



## 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:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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               |
| <b>Arm title</b>             | 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.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | 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.

|                  |                           |
|------------------|---------------------------|
| <b>Arm title</b> | Brimonidine tartrate 0.2% |
|------------------|---------------------------|

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**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.

| <b>Number of subjects in period 1</b>           | 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/m <sup>2</sup> |   |  |  |
| 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



| <b>End point values</b>     | Somatostatin<br>0.1% | Placebo            | Brimonidine<br>tartrate 0.2% |  |
|-----------------------------|----------------------|--------------------|------------------------------|--|
| Subject group type          | Reporting group      | Reporting group    | Reporting group              |  |
| Number of subjects analysed | 120 <sup>[1]</sup>   | 123 <sup>[2]</sup> | 96 <sup>[3]</sup>            |  |
| 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

| <b>Statistical analysis title</b> | 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                     |

| <b>Statistical analysis title</b> | 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 <sup>[4]</sup> | 123 <sup>[5]</sup> | 96 <sup>[6]</sup>         |  |
| 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 <sup>[7]</sup> | 84 <sup>[8]</sup> | 57 <sup>[9]</sup>         |  |
| 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 <sup>[10]</sup> | 94 <sup>[11]</sup> | 70 <sup>[12]</sup>        |  |
| 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

| <b>End point values</b>     | Somatostatin 0.1%  | Placebo            | Brimonidine tartrate 0.2% |  |
|-----------------------------|--------------------|--------------------|---------------------------|--|
| Subject group type          | Reporting group    | Reporting group    | Reporting group           |  |
| Number of subjects analysed | 41 <sup>[13]</sup> | 39 <sup>[14]</sup> | 39 <sup>[15]</sup>        |  |
| 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**

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | 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       |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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 <sup>[16]</sup> | 29 <sup>[17]</sup> | 26 <sup>[18]</sup>        |  |
| 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

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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                                       |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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 |           |

| <b>End point values</b>     | Somatostatin 0.1%  | Placebo            | Brimonidine tartrate 0.2% |  |
|-----------------------------|--------------------|--------------------|---------------------------|--|
| Subject group type          | Reporting group    | Reporting group    | Reporting group           |  |
| Number of subjects analysed | 41 <sup>[19]</sup> | 39 <sup>[20]</sup> | 39 <sup>[21]</sup>        |  |
| 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

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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                                       |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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 <sup>[22]</sup> | 29 <sup>[23]</sup> | 26 <sup>[24]</sup>        |  |
| 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

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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                                       |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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 <sup>[25]</sup> | 123 <sup>[26]</sup> | 96 <sup>[27]</sup>        |  |
| 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.<br>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 <sup>[28]</sup> | 123 <sup>[29]</sup> | 96 <sup>[30]</sup>        |  |
| 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 <sup>[31]</sup> | 123 <sup>[32]</sup> | 96 <sup>[33]</sup>        |  |
| 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       |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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 <sup>[34]</sup> | 123 <sup>[35]</sup> | 96 <sup>[36]</sup>        |  |
| 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 30°/35° eye progression assessed by ETDRS

|                         |   |
|-------------------------|---|
| End point title         | A.2. CFP 30°/35° 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 |   |

| <b>End point values</b>     | Somatostatin<br>0.1% | Placebo             | Brimonidine<br>tartrate 0.2% |  |
|-----------------------------|----------------------|---------------------|------------------------------|--|
| Subject group type          | Reporting group      | Reporting group     | Reporting group              |  |
| Number of subjects analysed | 119 <sup>[37]</sup>  | 123 <sup>[38]</sup> | 96 <sup>[39]</sup>           |  |
| 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

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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                                       |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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 measured 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<br>0.1% | Placebo             | Brimonidine<br>tartrate 0.2% |  |
|--------------------------------------|----------------------|---------------------|------------------------------|--|
| Subject group type                   | Reporting group      | Reporting group     | Reporting group              |  |
| Number of subjects analysed          | 135 <sup>[40]</sup>  | 136 <sup>[41]</sup> | 139 <sup>[42]</sup>          |  |
| 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<br>0.1% | Placebo             | Brimonidine<br>tartrate 0.2% |  |
|--------------------------------------|----------------------|---------------------|------------------------------|--|
| Subject group type                   | Reporting group      | Reporting group     | Reporting group              |  |
| Number of subjects analysed          | 133 <sup>[43]</sup>  | 134 <sup>[44]</sup> | 139 <sup>[45]</sup>          |  |
| 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 <sup>[46]</sup> | 106 <sup>[47]</sup> | 105 <sup>[48]</sup>       |  |
| 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 <sup>[49]</sup> | 122 <sup>[50]</sup> | 96 <sup>[51]</sup>        |  |
| 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

