Clinical trial results:
Neurodegeneration as an early event in the pathogenesis of Diabetic Retinopathy: A multicentric, prospective, phase II-III, randomized controlled trial to assess the efficacy of neuroprotective drugs administered topically to prevent or arrest Diabetic Retinopathy.

Summary

EudraCT number	2012-001200-38
Trial protocol	DE GB PT DK
Global end of trial date	03 November 2015

Results information

Result version number	v1 (current)
This version publication date	29 December 2019
First version publication date	29 December 2019
Summary attachment (see zip file)	Synopsis of the Clinical Study Report (Synopsis_CSR_Final 1.0_2019-03-29.pdf)

Trial information

Trial identification

Sponsor protocol code	4C-2011-02

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	BCN Peptides SA
Sponsor organisation address	Poligon Industrial Els Vinyets-Els Fogars II, Sant Quintí de Mediona, Spain, 08777
Public contact	Clinical Trial Info Desk, BCN Peptides SA, 0034 938191399, ctinfodesk@bcnpeptides.com
Scientific contact	Clinical Trial Info Desk, BCN Peptides SA, 0034 938191399, ctinfodesk@bcnpeptides.com

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	29 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 November 2015
Global end of trial reached?	Yes
Global end of trial date	03 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate whether Somatostatin 0.1% and Brimonidine tartrate 0.2% eye drops, administered twice a day for 2 years to type 2 diabetes patients with early-stage diabetic retinopathy (DR), were able to prevent or arrest the development and progression of DR.

Protection of trial subjects:

This study was designed, implemented and reported in accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labour, and Welfare), and with the latest revision of the Declaration of Helsinki as adopted by the World Medical Association the Declaration of Helsinki.
The Investigator ensured that each patient was fully informed about the nature and objective of the study and possible risks associated with participation. Patient indicated assent to participate in the study by personally signing and dating the written informed consent form. The process of obtaining informed consent was documented in the patient's source documents. The informed consent form used in this study, and any changes made during the course of the study, was prospectively approved by both the IRB/IEC/REB and the EUROCONDOR Ethics Committee before used.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 September 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Portugal: 78
Country: Number of subjects enrolled	Spain: 49
Country: Number of subjects enrolled	United Kingdom: 141
Country: Number of subjects enrolled	Denmark: 47
Country: Number of subjects enrolled	Germany: 35
Country: Number of subjects enrolled	Italy: 79
Country: Number of subjects enrolled	France: 20
Worldwide total number of subjects	449
EEA total number of subjects	449

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)	250
From 65 to 84 years	199
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible participants at screening and baseline visits were randomized 1:1:1 to Somatostatin 0.1%, Brimonidine tartrate 0.2% or Placebo and were treated and followed for 96 weeks. The randomisation was stratified by ETDRS level < 20 (MAs absent) (50% of enrolled patients) and ETDRS levels 20 or 35 with presence of at least 1 MA in the study eye.

Pre-assignment

Screening details:

A total of 569 adult patients were screened out of which 450 patients were randomized. 449 patients received at least one dose of study medication and were included in the Safety population.

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, Data analyst

Blinding implementation details:

The treatment was double-blind for Somatostatin and Placebo. The 3 treatment groups were masked to the Central Reading Centre to reduce bias in the assessment of the study outcomes.

Arms

Are arms mutually exclusive?	Yes
Arm title	Somatostatin 0.1%

Arm description:

Primary efficacy (PE) population patients who received Somatostatin 0.1% as eye drops, 1 drop in each eye twice a day.

Arm type	Experimental
Investigational medicinal product name	COLIRIOBCN070660
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution in single-dose container
Routes of administration	Ophthalmic use

Dosage and administration details:

Somatostatin 0.1% was administered as eye drops, 1 drop in each eye twice a day; once in the morning and once in the evening.

Arm title	Placebo

Arm description:

Primary efficacy (PE) population patients who received Placebo as eye drops, 1 drop in each eye twice a day.

Arm type	Placebo
Investigational medicinal product name	Placebo eye drops
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution in single-dose container
Routes of administration	Ophthalmic use

Dosage and administration details:

Placebo was administered as eye drops, 1 drop in each eye twice a day; once in the morning and once in the evening.

Arm title	Brimonidine tartrate 0.2%

Arm description:

Primary efficacy (PE) population patients who received Brimonidine tartrate 0.2% as eye drops, 1 drop in each eye twice a day.

Arm type	Experimental
Investigational medicinal product name	Brimonidine tartrate 0.2%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Brimonidine tartrate 0.2% was administered as eye drops, 1 drop in each eye twice a day; once in the morning and once in the evening.

Number of subjects in period 1	Somatostatin 0.1%	Placebo	Brimonidine tartrate 0.2%
Started	145	152	152
Completed	120	124	97
Not completed	25	28	55
Consent withdrawn by subject	13	11	7
Intraocular pressure higher than 22 mmHg	-	-	2
Development of allergic reactions to study drug	-	1	15
Adverse event, non-fatal	-	1	9
Other	7	10	10
Development of DR complications	1	-	-
Interruption of treatment for more than 1 month	3	4	12
Protocol deviation	1	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Somatostatin 0.1%
Reporting group description:	
Primary efficacy (PE) population patients who received Somatostatin 0.1% as eye drops, 1 drop in each eye twice a day.	
Reporting group title	Placebo
Reporting group description:	
Primary efficacy (PE) population patients who received Placebo as eye drops, 1 drop in each eye twice a day.	
Reporting group title	Brimonidine tartrate 0.2%
Reporting group description:	
Primary efficacy (PE) population patients who received Brimonidine tartrate 0.2% as eye drops, 1 drop in each eye twice a day.	

Reporting group values	Somatostatin 0.1%	Placebo	Brimonidine tartrate 0.2%
Number of subjects	145	152	152
Age categorical			
The age range of all patients at baseline was 45-80 years.			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	63.2	63.2	63.5
standard deviation	± 6.8	± 7.0	± 6.3
Gender categorical			
Units: Subjects			
Female	52	48	53
Male	93	104	99
Body Mass Index (BMI)			
Units: Kg/m2			
arithmetic mean	31.0	30.6	30.7
standard deviation	± 5.2	± 5.5	± 5.8

Reporting group values	Total		
Number of subjects	449		
Age categorical			
The age range of all patients at baseline was 45-80 years.			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	153		
Male	296		

Body Mass Index (BMI) Units: Kg/m2 arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	Somatostatin 0.1%
Reporting group description:	
Primary efficacy (PE) population patients who received Somatostatin 0.1% as eye drops, 1 drop in each eye twice a day.	
Reporting group title	Placebo
Reporting group description:	
Primary efficacy (PE) population patients who received Placebo as eye drops, 1 drop in each eye twice a day.	
Reporting group title	Brimonidine tartrate 0.2%
Reporting group description:	
Primary efficacy (PE) population patients who received Brimonidine tartrate 0.2% as eye drops, 1 drop in each eye twice a day.	
Subject analysis set title	MA>1 at screening subpopulation - Somatostatin 0.1%
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subset of the Primary efficacy (PE) population with more than 1 microaneurysm (MA) at screening treated with Somatostatin 0.1%. Placebo-treated patients of the PE did not show disease progression during the 2 years of the clinical trial on the different efficacy variables analysed, making it unfeasible to evaluate the neuroprotective role of Somatostatin and Brimonidine eye drops in the PE (see endpoints named as A). For this reason, complementary analyses were performed focused on retinal microaneurysms (MAs), a classical macroscopic parameter commonly used for diagnosis of DR (see endpoints named as B). A subpopulation of patients more affected in terms of MAs was selected since the presence of 1 or 2 of MAs is associated with disease worsening in the early stages of DR. Specifically, the efficacy of Somatostatin and Brimonidine eye drops in a subpopulation of the PE with early microvascular effects, i.e. >1 MA at screening, was evaluated.	
Subject analysis set title	MA>1 at screening subpopulation - Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subset of the Primary efficacy (PE) population with more than 1 microaneurysm (MA) at screening treated with Placebo.	
Subject analysis set title	MA>1 at screening subpopulation - Brimonidine tartrate 0.2%
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subset of the Primary efficacy (PE) population with more than 1 microaneurysm (MA) at screening treated with Brimonidine tartrate 0.2%.	

Primary: A.1. Change in total number of abnormal hexagons with respect to Implicit Time (IT): success (no increase) versus failure (increase)

End point title	A.1. Change in total number of abnormal hexagons with respect to Implicit Time (IT): success (no increase) versus failure (increase)
End point description:	
For mfERG analysis, the study eye was divided into 103 hexagons and each hexagon was classified as normal or abnormal based on reference Implicit Time values from healthy volunteers.	
End point type	Primary
End point timeframe:	
Baseline and 24 months	

End point values	Somatostatin 0.1%	Placebo	Brimonidine tartrate 0.2%	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120[1]	123[2]	96[3]	
Units: Subjects				
Success	55	69	47	
Failure	65	54	49	

Notes:

[1] - Primary efficacy (PE) population with data at 24 months

[2] - Primary efficacy (PE) population with data at 24 months

[3] - Primary efficacy (PE) population with data at 24 months

Statistical analyses

Statistical analysis title	Statistical analysis 1_Somatostatin v Placebo

Statistical analysis description:

Chi-square test was performed to analyse the rate of success in the primary efficacy endpoint between Somatostatin and Placebo

Comparison groups	Somatostatin 0.1% v Placebo
Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11
Method	Chi-squared
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 2_Brimonidine v Placebo

Statistical analysis description:

Chi-square test was performed to analyse the rate of success in the primary efficacy endpoint between Brimonidine and Placebo

Comparison groups	Placebo v Brimonidine tartrate 0.2%
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.294
Method	Chi-squared
Confidence interval	
level	95 %
sides	2-sided

Secondary: A.1.1. Change in total number of abnormal hexagons with respect to Amplitude: success (no increase) versus failure (increase)

End point title	A.1.1. Change in total number of abnormal hexagons with respect to Amplitude: success (no increase) versus failure (increase)

End point description:
For mfERG analysis, the study eye was divided into 103 hexagons and each hexagon was classified as normal or abnormal based on reference Amplitude values from healthy volunteers.

End point type	Secondary

End point timeframe:
Baseline and 24 months

End point values	Somatostatin 0.1%	Placebo	Brimonidine tartrate 0.2%	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120[4]	123[5]	96[6]	
Units: Subjects				
Success	69	67	61	
Failure	51	56	35	

Notes:

[4] - Primary efficacy (PE) population with data at 24 months

[5] - Primary efficacy (PE) population with data at 24 months

[6] - Primary efficacy (PE) population with data at 24 months

Statistical analyses

Statistical analysis title	Statistical analysis 1_Somatostatin v Placebo
Comparison groups	Somatostatin 0.1% v Placebo
Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.634
Method	Chi-squared
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 2_Brimonidine v Placebo
Comparison groups	Placebo v Brimonidine tartrate 0.2%
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.177
Method	Chi-squared
Confidence interval	
level	95 %
sides	2-sided

Secondary: A.1.2. Primary efficacy related endpoint 1 (Prevention) - Implicit Time (IT)

End point title	A.1.2. Primary efficacy related endpoint 1 (Prevention) - Implicit Time (IT)

End point description:

For mfERG analysis, the study eye was divided into 103 hexagons and each hexagon was classified as normal or abnormal based on reference IT values from healthy volunteers. An eye was considered normal if less than 6 pathological hexagons were found, otherwise an eye was considered abnormal. Primary efficacy related endpoint 1 was assessed on a subset of patients that were identified as normal with respect to IT at Baseline (less than 6 abnormal hexagons). "Prevention" was defined as follows: an eye remained normal with respect to IT at 24 months. "No prevention" was defined as follows: a normal eye turned to be abnormal with respect to IT at 24 months.

End point type	Secondary

End point timeframe:

Baseline and 24 months

End point values	Somatostatin 0.1%	Placebo	Brimonidine tartrate 0.2%	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79[7]	84[8]	57[9]	
Units: Subjects				
Prevention	54	66	38	
No prevention	25	18	19	

Notes:

[7] - Subset of the PE identified as normal with respect to IT at Baseline

[8] - Subset of the PE identified as normal with respect to IT at Baseline

[9] - Subset of the PE identified as normal with respect to IT at Baseline

Statistical analyses

Statistical analysis title	Statistical analysis 1_Somatostatin v Placebo
Comparison groups	Somatostatin 0.1% v Placebo
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.157
Method	Fisher exact
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 2_Brimonidine v Placebo
Comparison groups	Placebo v Brimonidine tartrate 0.2%
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.124
Method	Fisher exact

Confidence interval	
level	95 %
sides	2-sided

Secondary: A.1.3. Primary efficacy related endpoint 1 (Prevention) - Amplitude

End point title	A.1.3. Primary efficacy related endpoint 1 (Prevention) - Amplitude

End point description:

For mfERG analysis, the study eye was divided into 103 hexagons and each hexagon was classified as normal or abnormal based on reference Amplitude values from healthy volunteers. An eye was considered normal if less than 6 pathological hexagons were found, otherwise an eye was considered abnormal.
Primary efficacy related endpoint 1 was assessed on a subset of patients that were identified as normal with respect to Amplitude at Baseline (less than 6 abnormal hexagons). "Prevention" was defined as follows: an eye remained normal with respect to Amplitude at 24 months. "No prevention" was defined as follows: a normal eye turned to be abnormal with respect to Amplitude at 24 months.

End point type	Secondary

End point timeframe:

Baseline and 24 months

End point values	Somatostatin 0.1%	Placebo	Brimonidine tartrate 0.2%	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	91[10]	94[11]	70[12]	
Units: Subjects				
Prevention	78	81	63	
No prevention	13	13	7	

Notes:

[10] - Subset of the PE identified as normal with respect to Amplitude at Baseline

[11] - Subset of the PE identified as normal with respect to Amplitude at Baseline

[12] - Subset of the PE identified as normal with respect to Amplitude at Baseline

Statistical analyses

Statistical analysis title	Statistical analysis 1_Somatostatin v Placebo
Comparison groups	Somatostatin 0.1% v Placebo
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 2_Brimonidine v Placebo

Comparison groups	Placebo v Brimonidine tartrate 0.2%
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.63
Method	Fisher exact
Confidence interval	
level	95 %
sides	2-sided

Secondary: A.1.4. Primary efficacy related endpoint 2 (Progression arrest) - Implicit Time (IT)

End point title	A.1.4. Primary efficacy related endpoint 2 (Progression arrest) - Implicit Time (IT)

End point description:

For mfERG analysis, the study eye was divided into 103 hexagons and each hexagon was classified as normal or abnormal based on reference IT values from healthy volunteers. An eye was considered normal if less than 6 pathological hexagons were found, otherwise an eye was considered abnormal. Primary efficacy related endpoint 2 was assessed on a subset of patients that were identified as abnormal with respect to IT at Baseline (6 or more abnormal hexagons). "No Progression" was defined as follows: the number of abnormal hexagons with respect to IT at 24 months did not increase compared to Baseline. "Progression" was defined as follows: number of abnormal hexagons with respect to IT at 24 months increased compared to Baseline.

End point type	Secondary

End point timeframe:

Baseline and 24 months

End point values	Somatostatin 0.1%	Placebo	Brimonidine tartrate 0.2%	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41[13]	39[14]	39[15]	
Units: Subjects				
No progression	21	19	25	
Progression	20	20	14	

Notes:

[13] - Subset of the PE identified as abnormal with respect to IT at Baseline

[14] - Subset of the PE identified as abnormal with respect to IT at Baseline

[15] - Subset of the PE identified as abnormal with respect to IT at Baseline

Statistical analyses

Statistical analysis title	Statistical analysis 1_Somatostatin v Placebo
Comparison groups	Placebo v Somatostatin 0.1%

Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 2_Brimonidine v Placebo
Comparison groups	Placebo v Brimonidine tartrate 0.2%
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.253
Method	Fisher exact
Confidence interval	
level	95 %
sides	2-sided

Secondary: A.1.5. Primary efficacy related endpoint 2 (Progression arrest) - Amplitude

End point title	A.1.5. Primary efficacy related endpoint 2 (Progression arrest) - Amplitude

End point description:

For mfERG analysis, the study eye was divided into 103 hexagons and each hexagon was classified as normal or abnormal based on reference Amplitude values from healthy volunteers. An eye was considered normal if less than 6 pathological hexagons were found, otherwise an eye was considered abnormal.
Primary efficacy related endpoint 2 was assessed on a subset of patients that were identified as abnormal with respect to Amplitude at Baseline (6 or more abnormal hexagons). "Progression arrest" was defined as follows: the number of abnormal hexagons with respect to Amplitude at 24 months did not increase compared to Baseline. "Progression" was defined as follows: number of abnormal hexagons with respect to Amplitude at 24 months increased compared to Baseline.

End point type	Secondary

End point timeframe:

Baseline and 24 months

End point values	Somatostatin 0.1%	Placebo	Brimonidine tartrate 0.2%	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29[16]	29[17]	26[18]	
Units: Subjects				
No progression	19	21	18	
Progression	10	8	8	

Notes:

[16] - Subset of the PE identified as abnormal with respect to Amplitude at Baseline

[17] - Subset of the PE identified as abnormal with respect to Amplitude at Baseline

[18] - Subset of the PE identified as abnormal with respect to Amplitude at Baseline

Statistical analyses

Statistical analysis title	Statistical analysis 1_Somatostatin v Placebo
Comparison groups	Somatostatin 0.1% v Placebo
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.777
Method	Fisher exact
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 2_Brimonidine v Placebo
Comparison groups	Placebo v Brimonidine tartrate 0.2%
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact
Confidence interval	
level	95 %
sides	2-sided

Secondary: A.1.6. Primary efficacy related endpoint 3 (Regression) - Implicit Time (IT)

End point title	A.1.6. Primary efficacy related endpoint 3 (Regression) - Implicit Time (IT)

End point description:

For mfERG analysis, the study eye was divided into 103 hexagons and each hexagon was classified as normal or abnormal based on reference IT values from healthy volunteers. An eye was considered normal if less than 6 pathological hexagons were found, otherwise an eye was considered abnormal. Primary efficacy related endpoint 3 was assessed on a subset of patients that were identified as abnormal with respect to IT at Baseline (6 or more abnormal hexagons). "Regression" was defined as follows: a subject turned to be normal at 24 months. "No regression" was defined as follows: a subject remained to be abnormal at 24 months.

End point type	Secondary

End point timeframe:

Baseline and 24 months

End point values	Somatostatin 0.1%	Placebo	Brimonidine tartrate 0.2%	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41[19]	39[20]	39[21]	
Units: Subjects				
Regression	13	9	15	
No regression	28	30	24	

Notes:

[19] - Subset of the PE identified as abnormal with respect to IT at Baseline

[20] - Subset of the PE identified as abnormal with respect to IT at Baseline

[21] - Subset of the PE identified as abnormal with respect to IT at Baseline

Statistical analyses

Statistical analysis title	Statistical analysis 1_Somatostatin v Placebo
Comparison groups	Somatostatin 0.1% v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.457
Method	Fisher exact
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 2_Brimonidine v Placebo
Comparison groups	Placebo v Brimonidine tartrate 0.2%
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.22
Method	Fisher exact
Confidence interval	
level	95 %
sides	2-sided

Secondary: A.1.7. Primary efficacy related endpoint 3 (Regression) - Amplitude

End point title	A.1.7. Primary efficacy related endpoint 3 (Regression) - Amplitude

End point description:

For mfERG analysis, the study eye was divided into 103 hexagons and each hexagon was classified as normal or abnormal based on reference Amplitude values from healthy volunteers. An eye was considered normal if less than 6 pathological hexagons were found, otherwise an eye was considered abnormal.
Primary efficacy related endpoint 3 was assessed on a subset of patients that were identified as

abnormal with respect to Amplitude at Baseline (6 or more abnormal hexagons) at Baseline. "Regression" was defined as follows: a subject turned to be normal with respect to Amplitude at 24 months. "No regression" was defined as follows: a subject remained to be abnormal with respect to Amplitude at 24 months.

End point type	Secondary

End point timeframe:

Baseline and 24 months

End point values	Somatostatin 0.1%	Placebo	Brimonidine tartrate 0.2%	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29[22]	29[23]	26[24]	
Units: Subjects				
Regression	11	19	10	
No regression	18	10	16	

Notes:

[22] - Subset of the PE identified as abnormal with respect to Amplitude at Baseline

[23] - Subset of the PE identified as abnormal with respect to Amplitude at Baseline

[24] - Subset of the PE identified as abnormal with respect to Amplitude at Baseline

Statistical analyses

Statistical analysis title	Statistical analysis 1_Somatostatin v Placebo
Comparison groups	Somatostatin 0.1% v Placebo
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.065
Method	Fisher exact
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 2_Brimonidine v Placebo
Comparison groups	Placebo v Brimonidine tartrate 0.2%
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06
Method	Fisher exact
Confidence interval	
level	95 %
sides	2-sided

Secondary: A.1.8. Primary efficacy related endpoint 4. Change in total number of

abnormal hexagons (mean) - Implicit time (IT)	
End point title	A.1.8. Primary efficacy related endpoint 4. Change in total number of abnormal hexagons (mean) - Implicit time (IT)

End point description:

For mfERG analysis, the study eye was divided into 103 hexagons and each hexagon was classified as normal or abnormal based on reference IT values from healthy volunteers. An eye was considered normal if less than 6 pathological hexagons were found, otherwise an eye was considered abnormal. Primary efficacy related endpoint 4 was defined as the difference between the total number of abnormal hexagons (mean) with respect to IT at 24 months and baseline.

End point type	Secondary

End point timeframe:

Baseline and 24 months

End point values	Somatostatin 0.1%	Placebo	Brimonidine tartrate 0.2%	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120[25]	123[26]	96[27]	
Units: Change in number of abnormal hexagons				
arithmetic mean (standard deviation)	2.2 (± 10.1)	0.9 (± 8.9)	1.2 (± 9.8)	

Notes:

[25] - Primary efficacy (PE) population with data at 24 months

[26] - Primary efficacy (PE) population with data at 24 months

[27] - Primary efficacy (PE) population with data at 24 months

Statistical analyses

Statistical analysis title	Statistical analysis 1_Somatostatin v Placebo
Comparison groups	Somatostatin 0.1% v Placebo
Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.347
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 2_Brimonidine v Placebo
Comparison groups	Placebo v Brimonidine tartrate 0.2%
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.819
Method	Wilcoxon (Mann-Whitney)

Confidence interval	
level	95 %
sides	2-sided

Secondary: A.1.9. Primary efficacy related endpoint 4. Change in total number of abnormal hexagons (mean) - Amplitude

End point title	A.1.9. Primary efficacy related endpoint 4. Change in total number of abnormal hexagons (mean) - Amplitude

End point description:

For mfERG analysis, the study eye was divided into 103 hexagons and each hexagon was classified as normal or abnormal based on reference Amplitude values from healthy volunteers. An eye was considered normal if less than 6 pathological hexagons were found, otherwise an eye was considered abnormal.
Primary efficacy related endpoint 4 was defined as the difference between the total number of abnormal hexagons (mean) with respect to Amplitude at 24 months and baseline.

End point type	Secondary

End point timeframe:

Baseline and 24 months

End point values	Somatostatin 0.1%	Placebo	Brimonidine tartrate 0.2%	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120[28]	123[29]	96[30]	
Units: Change in number of abnormal hexagons				
arithmetic mean (standard deviation)	1.3 (± 7.6)	0.1 (± 8.1)	-0.3 (± 7.0)	

Notes:

[28] - Primary efficacy (PE) population with data at 24 months

[29] - Primary efficacy (PE) population with data at 24 months

[30] - Primary efficacy (PE) population with data at 24 months

Statistical analyses

Statistical analysis title	Statistical analysis 1_Somatostatin v Placebo
Comparison groups	Somatostatin 0.1% v Placebo
Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.733
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 2_Brimonidine v Placebo
Comparison groups	Placebo v Brimonidine tartrate 0.2%

Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.365
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided

Secondary: A.1.10. Primary efficacy related endpoint 5 (Prevention and Progression Arrest) - Implicit Time (IT)

End point title	A.1.10. Primary efficacy related endpoint 5 (Prevention and Progression Arrest) - Implicit Time (IT)

End point description:

For mfERG analysis, the study eye was divided into 103 hexagons and each hexagon was classified as normal or abnormal based on reference IT values from healthy volunteers. An eye was considered normal if less than 6 pathological hexagons were found, otherwise an eye was considered abnormal. Primary efficacy related endpoint 5 was defined to test prevention in normal subjects together with progression arrest in abnormal subjects.
"Success" was defined as follows: subject was Normal at Baseline and remained Normal at 24 months or subject was Abnormal at Baseline and the number of abnormal hexagons decreased or remain unchanged at 24 months. "Failure" was defined as follows: subject was Normal at Baseline and became Abnormal at 24 months or subject was Abnormal at Baseline and the number of abnormal hexagons increased at 24 months.

End point type	Secondary

End point timeframe:

Baseline and 24 months

End point values	Somatostatin 0.1%	Placebo	Brimonidine tartrate 0.2%	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120[31]	123[32]	96[33]	
Units: Subjects				
Success	75	85	63	
Failure	45	38	33	

Notes:

[31] - Primary efficacy (PE) population with data at 24 months

[32] - Primary efficacy (PE) population with data at 24 months

[33] - Primary efficacy (PE) population with data at 24 months

Statistical analyses

Statistical analysis title	Statistical analysis 1_Somatostatin v Placebo
Comparison groups	Placebo v Somatostatin 0.1%

Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.278
Method	Chi-squared
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 2_Brimonidine v Placebo
Comparison groups	Placebo v Brimonidine tartrate 0.2%
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.585
Method	Chi-squared
Confidence interval	
level	95 %
sides	2-sided

Secondary: A.1.11. Primary efficacy related endpoint 5 (Prevention and Progression Arrest) - Amplitude

End point title	A.1.11. Primary efficacy related endpoint 5 (Prevention and Progression Arrest) - Amplitude

End point description:

For mfERG analysis, the study eye was divided into 103 hexagons and each hexagon was classified as normal or abnormal based on reference Amplitude values from healthy volunteers. An eye was considered normal if less than 6 pathological hexagons were found, otherwise an eye was considered abnormal.
Primary efficacy related endpoint 5 was defined to test prevention in normal subjects together with progression arrest in abnormal subjects.
"Success" was defined as follows: subject was Normal at Baseline and remained Normal at 24 months or subject was Abnormal at Baseline and the number of abnormal hexagons decreased or remain unchanged at 24 months. "Failure" was defined as follows: subject was Normal at Baseline and became Abnormal at 24 months or subject was Abnormal at Baseline and the number of abnormal hexagons increased at 24 months.

End point type	Secondary

End point timeframe:

Baseline and 24 months

End point values	Somatostatin 0.1%	Placebo	Brimonidine tartrate 0.2%	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120[34]	123[35]	96[36]	
Units: Subjects				
Success	97	102	81	
Failure	23	21	15	

Notes:

[34] - Primary efficacy (PE) population with data at 24 months

[35] - Primary efficacy (PE) population with data at 24 months

[36] - Primary efficacy (PE) population with data at 24 months

Statistical analyses

Statistical analysis title	Statistical analysis 1_Somatostatin v Placebo
Comparison groups	Somatostatin 0.1% v Placebo
Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.672
Method	Chi-squared
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 2_Brimonidine v Placebo
Comparison groups	Placebo v Brimonidine tartrate 0.2%
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.774
Method	Chi-squared
Confidence interval	
level	95 %
sides	2-sided

Secondary: A.2. CFP 30º/35º eye progression assessed by ETDRS

End point title	A.2. CFP 30º/35º eye progression assessed by ETDRS

End point description:

"Eye progression" was defined as follows: ETDRS at 24 months increased by at least two steps (on classification) as compared to screening. Otherwise "No eye progression" was defined as follows: ETDRS at 24 months decreased as compared to screening, did not change or increased by one step.

End point type	Secondary

End point timeframe:

Screening and 24 months

End point values	Somatostatin 0.1%	Placebo	Brimonidine tartrate 0.2%	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119[37]	123[38]	96[39]	
Units: Subjects				
Eye progression	4	6	6	
No eye progression	115	117	90	

Notes:

[37] - Primary efficacy (PE) population with data at 24 months

[38] - Primary efficacy (PE) population with data at 24 months

[39] - Primary efficacy (PE) population with data at 24 months

Statistical analyses

Statistical analysis title	Statistical analysis 1_Somatostatin v Placebo
Comparison groups	Placebo v Somatostatin 0.1%
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.749
Method	Fisher exact
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 2_Brimonidine v Placebo
Comparison groups	Placebo v Brimonidine tartrate 0.2%
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.768
Method	Fisher exact
Confidence interval	
level	95 %
sides	2-sided

Secondary: A.3. Best Corrected Visual Acuity (BCVA) score

End point title	A.3. Best Corrected Visual Acuity (BCVA) score

End point description:

Best Corrected Visual Acuity (BCVA) was mesured according to the ETDRS protocol and is presented as descriptive statistics.

End point type	Secondary

End point timeframe:

Baseline and 24 months

End point values	Somatostatin 0.1%	Placebo	Brimonidine tartrate 0.2%	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	135[40]	136[41]	139[42]	
Units: score				
arithmetic mean (standard deviation)				
BCVA score (Baseline)	86.0 (± 5.0)	86.2 (± 4.9)	86.2 (± 5.3)	
BCVA score (24 months)	86.2 (± 5.5)	86.7 (± 4.4)	85.7 (± 6.1)	

Notes:

[40] - Primary efficacy (PE) population: 135 (Baseline); 120 (24 months)

[41] - Primary efficacy (PE) population: 136 (Baseline); 124 (24 months)

[42] - Primary efficacy (PE) population: 139 (Baseline); 97 (24 months)

Statistical analyses

No statistical analyses for this end point

Secondary: A.4. Visual field test

End point title	A.4. Visual field test

End point description:

Visual Fields defects assessed by Visual Fields Test. Descriptive statistics for global mean deviation and pattern mean deviation are presented.

End point type	Secondary

End point timeframe:

Baseline and 24 months

End point values	Somatostatin 0.1%	Placebo	Brimonidine tartrate 0.2%	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	133[43]	134[44]	139[45]	
Units: dB				
arithmetic mean (standard deviation)				
Global mean deviation (Baseline)	-1.36 (± 2.25)	-1.43 (± 3.31)	-1.41 (± 3.58)	
Global mean deviation (24 months)	-1.30 (± 2.60)	-1.22 (± 3.06)	-1.63 (± 3.00)	
Pattern deviation (Baseline)	2.10 (± 1.30)	2.07 (± 1.45)	2.18 (± 1.64)	
Pattern deviation (24 months)	2.08 (± 1.30)	1.82 (± 1.12)	2.38 (± 1.60)	

Notes:

[43] - Primary efficacy (PE) population: 133 (Baseline); 120 (24 months)

[44] - Primary efficacy (PE) population: 134 (Baseline); 122 (24 months)

[45] - Primary efficacy (PE) population: 139 (Baseline); 97 (24 months)

Statistical analyses

No statistical analyses for this end point

Secondary: A.5. Visual Function Questionnaire (VFQ-25)

End point title	A.5. Visual Function Questionnaire (VFQ-25)

End point description:

Overall composite score for the Visual Function Questionnaire (VFQ-25) is presented as descriptive statistics. Overall composite score is defined as mean of each sub-scale item excluding question on general health.

End point type	Secondary

End point timeframe:

Baseline and 24 months

End point values	Somatostatin 0.1%	Placebo	Brimonidine tartrate 0.2%	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	103[46]	106[47]	105[48]	
Units: score				
arithmetic mean (standard deviation)				
Overall composite score (Baseline)	92.91 (± 5.89)	92.49 (± 5.70)	90.72 (± 7.67)	
Overall composite score (24 months)	92.87 (± 7.25)	92.80 (± 5.64)	91.48 (± 6.91)	

Notes:

[46] - Primary efficacy (PE) population: 103 (Baseline); 92 (24 months)

[47] - Primary efficacy (PE) population: 106 (Baseline); 90 (24 months)

[48] - Primary efficacy (PE) population: 105 (Baseline); 70 (24 months)

Statistical analyses

No statistical analyses for this end point

Secondary: B.1. Mean Microaneurysm (MA) number. PE population

End point title	B.1. Mean Microaneurysm (MA) number. PE population

End point description:

Number of microaneurysms (mean) at screening and 24 months.

End point type	Secondary

End point timeframe:

Screening and 24 months

End point values	Somatostatin 0.1%	Placebo	Brimonidine tartrate 0.2%	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119[49]	122[50]	96[51]	
Units: Number of microaneurysms				
arithmetic mean (standard deviation)				
MA number screening	0.9 (± 1.9)	0.8 (± 1.0)	0.8 (± 1.4)	
MA number 24 months	1.0 (± 1.6)	1.1 (± 1.8)	1.2 (± 2.0)	

Notes:

[49] - Primary efficacy (PE) population with data at 24 months

[50] - Primary efficacy (PE) population with data at 24 months

[51] - Primary efficacy (PE) population with data at 24 months

Statistical analyses

Statistical analysis title	Statistical analysis 1_MA number_Somatostatin

Statistical analysis description:

INTRAGROUP ANALYSIS between initial (screening) and final (24 months) values by using a paired Wilcoxon test afforded:

P-value=0.4079 (Somatostatin). Arrest in the appearance of microaneurysms.
P-value=0.0608 (Placebo). Almost statistically significant increase in the number of microaneurysms.

INTERGROUP ANALYSIS. Unpaired Wilcoxon test to compare number of MAs at 24 months between treatments has been performed:

Comparison groups	Somatostatin 0.1% v Placebo
Number of subjects included in analysis	241
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.8178
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 2_MA number_Brimonidine

Statistical analysis description:

INTRAGROUP ANALYSIS between initial (screening) and final (24 months) values by using a paired Wilcoxon test afforded:

P-value=0.0158* (Brimonidine). Statistically significant increase in the number of microaneurysms.
P-value=0.0608 (Placebo). Almost statistically significant increase in the number of microaneurysms.

INTERGROUP ANALYSIS. Unpaired Wilcoxon test to compare number of MAs at 24 months between treatments has been performed:

Comparison groups	Placebo v Brimonidine tartrate 0.2%
Number of subjects included in analysis	218
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.8519
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided

Secondary: B.1.1. Mean Microaneurysm (MA) number. MA>1 at screening subpopulation

End point title	B.1.1. Mean Microaneurysm (MA) number. MA>1 at screening subpopulation

End point description:

Number of microaneurysms (mean) at screening and 24 months.

End point type	Secondary

End point timeframe:

Screening and 24 months

End point values	MA>1 at screening subpopulation - Somatostatin 0.1%	MA>1 at screening subpopulation - Placebo	MA>1 at screening subpopulation - Brimonidine tartrate 0.2%	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	23[52]	21[53]	14[54]	
Units: number of MA				
arithmetic mean (standard deviation)				
MA number screening	3.8 (± 2.9)	2.7 (± 0.9)	3.6 (± 1.7)	
MA number 24 months	2.3 (± 2.2)	2.2 (± 3.1)	3.1 (± 3.6)	

Notes:

[52] - Subset of PE with more than 1 microaneurysm (MA) at screening

[53] - Subset of PE with more than 1 microaneurysm (MA) at screening

[54] - Subset of PE with more than 1 microaneurysm (MA) at screening

Statistical analyses

Statistical analysis title	Statistical analysis 1_MA number_Somatostatin

Statistical analysis description:

INTRAGROUP ANALYSIS between initial (screening) and final (24 months) values by using a paired Wilcoxon test afforded:

P-value=0.0089* (Somatostatin). Statistically significant reduction in the number of microaneurysms.
P-value=0.1630 (Placebo). Not statistically significant. Number of microaneurysms was not reduced.

INTERGROUP ANALYSIS. Unpaired Wilcoxon test to compare number of MAs at 24 months between treatments has been performed:

Comparison groups	MA>1 at screening subpopulation - Somatostatin 0.1% v MA>1 at screening subpopulation - Placebo
Number of subjects included in analysis	44
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.4252
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 2_MA number_Brimonidine

Statistical analysis description:

INTRAGROUP ANALYSIS between initial (screening) and final (24 months) values by using a paired Wilcoxon test afforded:

P-value=0.5852 (Brimonidine). Not statistically significant.
P-value=0.1630 (Placebo). Not statistically significant.

INTERGROUP ANALYSIS. Unpaired Wilcoxon test to compare number of MAs at 24 months between treatments has been performed:

Comparison groups	MA>1 at screening subpopulation - Brimonidine tartrate 0.2% v MA>1 at screening subpopulation - Placebo
Number of subjects included in analysis	35
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.4919
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided

Secondary: B.1.2. Mean Microaneurysm (MA) formation rate. PE population

End point title	B.1.2. Mean Microaneurysm (MA) formation rate. PE population
End point description:	
Mean Microaneurysm formation rate (new MA/year) at 24 months.	
End point type	Secondary
End point timeframe:	
Screening and 24 months	

End point values	Somatostatin 0.1%	Placebo	Brimonidine tartrate 0.2%	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	118[55]	122[56]	96[57]	
Units: new MA/year				
arithmetic mean (standard deviation)				
arithmetic mean (standard deviation)	0.22 (± 0.47)	0.31 (± 0.69)	0.27 (± 0.52)	

Notes:

[55] - Primary efficacy (PE) population with data at 24 months

[56] - Primary efficacy (PE) population with data at 24 months

[57] - Primary efficacy (PE) population with data at 24 months

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Somatostatin 0.1% v Placebo

Number of subjects included in analysis	240
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.3743
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
sides	2-sided

Statistical analysis title	Statistical analysis 2
Comparison groups	Placebo v Brimonidine tartrate 0.2%
Number of subjects included in analysis	218
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.7956
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided

Secondary: B.1.3. Mean Microaneurysm (MA) formation rate. MA>1 at screening subpopulation

End point title	B.1.3. Mean Microaneurysm (MA) formation rate. MA>1 at screening subpopulation
End point description: Microaneurysm formation rate (new MA/year) at 24 months.	
End point type	Secondary
End point timeframe: Screening and 24 months	

End point values	MA>1 at screening subpopulation - Somatostatin 0.1%	MA>1 at screening subpopulation - Placebo	MA>1 at screening subpopulation - Brimonidine tartrate 0.2%	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	23[58]	21[59]	14[60]	
Units: new MA/year				
arithmetic mean (standard deviation)				
arithmetic mean (standard deviation)	0.23 (± 0.39)	0.51 (± 1.17)	0.67 (± 0.86)	

Notes:

[58] - Subset of PE with more than 1 microaneurysm (MA) at screening

[59] - Subset of PE with more than 1 microaneurysm (MA) at screening

[60] - Subset of PE with more than 1 microaneurysm (MA) at screening

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	MA>1 at screening subpopulation - Somatostatin 0.1% v MA>1 at screening subpopulation - Placebo
Number of subjects included in analysis	44
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.4413
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 2
Comparison groups	MA>1 at screening subpopulation - Placebo v MA>1 at screening subpopulation - Brimonidine tartrate 0.2%
Number of subjects included in analysis	35
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.3622
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided

Secondary: B.1.4. Mean Microaneurysm (MA) disappearance rate. PE population	
End point title	B.1.4. Mean Microaneurysm (MA) disappearance rate. PE population
End point description: Mean microaneurysm disappearance rate (disappeared MA/year) at 24 months.	
End point type	Secondary
End point timeframe: Screening and 24 months	

End point values	Somatostatin 0.1%	Placebo	Brimonidine tartrate 0.2%	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	118[61]	122[62]	96[63]	
Units: Disappeared MA/year				
arithmetic mean (standard deviation)				
arithmetic mean (standard deviation)	0.29 (± 0.68)	0.23 (± 0.42)	0.20 (± 0.40)	

Notes:

[61] - Primary efficacy (PE) population with data at 24 months

[62] - Primary efficacy (PE) population with data at 24 months

[63] - Primary efficacy (PE) population with data at 24 months

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Somatostatin 0.1% v Placebo
Number of subjects included in analysis	240
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.7513
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 2
Comparison groups	Placebo v Brimonidine tartrate 0.2%
Number of subjects included in analysis	218
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.4631
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided

Secondary: B.1.5. Mean Microaneurysm (MA) disappearance rate. MA>1 at screening subpopulation

End point title	B.1.5. Mean Microaneurysm (MA) disappearance rate. MA>1 at screening subpopulation
End point description:	
Mean microaneurysm disappearance rate (disappeared MA/year) at 24 months.	
End point type	Secondary
End point timeframe:	
Screening and 24 months	

End point values	MA>1 at screening subpopulation - Somatostatin 0.1%	MA>1 at screening subpopulation - Placebo	MA>1 at screening subpopulation - Brimonidine tartrate 0.2%	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	23[64]	21[65]	14[66]	
Units: Disappeared MA/year				
arithmetic mean (standard deviation)				
arithmetic mean (standard deviation)	1.17 (± 1.15)	0.89 (± 0.56)	0.90 (± 0.59)	

Notes:

[64] - Subset of PE with more than 1 microaneurysm (MA) at screening

[65] - Subset of PE with more than 1 microaneurysm (MA) at screening

[66] - Subset of PE with more than 1 microaneurysm (MA) at screening

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	MA>1 at screening subpopulation - Placebo v MA>1 at screening subpopulation - Somatostatin 0.1%
Number of subjects included in analysis	44
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.8151
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 2
Comparison groups	MA>1 at screening subpopulation - Placebo v MA>1 at screening subpopulation - Brimonidine tartrate 0.2%
Number of subjects included in analysis	35
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.7253
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided

Secondary: B.2. Mean Implicit Time (IT) (ms). MA>1 at screening subpopulation

End point title	B.2. Mean Implicit Time (IT) (ms). MA>1 at screening subpopulation
End point description:	
Mean Implicit Time (ms) at baseline and 24 months.	
End point type	Secondary
End point timeframe:	
Baseline and 24 months	

End point values	MA>1 at screening subpopulation - Somatostatin 0.1%	MA>1 at screening subpopulation - Placebo	MA>1 at screening subpopulation - Brimonidine tartrate 0.2%	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	23[67]	21[68]	14[69]	
Units: ms				
arithmetic mean (standard deviation)				
IT (mean +-SD) Baseline	35.0 (± 1.6)	35.3 (± 1.1)	34.8 (± 1.2)	
IT (mean+- SD) 24 months	35.1 (± 1.8)	35.2 (± 1.6)	34.8 (± 1.4)	

Notes:

[67] - Subset of PE with more than 1 microaneurysm (MA) at screening

[68] - Subset of PE with more than 1 microaneurysm (MA) at screening

[69] - Subset of PE with more than 1 microaneurysm (MA) at screening

Statistical analyses

Statistical analysis title	Statistical analysis 1_IT_Somatostatin

Statistical analysis description:

INTRAGROUP ANALYSIS between initial (baseline) and final (24 months) values by using a paired Wilcoxon test afforded:

P-value=0.5642 (Somatostatin). Not statistically significant.
P-value=0.6902 (Placebo). Not statistically significant.

INTERGROUP ANALYSIS. Unpaired Wilcoxon test to compare mean IT values at 24 months between treatments has been performed:

Comparison groups	MA>1 at screening subpopulation - Somatostatin 0.1% v MA>1 at screening subpopulation - Placebo
Number of subjects included in analysis	44
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.831
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 2_IT_Brimonidine

Statistical analysis description:

INTRAGROUP ANALYSIS between initial (baseline) and final (24 months) values by using a paired Wilcoxon test afforded:

P-value=0.5313 (Brimonidine). Not statistically significant.
P-value=0.6902 (Placebo). Not statistically significant.

INTERGROUP ANALYSIS. Unpaired Wilcoxon test to compare mean IT values at 24 months between treatments has been performed:

Comparison groups	MA>1 at screening subpopulation - Placebo v MA>1 at screening subpopulation - Brimonidine tartrate 0.2%
Number of subjects included in analysis	35
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.4452
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided

Secondary: B.3. Mean Amplitude (nV/deg2). MA>1 at screening subpopulation

End point title	B.3. Mean Amplitude (nV/deg2). MA>1 at screening subpopulation

End point description:

Mean Amplitude (nV/deg2) at baseline and 24 months.

End point type	Secondary

End point timeframe:

Baseline and 24 months

End point values	MA>1 at screening subpopulation - Somatostatin 0.1%	MA>1 at screening subpopulation - Placebo	MA>1 at screening subpopulation - Brimonidine tartrate 0.2%	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	23[70]	21[71]	14[72]	
Units: nV/deg2				
arithmetic mean (standard deviation)				
Amplitude (mean +- SD) Baseline	17.2 (± 6.0)	18.8 (± 6.2)	20.1 (± 5.1)	
Amplitude (mean +- SD) 24 months	20.0 (± 7.4)	19.1 (± 5.4)	18.9 (± 6.0)	

Notes:

[70] - Subset of PE with more than 1 microaneurysm (MA) at screening

[71] - Subset of PE with more than 1 microaneurysm (MA) at screening

[72] - Subset of PE with more than 1 microaneurysm (MA) at screening

Statistical analyses

Statistical analysis title	Statistical analysis 1_Amplitude_Somatostatin

Statistical analysis description:

INTRAGROUP ANALYSIS between initial (baseline) and final (24 months) values by using a paired t-test afforded:

P-value=0.0203* (Somatostatin). Statistically significant increase (improvement) of Amplitude.
P-value=0.8178 (Placebo). Not statistically significant increase of Amplitude.

INTERGROUP ANALYSIS. Unpaired t-test to compare mean Amplitude values at 24 months between treatments has been performed:

Comparison groups	MA>1 at screening subpopulation - Somatostatin 0.1% v MA>1 at screening subpopulation - Placebo

Number of subjects included in analysis	44
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.6484
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 2_Amplitude_Brimonidine

Statistical analysis description:

INTRAGROUP ANALYSIS between initial (baseline) and final (24 months) values by using a paired t-test afforded:

P-value=0.4079 (Brimonidine). Not statistically significant.
P-value=0.8178 (Placebo). Not statistically significant.

INTERGROUP ANALYSIS. Unpaired t-test to compare mean Amplitude values at 24 months between treatments has been performed:

Comparison groups	MA>1 at screening subpopulation - Placebo v MA>1 at screening subpopulation - Brimonidine tartrate 0.2%
Number of subjects included in analysis	35
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.9095
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided

Secondary: B.4. Mean Retinal thickness (RT). MA>1 at screening subpopulation

End point title	B.4. Mean Retinal thickness (RT). MA>1 at screening subpopulation

End point description:

Mean Retinal thickness at Central Subfield (CSF), Inner Ring (IR) and Outer Ring (OR) at baseline and 24 months.

End point type	Secondary

End point timeframe:

Baseline and 24 months

End point values	MA>1 at screening subpopulation - Somatostatin 0.1%	MA>1 at screening subpopulation - Placebo	MA>1 at screening subpopulation - Brimonidine tartrate 0.2%	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	23[73]	21[74]	14[75]	
Units: micra				
arithmetic mean (standard deviation)				
Mean CSF thickness (Baseline)	269.3 (± 32.0)	261.2 (± 19.3)	259.6 (± 26.2)	
Mean CSF thickness (24 months)	270.8 (± 34.8)	260.8 (± 20.5)	256.2 (± 24.7)	
Mean IR thickness (Baseline)	323.1 (± 24.8)	317.7 (± 18.4)	328.3 (± 17.4)	
Mean IR thickness (24 months)	322.6 (± 25.9)	315.8 (± 19.0)	325.8 (± 15.7)	
Mean OR thickness (Baseline)	278.8 (± 22.9)	276.4 (± 14.3)	284.9 (± 18.1)	
Mean OR thickness (24 months)	278.2 (± 23.1)	274.4 (± 13.8)	283.5 (± 17.1)	

Notes:

[73] - Subset of PE with more than 1 microaneurysm (MA) at screening

[74] - Subset of PE with more than 1 microaneurysm (MA) at screening

[75] - Subset of PE with more than 1 microaneurysm (MA) at screening

Statistical analyses

Statistical analysis title	Statistical analysis 1_CSF thickness_Somatostatin

Statistical analysis description:

INTRAGROUP ANALYSIS between initial (baseline) and final (24 months) values by using a paired t-test test afforded:

P-value=0.2773 (Somatostatin). Not statistically significant.
P-value=0.8060 (Placebo). Not statistically significant.

INTERGROUP ANALYSIS. Unpaired t-test to compare Mean CSF Retinal Thickness at 24 months between treatments has been performed:

Comparison groups	MA>1 at screening subpopulation - Placebo v MA>1 at screening subpopulation - Somatostatin 0.1%
Number of subjects included in analysis	44
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.3202
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 2_CSF thickness_Brimonidine

Statistical analysis description:

INTRAGROUP ANALYSIS between initial (baseline) and final (24 months) values by using a paired t-test afforded:

P-value=0.0601 (Brimonidine). Not statistically significant.
P-value=0.8060 (Placebo). Not statistically significant.

INTERGROUP ANALYSIS. Unpaired t-test to compare Mean CSF Retinal Thickness at 24 months between treatments has been performed:

Comparison groups	MA>1 at screening subpopulation - Placebo v MA>1 at screening subpopulation - Brimonidine tartrate 0.2%
Number of subjects included in analysis	35
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.551
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 3_IR thickness_Somatostatin

Statistical analysis description:

INTRAGROUP ANALYSIS between initial (baseline) and final (24 months) values by using a paired t-test afforded:

P-value=0.6295 (Somatostatin). Not statistically significant. Somatostatin arrested the thinning of the inner ring (IR) of the retina.
P-value=0.0477* (Placebo). Statistically significant thinning of the inner ring (IR) of the retina.

INTERGROUP ANALYSIS. Unpaired t-test to compare Mean IR Retinal Thickness at 24 months between treatments has been performed:

Comparison groups	MA>1 at screening subpopulation - Placebo v MA>1 at screening subpopulation - Somatostatin 0.1%
Number of subjects included in analysis	44
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.3316
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 4_IR thickness_Brimonidine

Statistical analysis description:

INTRAGROUP ANALYSIS between initial (baseline) and final (24 months) values by using a paired t-test afforded:

P-value=0.0587 (Brimonidine). Almost significant thinning of the inner ring (IR) of the retina.
P-value=0.0477* (Placebo). Statistically significant thinning of the inner ring (IR) of the retina.

INTERGROUP ANALYSIS. unpaired t-test to compare Mean IR Retinal Thickness at 24 months between treatments has been performed:

Comparison groups	MA>1 at screening subpopulation - Placebo v MA>1 at screening subpopulation - Brimonidine tartrate 0.2%

Number of subjects included in analysis	35
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.1124
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 5_OR thickness_Somatostatin

Statistical analysis description:

INTRAGROUP ANALYSIS between initial (baseline) and final (24 months) values by using a paired t-test afforded:

P-value=0.5189 (Somatostatin). Not statistically significant. Somatostatin arrested the thinning of the outer ring (OR) of the retina.
P-value=0.0349* (Placebo). Statistically significant thinning of the outer ring (OR) of the retina.

INTERGROUP ANALYSIS. Unpaired t-test to compare Mean OR Retinal Thickness at 24 months between treatments has been performed:

Comparison groups	MA>1 at screening subpopulation - Placebo v MA>1 at screening subpopulation - Somatostatin 0.1%
Number of subjects included in analysis	44
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.519
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 6_OR thickness_Brimonidine

Statistical analysis description:

INTRAGROUP ANALYSIS between initial (baseline) and final (24 months) values by using a paired t-test afforded:

P-value=0.1337 (Brimonidine). Not statistically significant.
P-value=0.0349* (Placebo). Statistically significant thinning of the outer ring (OR) of the retina.

INTERGROUP ANALYSIS. Unpaired t-test to compare mean OR Retinal Thickness at 24 months between treatments has been performed:

Comparison groups	MA>1 at screening subpopulation - Placebo v MA>1 at screening subpopulation - Brimonidine tartrate 0.2%
Number of subjects included in analysis	35
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0932
Method	t-test, 2-sided

Confidence interval	
level	95 %
sides	2-sided

Secondary: B.5. Blood biomarkers: Laminin, ADMA and CML. PE population

End point title	B.5. Blood biomarkers: Laminin, ADMA and CML. PE population

End point description:

Blood levels of Laminin, ADMA (Asymmetric Dimethylarginine) and CML (N-carboxymethyl-lysine) (3 biomarkers associated with Diabetic Retinopathy) at screening and 12 months.

End point type	Secondary

End point timeframe:

Screening and 12 months

End point values	Somatostatin 0.1%	Placebo	Brimonidine tartrate 0.2%	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108[76]	118[77]	90[78]	
Units: ng/mL				
arithmetic mean (standard deviation)				
Laminin concentration (screening)	423.1 (± 399.6)	492.9 (± 534.4)	467.1 (± 383.9)	
Laminin concentration (12 months)	398.2 (± 408.1)	474.2 (± 481.9)	488.4 (± 507.6)	
ADMA concentration (screening)	103.8 (± 59.8)	94.6 (± 53.2)	98.8 (± 67.8)	
ADMA concentration (12 months)	103.5 (± 61.9)	113.1 (± 70.5)	107.9 (± 69.6)	
CML concentration (Screening)	276.8 (± 154.0)	277.6 (± 183.8)	262.8 (± 160.4)	
CML concentration (12 months)	265.6 (± 150.5)	295.7 (± 206.2)	287.3 (± 170.0)	

Notes:

[76] - Primary efficacy (PE) population with data at 24 months

[77] - Primary efficacy (PE) population with data at 24 months

[78] - Primary efficacy (PE) population with data at 24 months

Statistical analyses

Statistical analysis title	Statistical analysis 1_Laminin_Somatostatin

Statistical analysis description:

INTRAGROUP ANALYSIS between initial (screening) and final (12 months) values by using a paired Wilcoxon test afforded:

P-value=0.1757 (Somatostatin). Not statistically significant.
P-value=0.2816 (Placebo). Not statistically significant.

INTERGROUP ANALYSIS. Unpaired Wilcoxon test to compare Laminin values at 12 months between treatments has been performed:

Comparison groups	Somatostatin 0.1% v Placebo

Number of subjects included in analysis	226
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.2113
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 2 _Laminin_Brimonidine

Statistical analysis description:

INTRAGROUP ANALYSIS between initial (screening) and final (12 months) values by using a paired Wilcoxon test afforded:

P-value=0.9873 (Brimonidine). Not statistically significant.
P-value=0.2816 (Placebo). Not statistically significant.

INTERGROUP ANALYSIS. Unpaired Wilcoxon test to compare Laminin values at 12 months between treatments has been performed:

Comparison groups	Placebo v Brimonidine tartrate 0.2%
Number of subjects included in analysis	208
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.8209
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 3 _ADMA_Somatostatin

Statistical analysis description:

INTRAGROUP ANALYSIS between initial (screening) and final (12 months) values by using a paired t-test afforded:

P-value=0.9715 (Somatostatin). Not statistically significant. Somatostatin-treated patients did not show an increase of ADMA levels.
P-value=0.0082* (Placebo). Statistically significant increase of ADMA Levels (Diabetic Retinopathy progression).

INTERGROUP ANALYSIS. Unpaired t-test to compare ADMA values at 12 months between treatments has been performed:

Comparison groups	Somatostatin 0.1% v Placebo
Number of subjects included in analysis	226
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.2799
Method	t-test, 2-sided

Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 4 _ADMA_Brimonidine

Statistical analysis description:

INTRAGROUP ANALYSIS between initial (screening) and final (12 months) values by using a paired t-test afforded:

P-value=0.1807 (Brimonidine). Not statistically significant.
P-value=0.0082* (Placebo). Statistically significant increase of ADMA levels (Diabetic Retinopathy progression)

INTERGROUP ANALYSIS. Unpaired t-test to compare ADMA values at 12 months between treatments has been performed:

Comparison groups	Placebo v Brimonidine tartrate 0.2%
Number of subjects included in analysis	208
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.5951
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 5 _CML_Somatostatin

Statistical analysis description:

INTRAGROUP ANALYSIS between initial (screening) and final (12 months) values by using a paired t-test afforded:

P-value=0.4103 (Somatostatin). Not statistically significant.
P-value=0.2192 (Placebo). Not statistically significant.

INTERGROUP ANALYSIS. Unpaired t-test to compare CML values at 12 months between treatments has been performed:

Comparison groups	Placebo v Somatostatin 0.1%
Number of subjects included in analysis	226
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.2155
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 6_CML_Brimonidine

Statistical analysis description:

INTRAGROUP ANALYSIS between initial (screening) and final (12 months) values by using a paired t-test afforded:

P-value=0.1265 (Brimonidine). Not statistically significant.
P-value=0.2192 (Placebo). Not statistically significant.

INTERGROUP ANALYSIS. Unpaired t-test to compare CML values at 12 months between treatments has been performed:

Comparison groups	Placebo v Brimonidine tartrate 0.2%
Number of subjects included in analysis	208
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.756
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided

Secondary: B.5.1. Blood biomarkers: Laminin, ADMA and CML. MA>1 at screening subpopulation

End point title	B.5.1. Blood biomarkers: Laminin, ADMA and CML. MA>1 at screening subpopulation

End point description:

Blood levels of Laminin, ADMA (Asymmetric Dimethylarginine) and CML (N-carboxymethyl-lysine) (3 biomarkers associated with Diabetic Retinopathy) at screening and 12 months.

End point type	Secondary

End point timeframe:

Screening and 12 months

End point values	MA>1 at screening subpopulation - Somatostatin 0.1%	MA>1 at screening subpopulation - Placebo	MA>1 at screening subpopulation - Brimonidine tartrate 0.2%	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	19[79]	21[80]	14[81]	
Units: ng/mL				
arithmetic mean (standard deviation)				
Laminin concentration (screening)	461.2 (± 381.3)	649.9 (± 667.4)	449.2 (± 383.2)	
Laminin concentration (12 months)	382.3 (± 390.3)	679.6 (± 591.2)	562.6 (± 660.1)	
ADMA concentration (screening)	114.6 (± 63.0)	73.4 (± 34.0)	106.6 (± 74.2)	
ADMA concentration (12 months)	116.0 (± 61.4)	96.3 (± 57.2)	114.4 (± 70.4)	
CML concentration (Screening)	287.9 (± 110.5)	262.5 (± 155.4)	338.6 (± 196.2)	
CML concentration (12 months)	277.4 (± 128.9)	251.7 (± 162.0)	346.5 (± 244.9)	

Notes:

[79] - Subset of PE with more than 1 microaneurysm (MA) at screening

[80] - Subset of PE with more than 1 microaneurysm (MA) at screening

[81] - Subset of PE with more than 1 microaneurysm (MA) at screening

Statistical analyses

Statistical analysis title	Statistical analysis 1_Laminin_Somatostatin

Statistical analysis description:

INTRAGROUP ANALYSIS between initial (screening) and final (12 months) values by using a paired Wilcoxon test afforded:

P-value=0.2935 (Somatostatin). Not statistically significant.
P-value=0.3339 (Placebo). Not statistically significant.

INTERGROUP ANALYSIS. Unpaired Wilcoxon test to compare Laminin values at 12 months between treatments has been performed:

Comparison groups	MA>1 at screening subpopulation - Somatostatin 0.1% v MA>1 at screening subpopulation - Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0551 [82]
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided

Notes:

[82] - Laminin levels of Somatostatin-treated patients were almost significantly lower than Laminin levels of placebo-treated patients at 12 months, indicating an arrest of Diabetic Retinopathy progression in Somatostatin group.

Statistical analysis title	Statistical analysis 2_Laminin_Brimonidine

Statistical analysis description:

INTRAGROUP ANALYSIS between initial (screening) and final (12 months) values by using a paired Wilcoxon test afforded:

P-value=0.7148 (Brimonidine). Not statistically significant.
P-value=0.3339 (Placebo). Not statistically significant.

INTERGROUP ANALYSIS. Unpaired Wilcoxon test to compare Laminin values at 12 months between treatments has been performed:

Comparison groups	MA>1 at screening subpopulation - Placebo v MA>1 at screening subpopulation - Brimonidine tartrate 0.2%
Number of subjects included in analysis	35
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.2153
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 3_ADMA_Somatostatin

Statistical analysis description:

INTRAGROUP ANALYSIS between initial (screening) and final (12 months) values by using a paired t-test afforded:

P-value=0.9208 (Somatostatin). Not statistically significant. Somatostatin-treated patients did not show an increase of ADMA levels.
P-value=0.0176* (Placebo). Statistically significant increase of ADMA levels (Diabetic Retinopathy progression).

INTERGROUP ANALYSIS. Unpaired t-test to compare ADMA values at 12 months between treatments has been performed:

Comparison groups	MA>1 at screening subpopulation - Placebo v MA>1 at screening subpopulation - Somatostatin 0.1%
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.2986
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 4_ADMA_Brimonidine

Statistical analysis description:

INTRAGROUP ANALYSIS between initial (screening) and final (12 months) values by using a paired t-test afforded:

P-value=0.4803 (Brimonidine). Not statistically significant.
P-value=0.0176* (Placebo). Statistically significant increase of ADMA levels (Diabetic Retinopathy progression).

INTERGROUP ANALYSIS. Unpaired t-test to compare ADMA values at 12 months between treatments has been performed:

Comparison groups	MA>1 at screening subpopulation - Placebo v MA>1 at screening subpopulation - Brimonidine tartrate 0.2%
Number of subjects included in analysis	35
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.409
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 5_CML_Somatostatin

Statistical analysis description:

INTRAGROUP ANALYSIS between initial (screening) and final (12 months) values by using a paired t-test afforded:

P-value=0.5705 (Somatostatin). Not statistically significant.
P-value=0.6848 (Placebo). Not statistically significant.

INTERGROUP ANALYSIS. Unpaired t-test to compare CML values at 12 months between treatments has been performed:

Comparison groups	MA>1 at screening subpopulation - Placebo v MA>1 at screening subpopulation - Somatostatin 0.1%
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.584
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Statistical analysis 6_CML_Brimonidine

Statistical analysis description:

INTRAGROUP ANALYSIS between initial (screening) and final (12 months) values by using a paired t-test afforded:

P-value=0.9023 (Brimonidine). Not statistically significant.
P-value=0.6848 (Placebo). Not statistically significant.

INTERGROUP ANALYSIS. Unpaired t-test to compare CML values at 12 months between treatments has been performed:

Comparison groups	MA>1 at screening subpopulation - Placebo v MA>1 at screening subpopulation - Brimonidine tartrate 0.2%
Number of subjects included in analysis	35
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.1761
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse Events (AEs) were reported from baseline visit to end of study visit (24 months).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups	
Reporting group title	Somatostatin 0.1%
Reporting group description:	
Patients received Somatostatin 0.1% as eye drops, 1 drop in each eye twice a day; once in the morning and once in the evening.	
Reporting group title	Placebo
Reporting group description:	
Patients received Placebo as eye drops, 1 drop in each eye twice a day; once in the morning and once in the evening.	
Reporting group title	Brimonidine tartrate 0.2%
Reporting group description:	
Patients received Brimonidine tartrate 0.2% as eye drops, 1 drop in each eye twice a day; once in the morning and once in the evening	

Serious adverse events	Somatostatin 0.1%	Placebo	Brimonidine tartrate 0.2%
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 145 (8.28%)	23 / 152 (15.13%)	21 / 152 (13.82%)
number of deaths (all causes)	0	2	1
number of deaths resulting from adverse events	0	2	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric cancer			

subjects affected / exposed	0 / 145 (0.00%)	0 / 152 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cancer			
subjects affected / exposed	0 / 145 (0.00%)	0 / 152 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma stage I			
subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Rectal adenocarcinoma			
subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal cancer			
subjects affected / exposed	0 / 145 (0.00%)	0 / 152 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma			
subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tongue neoplasm malignant stage unspecified			

subjects affected / exposed	0 / 145 (0.00%)	2 / 152 (1.32%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 145 (0.00%)	0 / 152 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			
subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Breast operation			
subjects affected / exposed	0 / 145 (0.00%)	0 / 152 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac pacemaker insertion			
subjects affected / exposed	1 / 145 (0.69%)	0 / 152 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip arthroplasty			
subjects affected / exposed	0 / 145 (0.00%)	0 / 152 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin neoplasm excision			
subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgery	Additional description: Planned spondylolistese operation.		
subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transurethral prostatectomy			

subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia repair			
subjects affected / exposed	0 / 145 (0.00%)	0 / 152 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	0 / 145 (0.00%)	0 / 152 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 145 (0.69%)	0 / 152 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 145 (0.69%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Priapism			
subjects affected / exposed	1 / 145 (0.69%)	0 / 152 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 145 (0.69%)	0 / 152 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diaphragmatic paralysis			

subjects affected / exposed	1 / 145 (0.69%)	0 / 152 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obliterative bronchiolitis			
subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 145 (0.69%)	0 / 152 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 145 (0.69%)	0 / 152 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 145 (0.00%)	0 / 152 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 145 (0.69%)	0 / 152 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 145 (0.00%)	2 / 152 (1.32%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 145 (0.69%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Atrial flutter			
subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 145 (0.00%)	0 / 152 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Atrioventricular block complete			
subjects affected / exposed	1 / 145 (0.69%)	0 / 152 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	2 / 145 (1.38%)	1 / 152 (0.66%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Basilar migraine			
subjects affected / exposed	0 / 145 (0.00%)	0 / 152 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coma			
subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			

subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radicular pain			
subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiculitis			
subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 145 (0.00%)	0 / 152 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ocular hyperaemia			
subjects affected / exposed	0 / 145 (0.00%)	0 / 152 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual impairment			
subjects affected / exposed	1 / 145 (0.69%)	0 / 152 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Colitis ischaemic			
subjects affected / exposed	0 / 145 (0.00%)	0 / 152 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 145 (0.69%)	0 / 152 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 145 (0.00%)	0 / 152 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 152 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			
subjects affected / exposed	0 / 145 (0.00%)	0 / 152 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 145 (0.00%)	0 / 152 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 145 (0.00%)	0 / 152 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis norovirus			
subjects affected / exposed	0 / 145 (0.00%)	0 / 152 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 145 (0.69%)	0 / 152 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 145 (0.69%)	0 / 152 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory tract infection			
subjects affected / exposed	1 / 145 (0.69%)	0 / 152 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 145 (0.00%)	0 / 152 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Somatostatin 0.1%	Placebo	Brimonidine tartrate 0.2%
Total subjects affected by non-serious adverse events			
subjects affected / exposed	107 / 145 (73.79%)	120 / 152 (78.95%)	133 / 152 (87.50%)
Investigations			
Blood triglycerides increased			
subjects affected / exposed	6 / 145 (4.14%)	9 / 152 (5.92%)	11 / 152 (7.24%)
occurrences (all)	7	10	11
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 145 (2.07%)	7 / 152 (4.61%)	6 / 152 (3.95%)
occurrences (all)	3	7	6
Sciatica			
subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	7 / 152 (4.61%)
occurrences (all)	0	1	7
Eye disorders			
Anterior chamber disorder			
subjects affected / exposed	10 / 145 (6.90%)	14 / 152 (9.21%)	8 / 152 (5.26%)
occurrences (all)	10	14	8
Conjunctival follicles			

subjects affected / exposed	1 / 145 (0.69%)	0 / 152 (0.00%)	15 / 152 (9.87%)
occurrences (all)	1	0	16
Conjunctival hyperaemia			
subjects affected / exposed	1 / 145 (0.69%)	0 / 152 (0.00%)	8 / 152 (5.26%)
occurrences (all)	1	0	9
Conjunctivitis allergic			
subjects affected / exposed	2 / 145 (1.38%)	1 / 152 (0.66%)	9 / 152 (5.92%)
occurrences (all)	2	1	10
Dry eye			
subjects affected / exposed	7 / 145 (4.83%)	9 / 152 (5.92%)	8 / 152 (5.26%)
occurrences (all)	10	9	9
Eye discharge			
subjects affected / exposed	9 / 145 (6.21%)	7 / 152 (4.61%)	3 / 152 (1.97%)
occurrences (all)	12	8	3
Eye pain			
subjects affected / exposed	16 / 145 (11.03%)	16 / 152 (10.53%)	32 / 152 (21.05%)
occurrences (all)	18	21	41
Eye pruritus			
subjects affected / exposed	11 / 145 (7.59%)	14 / 152 (9.21%)	13 / 152 (8.55%)
occurrences (all)	12	14	14
Eyelid oedema			
subjects affected / exposed	0 / 145 (0.00%)	1 / 152 (0.66%)	9 / 152 (5.92%)
occurrences (all)	0	1	12
Foreign body sensation in eyes			
subjects affected / exposed	6 / 145 (4.14%)	4 / 152 (2.63%)	12 / 152 (7.89%)
occurrences (all)	6	7	17
Lacrimation increased			
subjects affected / exposed	4 / 145 (2.76%)	6 / 152 (3.95%)	11 / 152 (7.24%)
occurrences (all)	4	7	13
Ocular hyperaemia			
subjects affected / exposed	12 / 145 (8.28%)	4 / 152 (2.63%)	33 / 152 (21.71%)
occurrences (all)	14	4	49
Vision blurred			
subjects affected / exposed	11 / 145 (7.59%)	1 / 152 (0.66%)	6 / 152 (3.95%)
occurrences (all)	14	2	7
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	7 / 145 (4.83%)	7 / 152 (4.61%)	4 / 152 (2.63%)
occurrences (all)	8	8	5
Back pain			
subjects affected / exposed	12 / 145 (8.28%)	10 / 152 (6.58%)	9 / 152 (5.92%)
occurrences (all)	14	11	9
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	8 / 145 (5.52%)	10 / 152 (6.58%)	5 / 152 (3.29%)
occurrences (all)	8	11	5
Nasopharyngitis			
subjects affected / exposed	26 / 145 (17.93%)	31 / 152 (20.39%)	24 / 152 (15.79%)
occurrences (all)	38	49	30
Urinary tract infection			
subjects affected / exposed	7 / 145 (4.83%)	4 / 152 (2.63%)	3 / 152 (1.97%)
occurrences (all)	9	8	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 June 2012	Protocol Amendment 1 (only applicable to France). A description of how travel expenses incurred by patients were to be reimbursed.
24 October 2012	Protocol Amendment 2 (All Countries). Change of party responsible for clinical operations. Biochemistry and urine samples were to be analysed locally instead of in a central laboratory.
20 February 2013	Protocol Amendment 3 (All countries). As an alternative to albumin excretion rate, albumin/creatinine ratio could be used to evaluate diabetic nephropathy.
03 September 2013	Protocol amendment 4 (All countries). The permitted window for scheduled follow-up visits and the discharge/early termination visit was widened from ± 5 days to ± 14 days.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported