonidine, it is evident that there are no differences associated with the fact that a conjunctival rupture has occurred or not. When we analyze the fact of having sutured the conjunctiva, no differences are found associated with the application of suture or not, but there is evidence of an important trend, since in patients who have had their sclerotomy sutured, the number of quadrants with hemorrhage subconjunctival is greater, as is logical due to the trauma on the conjunctiva.   |    |    |    |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |    |    |
| Conjunctival rupture                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 42 | 38 | 80 |
| Evolution of the size of the lesion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |    |    |    |
| Regarding the outcomes of interest, the size of the subconjunctival hemorrhage (in those patients where there was) is also representative of its scope. Remember that the maximum diameter of the smallest lesion has been considered as size large of the 4 quadrants. It is therefore accepted that at any time the size of the hemorrhage is similar in both groups.                                                                                                                                                                                                                                             |    |    |    |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |    |    |
| size of the lesion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 42 | 38 | 80 |
| Sclerotomy suture after vitrectomy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |    |    |    |
| When analyzing these variables on the effect of subconjunctival hemorrhage and the prophylactic effect of brimonidine, no differences are found associated with the application of suture or not, but there is evidence of an important trend, since in patients who have had their sclerotomy sutured, the number of quadrants with hemorrhage subconjunctival is greater, as is logical due to the trauma on the conjunctiva.                                                                                                                                                                                     |    |    |    |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |    |    |
| sclerotomy suture                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 42 | 38 | 80 |

## Subject analysis sets

|                            |                                     |
|----------------------------|-------------------------------------|
| Subject analysis set title | Treatment with tartrate brimonidine |
| Subject analysis set type  | Sub-group analysis                  |

### Subject analysis set description:

The presence of subconjunctival hemorrhage after 23G vitrectomy is lower in the group treated with brimonidine throughout the follow-up time, but the difference is much greater at the end of the follow-up. Treatment with brimonidine reduces the risk of bleeding by 80.3% compared to a control at one week of follow-up.

The number of quadrants affected by subconjunctival hemorrhage is similar between treated and untreated during the first 3 days; but at one week the number of quadrants affected by bleeding is statistically lower in the group treated with brimonidine.

The prophylactic role against subconjunctival hemorrhage after PPV 23G of brimonidine in patients taking antiaggregants has not been demonstrated, but it has been demonstrated in anticoagulated patients.

No associated beneficial role of prophylactic treatment with brimonidine against subconjunctival hemorrhage has been demonstrated in 23G PPV in hypertensive patients or in diabetics.

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | Without treatment |
| Subject analysis set type  | Full analysis     |

### Subject analysis set description:

Control group: Only the usual preoperative drops will be instilled.

| Reporting group values                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Treatment with tartrate brimonidine | Without treatment |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|-------------------|--|
| Number of subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 41                                  | 36                |  |
| Age categorical                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                     |                   |  |
| The sample is finally made up of 77 patients who underwent 23G vitrectomy surgery in PHYSABIO-OPHTHALMOLOGY by the team of surgeons from the vitreo-retina unit. A total of 39 men (50.6%) and 38 women (49.4%) participated in the study, with a mean age of $68.4 \pm 10.7$ years and a range between 28 and 86 years. The trial period was from February 2013 to December 2016. The patients were divided into 2 treated groups and controls, according to the treatment with brimonidine (n = 41) or not (n = 36). This work is a prospective controlled study with a 2-week follow-up and data recording at baseline    |                                     |                   |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                     |                   |  |
| Adults (18-64 years)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 12                                  | 7                 |  |
| From 65-84 years                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 28                                  | 28                |  |
| 85 years and over                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 1                                   | 1                 |  |
| Gender categorical                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                     |                   |  |
| The secondary variables are: age, sex, if the patient is hypertensive, if he is diabetic, takes anticoagulants or antiaggregants. This same model will be used to evaluate the influence of other demographic and clinical factors.                                                                                                                                                                                                                                                                                                                                                                                          |                                     |                   |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                     |                   |  |
| Female                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 20                                  | 18                |  |
| Male                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 21                                  | 18                |  |
| Number of bleeding quadrants                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                     |                   |  |
| Evolution of the incidence of bleeding<br>After surgery and the first 3 days, the rate of patients with subconjunctival hemorrhage is similar, there is only a statistical trend, with the percentage of bleeding being higher in the group of untreated patients. It is in the last visit where certain statistically significant differences are appreciated: 7.3% of eyes in the drug group presented subconjunctival hemorrhage, compared to 28.6% among the controls. Brimonidine treatment reduces the risk of bleeding by 80.3% compared to a control at the end of follow-up.<br>The following conclusions are drawn |                                     |                   |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                     |                   |  |
| bleeding quadrants                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 4                                   | 4                 |  |
| Evolution of the number of affected quadrants                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                     |                   |  |
| More than the incidence of bleeding, the number of quadrants affected is the main answer to evaluate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                     |                   |  |

the effect of brimonidine; since it adds to the first, the nuance of the scope of the alteration. Table 3 describes in detail the observed distribution, which is graphically summarized in Figure 2:  
In terms of the number of quadrants, it is noted (descriptively) that the control subjects have a greater predisposition to a greater number of quadrants affected by subconjunctival hemorrhage, than in the group treated with brimonidine.

It is accepted that in T2 the distributions of the number of

|                    |   |   |  |
|--------------------|---|---|--|
| Units: Subjects    |   |   |  |
| affected quadrants | 2 | 2 |  |
| Antiplatelet       |   |   |  |

We will present the results of this subgroup of patients, taking into account that the n is low: 6 patients with antiplatelet agents in the control group and 7 patients in the group treated with brimonidine.

According to the protocols of the anesthetists at the center, low-dose antiplatelet agents (eg, ADIRO 100) are not withdrawn before surgery, they are only withdrawn when the dose is higher (eg ADIRO 300, TROMALYT). Treatment with brimonidine does not specifically improve in an added way in patients who are antiaggregated, because they do not bleed more after 23G vitreoretinal surgery.

|                 |    |    |  |
|-----------------|----|----|--|
| Units: Subjects |    |    |  |
| Antiplatelet    | 41 | 36 |  |
| Anticoagulants  |    |    |  |

In this group, the n is very low: 4 patients in the control group and 3 patients in the brimonidine treatment group, so the results are not conclusive. We will still expose them.

According to the protocols of the anesthetists of the center, the anticoagulants are withdrawn before surgery and are replaced by low molecular weight heparins.

Most outstanding is the significant triple interaction ( $p = 0.033$ ). In this case, it is the slight worsening of the response in the controls taking anticoagulants that causes statistical significance.

Treatment with brimonidine specifically improves

|                       |    |    |  |
|-----------------------|----|----|--|
| Units: Subjects       |    |    |  |
| Anticoagulants        | 41 | 36 |  |
| Arterial hypertension |    |    |  |

Of the total sample size, 49.4% (n 38) of the patients did not have HT, compared to 50.9% (n 39) who did suffer from this disease.

The Brunner-Langer model shows that there is no relevant effect attributable to the arterial hypertension diagnosis in terms of subconjunctival hemorrhage after 23G vitrectomy.

|                        |    |    |  |
|------------------------|----|----|--|
| Units: Subjects        |    |    |  |
| Arterial hypertension  | 21 | 18 |  |
| Diabetes Mellitus (DM) |    |    |  |

Of the total of patients included in this study (n = 77), only 26 were diabetic, 6 were type I and 20 were type II. The Brunner-Langer model shows that there is no relevant effect attributable to the diagnosis of diabetes in terms of subconjunctival hemorrhage after 23G vitrectomy. If we do the analysis by type of diabetes, type I or type II, we also do not find any statistically significant results.

|                                       |    |    |  |
|---------------------------------------|----|----|--|
| Units: Subjects                       |    |    |  |
| Diabetes Mellitus                     | 14 | 12 |  |
| Conjunctival rupture after vitrectomy |    |    |  |