**Statistical analyses**

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | 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                     |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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:<br>Number of microaneurysms (mean) at screening and 24 months. |  |
| End point type  | Secondary  |
| End point timeframe:<br>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 <sup>[52]</sup>                                  | 21 <sup>[53]</sup>                        | 14 <sup>[54]</sup>  |  |
| 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:<br>INTRAGROUP ANALYSIS between initial (screening) and final (24 months) values by using a paired Wilcoxon test afforded:<br><br>P-value=0.0089* (Somatostatin). Statistically significant reduction in the number of microaneurysms.<br>P-value=0.1630 (Placebo). Not statistically significant. Number of microaneurysms was not reduced.<br><br>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   |

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Statistical analysis 2_MA number_Brimonidine   |
| Statistical analysis description:<br>INTRAGROUP ANALYSIS between initial (screening) and final (24 months) values by using a paired Wilcoxon test afforded:<br><br>P-value=0.5852 (Brimonidine). Not statistically significant.<br>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<br>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:<br>Mean Microaneurysm formation rate (new MA/year) at 24 months. |  |
| End point type  | Secondary  |
| End point timeframe:<br>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 <sup>[55]</sup> | 122 <sup>[56]</sup> | 96 <sup>[57]</sup>        |  |
| 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

|                                   |                             |
|-----------------------------------|-----------------------------|
| <b>Statistical analysis title</b> | 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                 |

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | 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  |

| <b>End point values</b>              | 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 <sup>[58]</sup>                                  | 21 <sup>[59]</sup>                        | 14 <sup>[60]</sup>  |  |
| 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

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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:<br>Mean microaneurysm disappearance rate (disappeared MA/year) at 24 months. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Screening and 24 months   |  |

| <b>End point values</b>              | Somatostatin 0.1%   | Placebo             | Brimonidine tartrate 0.2% |  |
|--------------------------------------|---------------------|---------------------|---------------------------|--|
| Subject group type                   | Reporting group     | Reporting group     | Reporting group           |  |
| Number of subjects analysed          | 118 <sup>[61]</sup> | 122 <sup>[62]</sup> | 96 <sup>[63]</sup>        |  |
| 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

**Statistical analyses**

|   |                             |
|---|-----------------------------|
| <b>Statistical analysis title</b>       | 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                     |

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | 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:<br>Mean microaneurysm disappearance rate (disappeared MA/year) at 24 months. |  |
| End point type  | Secondary  |
| End point timeframe:<br>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 <sup>[64]</sup>                                  | 21 <sup>[65]</sup>                        | 14 <sup>[66]</sup>  |  |
| 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                             |  |



| <b>End point values</b>              | 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 <sup>[67]</sup>                                  | 21 <sup>[68]</sup>                        | 14 <sup>[69]</sup>  |  |
| 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

| <b>Statistical analysis title</b> | 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   |

| <b>Statistical analysis title</b> | 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 <sup>[70]</sup>                                  | 21 <sup>[71]</sup>                        | 14 <sup>[72]</sup>  |  |
| 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         |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[73]</sup>                                  | 21 <sup>[74]</sup>                        | 14 <sup>[75]</sup>  |  |
| 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   |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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   |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | 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         |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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   |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | 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:<br>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:<br>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 <sup>[76]</sup> | 118 <sup>[77]</sup> | 90 <sup>[78]</sup>        |  |
| 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:<br>INTRAGROUP ANALYSIS between initial (screening) and final (12 months) values by using a paired Wilcoxon test afforded:<br><br>P-value=0.1757 (Somatostatin). Not statistically significant.<br>P-value=0.2816 (Placebo). Not statistically significant.<br><br>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                 |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | 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                             |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | 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 |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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                             |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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                     |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | 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 <sup>[79]</sup>                                  | 21 <sup>[80]</sup>                        | 14 <sup>[81]</sup>  |  |
| 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   |

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | 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   |

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | 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   |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | 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   |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 spondylolisthese 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 %

| <b>Non-serious adverse events</b>                     | 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 $\pm 5$ days to $\pm 14$ days.       |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported