



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
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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:

Results analysis stage

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:

General information about the trial

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:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group

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
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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
Arm title	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.

Arm title	Group 2: control group
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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.

Number of subjects in period 1	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
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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
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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 ± 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 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. 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: 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	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 ± 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 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. 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
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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
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Reporting group description:

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

Subject analysis set title	Treatment with tartrate brimonidine
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Subject analysis set type	Sub-group analysis
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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
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Subject analysis set type	Full analysis
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Subject analysis set description:

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

Primary: Primary Objective

End point title	Primary Objective
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End point description:

End point type	Primary
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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: Alfadine treatment group	Group 2: 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

Statistical analysis title	Brunner-Langer model ATS test.
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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 ^[1]
P-value	< 0.001 ^[2]
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
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End point description:

If the patient is taking antiaggregants.

End point type	Secondary
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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: Alfadine treatment group	Group 2: control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42 ^[3]	38 ^[4]		
Units: number of patients				
number (not applicable)	7	6		

Notes:

[3] - Patients taking antiaggregant

[4] - Patients taking antiaggregants

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	= 0.049
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: Alfadine treatment group	Group 2: control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42 ^[5]	38 ^[6]		
Units: number of patient				
number (not applicable)	3	4		

Notes:

[5] - Patient taking anticoagulants.

[6] - Patient taking anticoagulants.

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	= 0.033
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: Alfadine treatment group	Group 2: control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42 ^[7]	38 ^[8]		
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: Alfadine treatment group	Group 2: control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42 ^[9]	38 ^[10]		
Units: number of patients				
number (not applicable)	15	13		

Notes:

[9] - Arterila hypertension 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	= 0.633
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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	1
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Reporting groups

Reporting group title	Control Group
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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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

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