When analyzing these variables on the effect of subconjunctival hemorrhage and the prophylactic effect of brimonidine, it is evident that there are no differences associated with the fact that a conjunctival rupture has occurred or not. When we analyze the fact of having sutured the conjunctiva, no differences are found associated with the application of suture or not, but there is evidence of an important trend, since in patients who have had their sclerotomy sutured, the number of quadrants with hemorrhage subconjunctival is greater, as is logical due to the trauma on the conjunctiva.

|                                     |    |    |  |
|-------------------------------------|----|----|--|
| Units: Subjects                     |    |    |  |
| Conjunctival rupture                | 41 | 36 |  |
| Evolution of the size of the lesion |    |    |  |

Regarding the outcomes of interest, the size of the subconjunctival hemorrhage (in those patients where there was) is also representative of its scope. Remember that the maximum diameter of the smallest lesion has been considered as size large of the 4 quadrants.

It is therefore accepted that at any time the size of the hemorrhage is similar in both groups.

|                                    |  |  |  |
|------------------------------------|--|--|--|
| Units: Subjects                    |  |  |  |
| size of the lesion                 |  |  |  |
| Sclerotomy suture after vitrectomy |  |  |  |

When analyzing these variables on the effect of subconjunctival hemorrhage and the prophylactic effect of brimonidine, no differences are found associated with the application of suture or not, but there is

evidence of an important trend, since in patients who have had their sclerotomy sutured, the number of quadrants with hemorrhage subconjunctival is greater, as is logical due to the trauma on the conjunctiva.

|                   |    |    |  |
|-------------------|----|----|--|
| Units: Subjects   |    |    |  |
| sclerotomy suture | 41 | 36 |  |

## End points

### End points reporting groups

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | Group 1: Alfadine treatment group |
|-----------------------|-----------------------------------|

Reporting group description:

Group 1, Alfadine treatment group: They will be administered 2 drops of the medication 15 minutes before surgery and another round 5 minutes before, in addition to the usual preoperative ones. Brimonidine eye drops have been supplied by Bausch & Lomb.

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | Group 2: control group |
|-----------------------|------------------------|

Reporting group description:

Group 2, control group: Only the usual preoperative drops will be instilled.

|                            |                                     |
|----------------------------|-------------------------------------|
| Subject analysis set title | Treatment with tartrate brimonidine |
|----------------------------|-------------------------------------|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

The presence of subconjunctival hemorrhage after 23G vitrectomy is lower in the group treated with brimonidine throughout the follow-up time, but the difference is much greater at the end of the follow-up. Treatment with brimonidine reduces the risk of bleeding by 80.3% compared to a control at one week of follow-up.

The number of quadrants affected by subconjunctival hemorrhage is similar between treated and untreated during the first 3 days; but at one week the number of quadrants affected by bleeding is statistically lower in the group treated with brimonidine.

The prophylactic role against subconjunctival hemorrhage after PPV 23G of brimonidine in patients taking antiaggregants has not been demonstrated, but it has been demonstrated in anticoagulated patients.

No associated beneficial role of prophylactic treatment with brimonidine against subconjunctival hemorrhage has been demonstrated in 23G PPV in hypertensive patients or in diabetics.

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | Without treatment |
|----------------------------|-------------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Control group: Only the usual preoperative drops will be instilled.

### Primary: Primary Objective

|                 |                   |
|-----------------|-------------------|
| End point title | Primary Objective |
|-----------------|-------------------|

End point description:

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Primary Objective: determine if the appearance of subconjunctival hemorrhages after 23G vitrectomy surgery can be prevented and in what percentage, by using brimonidine eye drops in preoperative medication.

| End point values                                | Group 1:<br>Alfadine<br>treatment<br>group | Group 2:<br>control group |  |  |
|-------------------------------------------------|--------------------------------------------|---------------------------|--|--|
| Subject group type                              | Reporting group                            | Reporting group           |  |  |
| Number of subjects analysed                     | 42                                         | 38                        |  |  |
| Units: percentage of subconjunctival hemorrhage |                                            |                           |  |  |
| number (not applicable)                         | 7                                          | 29                        |  |  |

## Statistical analyses

|                                   |                                |
|-----------------------------------|--------------------------------|
| <b>Statistical analysis title</b> | Brunner-Langer model ATS test. |
|-----------------------------------|--------------------------------|

Statistical analysis description:

After surgery and the first 3 days, the rate of patients with subconjunctival hemorrhage is similar, there is only a statistical trend, with the percentage of bleeding being higher in the group of untreated patients. It is in the last visit where certain statistically significant differences are appreciated: 7.3% of eyes in the drug group presented subconjunctival hemorrhage, compared to 28.6% among the controls.

|                                         |                                                            |
|-----------------------------------------|------------------------------------------------------------|
| Comparison groups                       | Group 1: Alfadine treatment group v Group 2: control group |
| Number of subjects included in analysis | 80                                                         |
| Analysis specification                  | Pre-specified                                              |
| Analysis type                           | other <sup>[1]</sup>                                       |
| P-value                                 | < 0.001 <sup>[2]</sup>                                     |
| Method                                  | Chi-squared                                                |
| Parameter estimate                      | Odds ratio (OR)                                            |

Notes:

[1] - Percentage of affected and odds ratio (OR) of the association and Chi2 test at each time. Brunner-Langer model ATS test.

[2] - The following conclusions are drawn from the estimated Brunner-Langer model:

There is an evident time effect ( $p < 0.001$ ): the probability of bleeding decreases significantly over time.

## Secondary: Secondary objective - antiaggregants

|                 |                                      |
|-----------------|--------------------------------------|
| End point title | Secondary objective - antiaggregants |
|-----------------|--------------------------------------|

End point description:

If the patient is taking antiaggregants.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Secondary objective: The secondary objective will be to try to determine if there are individual preconditions that alter the response.

| End point values            | Group 1:<br>Alfadine<br>treatment<br>group | Group 2:<br>control group |  |  |
|-----------------------------|--------------------------------------------|---------------------------|--|--|
| Subject group type          | Reporting group                            | Reporting group           |  |  |
| Number of subjects analysed | 42 <sup>[3]</sup>                          | 38 <sup>[4]</sup>         |  |  |
| Units: number of patients   |                                            |                           |  |  |
| number (not applicable)     | 7                                          | 6                         |  |  |

Notes:

[3] - Patients taking antiaggregant

[4] - Patients taking antiaggregants

## Statistical analyses

|                                         |                                                            |
|-----------------------------------------|------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Brunner-Larger                                             |
| Comparison groups                       | Group 1: Alfadine treatment group v Group 2: control group |
| Number of subjects included in analysis | 80                                                         |
| Analysis specification                  | Pre-specified                                              |
| Analysis type                           |                                                            |
| P-value                                 | = 0.049                                                    |
| Method                                  | Test ATS                                                   |

### Secondary: Secondary objective - anticoagulants

|                                                                                                                                         |                                      |
|-----------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| End point title                                                                                                                         | Secondary objective - anticoagulants |
| End point description:                                                                                                                  |                                      |
| If the patient is taking anticoagulants.                                                                                                |                                      |
| End point type                                                                                                                          | Secondary                            |
| End point timeframe:                                                                                                                    |                                      |
| Secondary objective: The secondary objective will be to try to determine if there are individual preconditions that alter the response. |                                      |

| End point values            | Group 1:<br>Alfadine<br>treatment<br>group | Group 2:<br>control group |  |  |
|-----------------------------|--------------------------------------------|---------------------------|--|--|
| Subject group type          | Reporting group                            | Reporting group           |  |  |
| Number of subjects analysed | 42 <sup>[5]</sup>                          | 38 <sup>[6]</sup>         |  |  |
| Units: number of patient    |                                            |                           |  |  |
| number (not applicable)     | 3                                          | 4                         |  |  |

Notes:

[5] - Patient taking anticoagulants.

[6] - Patient taking anticoagulants.

### Statistical analyses

|                                         |                                                            |
|-----------------------------------------|------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Brunner-Larger                                             |
| Comparison groups                       | Group 1: Alfadine treatment group v Group 2: control group |
| Number of subjects included in analysis | 80                                                         |
| Analysis specification                  | Pre-specified                                              |
| Analysis type                           |                                                            |
| P-value                                 | = 0.033                                                    |
| Method                                  | Test ATS                                                   |

### Secondary: Secondary objective - Diabetic

|                        |                                |
|------------------------|--------------------------------|
| End point title        | Secondary objective - Diabetic |
| End point description: |                                |
| Diabetic patients      |                                |
| End point type         | Secondary                      |

End point timeframe:

Secondary objective: The secondary objective will be to try to determine if there are individual preconditions that alter the response.

| End point values            | Group 1:<br>Alfadine<br>treatment<br>group | Group 2:<br>control group |  |  |
|-----------------------------|--------------------------------------------|---------------------------|--|--|
| Subject group type          | Reporting group                            | Reporting group           |  |  |
| Number of subjects analysed | 42 <sup>[7]</sup>                          | 38 <sup>[8]</sup>         |  |  |
| Units: number of patients   |                                            |                           |  |  |
| number (not applicable)     | 9                                          | 4                         |  |  |

Notes:

[7] - Diabetic patients

[8] - Diabetic patients

### Statistical analyses

|                                         |                                                            |
|-----------------------------------------|------------------------------------------------------------|
| Statistical analysis title              | Brunner-Larger                                             |
| Comparison groups                       | Group 1: Alfadine treatment group v Group 2: control group |
| Number of subjects included in analysis | 80                                                         |
| Analysis specification                  | Pre-specified                                              |
| Analysis type                           |                                                            |
| P-value                                 | = 0.659                                                    |
| Method                                  | Test ATS                                                   |

### Secondary: Secondary objective - Arterial hypertension

|                                                                                                                                         |                                             |
|-----------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| End point title                                                                                                                         | Secondary objective - Arterial hypertension |
| End point description:                                                                                                                  | Arterial hypertension patients.             |
| End point type                                                                                                                          | Secondary                                   |
| End point timeframe:                                                                                                                    |                                             |
| Secondary objective: The secondary objective will be to try to determine if there are individual preconditions that alter the response. |                                             |

| End point values            | Group 1:<br>Alfadine<br>treatment<br>group | Group 2:<br>control group |  |  |
|-----------------------------|--------------------------------------------|---------------------------|--|--|
| Subject group type          | Reporting group                            | Reporting group           |  |  |
| Number of subjects analysed | 42 <sup>[9]</sup>                          | 38 <sup>[10]</sup>        |  |  |
| Units: number of patients   |                                            |                           |  |  |
| number (not applicable)     | 15                                         | 13                        |  |  |

Notes:

[9] - Arterila hypertension patients.

### Statistical analyses

|                                         |                                                            |
|-----------------------------------------|------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Brunner-Larger                                             |
| Comparison groups                       | Group 1: Alfadine treatment group v Group 2: control group |
| Number of subjects included in analysis | 80                                                         |
| Analysis specification                  | Pre-specified                                              |
| Analysis type                           |                                                            |
| P-value                                 | = 0.633                                                    |
| Method                                  | Test ATS                                                   |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

No adverse effect or serious adverse effect were recorded throughout the development of the trial.

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |   |
|--------------------|---|
| Dictionary version | 1 |
|--------------------|---|

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Control Group |
|-----------------------|---------------|

Reporting group description:

control group: Only the usual preoperative drops will be instilled.

| Serious adverse events                            | Control Group |  |  |
|---------------------------------------------------|---------------|--|--|
| Total subjects affected by serious adverse events |               |  |  |
| subjects affected / exposed                       | 0 / 1 (0.00%) |  |  |
| number of deaths (all causes)                     | 0             |  |  |
| number of deaths resulting from adverse events    | 0             |  |  |

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events                              | Control Group   |  |  |
|---------------------------------------------------------|-----------------|--|--|
| Total subjects affected by non-serious adverse events   |                 |  |  |
| subjects affected / exposed                             | 1 / 1 (100.00%) |  |  |
| Injury, poisoning and procedural complications          |                 |  |  |
| the patient had a fall and was unable to come to visits |                 |  |  |
| subjects affected / exposed                             | 1 / 1 (100.00%) |  |  |
| occurrences (all)                                       | 1               |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/34632270>