CLINICAL STUDY REPORT

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

Study code:	4C-2011-02 (EUROCONDOR)	Study development phase:	II-III
EudraCT number:	2012-001200-38	Investigational medicinal product:	Somatostatin Brimonidine
Indication:	Diabetic retinopathy		
First patient, first visit:	05 February 2013	Last patient, last visit:	03 November 2015
Version:	Final 1.0	Date:	29 March 2019

This study was performed in compliance with Good Clinical Practice (E6).

2 SYNOPSIS

Name of the Sponsor: BCN Peptides S.A.	**Individual Study Table Referring to Module 5 of the Dossier** **Volume:** **Page:** **Study No.:**	**(For National Authority Use only)**
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Name of Active Ingredient: Somatostatin Brimonidine tartrate		

STUDY CODE:

4C-2011-02 (EUROCONDOR)

TITLE OF STUDY:

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

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STUDY CENTRES:

- CS01: AIBILI (Association for Innovation and Biomedical Research on Light and Image), Coimbra
- CS10: Moorfields Eye Hospital NHS Foundation Trust, London
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- CS58: Clinical Eye Research Centre - St. Paul's Eye Unit, Royal Liverpool University Hospital, Liverpool
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PUBLICATION (REFERENCE):

The following publications are based on the study:

Simó R, Hernández C; European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR). Neurodegeneration is an early event in diabetic retinopathy: therapeutic implications. Br J Ophthalmol. 2012 Oct;96(10):1285–90.

Hernández C, Simó R; European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR). Somatostatin replacement: a new strategy for treating diabetic retinopathy. Curr Med Chem. 2013;20(26):3251–7.

Simó R, Hernández C; European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR). Neurodegeneration in the diabetic eye: new insights and therapeutic perspectives. Trends Endocrinol Metab. 2014 Jan;25(1):23–33.

Hernández C, Simó-Servat O, Simó R. Somatostatin and diabetic retinopathy: current concepts and new therapeutic perspectives. Endocrine. 2014 Jun;46(2):209–14.

Frydkjaer-Olsen, Soegaard Hansen R, Simó R, Cunha-Vaz J, Peto T, Grauslund J; EUROCONDOR. Correlation between retinal vessel calibre and neurodegeneration in patients with type 2 diabetes mellitus in the European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR). Ophthalmic Res. 2016;56(1):10–6.

Simão S, Costa MÂ, Sun JK, Cunha-Vaz J, Simó R; European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR). Development of a normative database for multifocal electroretinography in the context of a multicenter clinical trial. Ophthalmic Res. 2017;57(2):107–17.

Trento M, Durando O, Lavecchia S, Charrier L, Cavallo F, Costa MA, et al. Vision related quality of life in patients with type 2 diabetes in the EUROCONDOR trial. Endocrine. 2017 Jul;57(1):83–8.

Santos AR, Ribeiro L, Bandello F, Lattanzio R, Egan C, Frydkjaer-Olsen U, García-Arumí J, et al. Functional and structural findings of neurodegeneration in early stages of diabetic retinopathy: cross-sectional analyses of Baseline data of the EUROCONDOR project. Diabetes. 2017 Sep;66(9):2503–10.

Simó R, Hernández C, Porta M, Bandello F, Grauslund J, Harding SP, et al. Effects of topically administered neuroprotective drugs in early stages of diabetic retinopathy. Results of the EUROCONDOR clinical trial. Diabetes. 2019 Feb;68(2):457–63.

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STUDY PERIOD (YEARS):

Date of first patient first visit: 05 February 2013

Date of last patient last visit: 03 November 2015

PHASE OF DEVELOPMENT:

II-III

SUMMARY:

The objective of this clinical trial was 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.

Neurodegenerative changes were assessed, as defined in the protocol, by multifocal electroretinography (mfERG). Implicit time (IT) and amplitude variables were used to define eye abnormality. For these analyses, the study eye was divided into 103 hexagons and each hexagon was classified as normal or abnormal based on reference IT and amplitude values from healthy volunteers.

Changes in the number of abnormal hexagons with respect to IT and amplitude were used to evaluate the effects of somatostatin and brimonidine eye drops in terms of disease prevention, progression arrest and regression with respect to IT and amplitude during 2 years of treatment.

Also evaluated were other variables related to 1) microvascular disease (Early Treatment Diabetic Retinopathy Study [ETDRS] level and number and activity of retinal microaneurysms [MAs]) assessed by colour fundus photography [CFP], 2) neurodegeneration (retinal thickness [RT], ganglion cell layer [GCL] thickness and retinal nerve fibre layer [RNFL] thickness) assessed by spectral domain optical coherence tomography (SD-OCT), 3) quality of vision (assessed by best corrected visual acuity [BCVA], the visual field [VF] and the Visual Function Questionnaire [VFQ-25]) and 4) serum DR biomarkers (laminin, asymmetric dimethylarginine [ADMA] and N-carboxymethyl-lysine [CML]).

Efficacy analyses based on mfERG in the primary efficacy analysis population (PE: n=410) showed no significant differences between somatostatin (n=135) or brimonidine (n=139) and placebo (n=136). It should be noted that placebo-treated patients did not show disease progression during the 2 years of the clinical trial based on the different efficacy variables analysed, making it unfeasible to evaluate the neuroprotective role of somatostatin and brimonidine eye drops in the PE.

For this reason, and following the advice of the Spanish Agency of Medicines and Medical Devices (AEMPS), complementary analyses were performed focused on retinal microaneurysms (MAs), a classical macroscopic parameter commonly used for diagnosis of DR. A subpopulation of patients more affected in terms of MAs was selected as it is well known that 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 (n=58), was evaluated.

The complementary analysis was centred on the automated evaluation of retinal microvascular damage in the whole area of the CFP 45˚/50˚ field 2 image. In the MA>1 at screening subpopulation, patients treated with somatostatin eye drops for 2 years (n=23) showed a significantly reduced number of MAs at the end of the study (change -1.5, p=0.0089) while patients treated with placebo (n=21) did not show a significant reduction in MA number (change -0.5, p=0.1630). Moreover, the

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efficacy of somatostatin eye drops was also analysed in an actively affected microvascular subpopulation, defined as patients presenting an MA turnover rate higher than 2 during the first 6 months of the study. In this subpopulation, similar results were obtained in terms of MA evolution.

In the MA>1 at screening subpopulation, somatostatin eye drops also gave an improvement in terms of neurodysfunction. Patients treated with somatostatin for 24 months showed a significant improvement in mfERG with respect to amplitude (change +2.84 nV/deg^2, p=0.0203) whereas no changes were observed in placebo-treated patients (change +0.33 nV/deg^2, p=0.8178). Evaluation of anatomical changes by SD-OCT revealed a significant neurodegeneration-associated thinning of the retina in the inner ring (IR) (change -1.93 µm, p=0.048) and outer ring (OR) (change -2.03 µm, p=0.035) in the placebo group after 24 months of treatment, whereas similar thinning was not observed in patients who received somatostatin eye drops (IR: change -0.57 µm, p=0.6295; OR: change -0.58 µm, p=0.5189).

In contrast, brimonidine eye drops did not show efficacy in the MA>1 at screening subpopulation. No significant differences in microvascular disease, mfERG or RT were observed in the brimonidine group (n=14) compared with the placebo group (n=21). Analysis of the evolution of these variables during the study in the brimonidine group revealed no significant changes at 24 months (MA number: change -0.6, p=0.5852; amplitude: change -1.16 nV/deg^2, p=0.4079), with the exception of a tendency of thinning of the retina in the IR (change -2.50 µm, p=0.0587) and OR (change -1.41 µm, p=0.1337), which indicates DR-associated retinal neurodegeneration.

A safety analysis was done in the population of patients who received at least one dose of study treatment (n=449). The main finding was that the percentage of patients with adverse events (AEs) that led to permanent discontinuation of study drug was higher for brimonidine (21.7%; most AEs were eye related) than for placebo (8.6%) and somatostatin (4.1%). Based on these safety results it can be concluded that brimonidine tartrate 0.2% has an unfavourable safety and tolerability profile and that somatostatin 0.1%, when administered twice daily (BID) for 2 years, has a favourable safety and tolerability profile.

In conclusion, brimonidine tartrate 0.2% eye drops did not arrest disease progression in DR patients with early microvascular effects. This, together with the unfavourable safety and tolerability profile, exclude brimonidine as a therapeutic option for DR.

Regarding somatostatin 0.1% eye drops, efficacy in the arrest of DR progression in diabetes patients with early microvascular effects has been demonstrated. Specifically, treatment with somatostatin eye drops for 2 years significantly reduced the number of MAs and arrested thinning of the retina in the IR and OR, indicating arrest of the gradual loss of retinal neurons, in a subpopulation of patients with MA>1 at screening. Thus, somatostatin prevented the progression of two of the main macroscopic hallmarks of the disease. Moreover, the neuroprotective role of somatostatin has been demonstrated, since an mfERG analysis based on changes in amplitude revealed that somatostatin eye drops significantly improved the neurofunction of retinal cells in diabetes patients with early microvascular effects.

These results, together with the favourable safety profile, identify somatostatin eye drops as an attractive non-invasive therapeutic approach for DR arrest in diabetes patients with early microvascular effects, for whom no treatment is currently approved.

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OBJECTIVES:

Primary Objectives:

- To assess whether somatostatin, administered topically, is able to prevent or arrest the development and progression of neurodegenerative changes.
- To assess whether brimonidine, administered topically, is able to prevent or arrest the development and progression of neurodegenerative changes.

Secondary Objectives:

- To determine the prevalence and to characterise functional and structural abnormalities related to neurodegeneration in those patients with or without detectable microvascular damage.
- To identify those patients most prone to progressive worsening of the retinopathy by identifying progression of DR using the ETDRS severity scale, BCVA, microvascular disease activity (MA turnover and RT) and neurodegenerative changes.
- To assess the correlation between the presence and progression of neuronal and glial alterations (mfERG abnormalities and GCL thickness) and the appearance and progression of the microvascular lesions (MA turnover and overall RT).
- To assess whether there is an effect on the visual-related quality of life in the early stages of nonproliferative DR as measured by the VFQ-25.
- To evaluate the local and systemic AEs of the selected drugs.

METHODOLOGY:

This was a multicentric, prospective, phase II-III, randomised controlled trial of parallel groups performed in reference institutions and involving close collaboration between medical assistants, endocrinologists and ophthalmologists.

This clinical trial comprised the 3 following phases:

Screening Phase

Recruitment and selection of patients were performed by the medical assistant, endocrinologist, and/or ophthalmologist as a team. Patients who signed the informed consent form participated in the clinical trial.

Inclusion

Patients selected in the Screening Phase were sent to the ophthalmologist for patient eligibility and randomisation.

Patient eligibility was assessed based on the ophthalmological examinations. Eligible patients were included in the clinical trial and randomly allocated in a 1:1:1 ratio to one of three treatment arms:

- Placebo (1 drop BID in each eye)
- Somatostatin 0.1% (1 drop BID in each eye)
- Brimonidine tartrate 0.2% (2 mg/ml: 1 drop BID in each eye)

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Treatment Phase

Patients were followed and treated during a 96-week period (24 months).

NUMBER OF PATIENTS (planned and analysed):

	Placebo	Somatostatin	Brimonidine	Total
No. planned:	150	150	150	450
No. screened:				569
No. randomised and treated:	152	145	152	449
Males/females:	104/48	93/52	99/53	296/153
Mean age (range):	63.2 (46.8-76.6)	63.2 (45.4-75.3)	63.5 (48.6-75.6)	63.3 (45.4-76.6)
No. analysed for efficacy:				
Primary efficacy analysis population (PE)	136	135	139	410
Complementary efficacy population (CE)	124	120	97	341
MA>1 at screening subpopulation	21	23	14	58
MA turnover>2 subpopulation	24	27	17	68
No. analysed for safety:				
Safety analysis population	152	145	152	449
No. who completed the study:	124	120	97	341

[NOTE: Definitions of populations are given in Statistical Methods section of the Synopsis (page 11)]

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Condition/Disease:

This outpatient study population consisted of a representative group of male and female type 2 diabetes patients with diabetic retinal disease with ETDRS level < 20 (50% of enrolled patients) or ETDRS levels 20 or 35 with presence of at least 1 MA in Field 2 between the superior and inferior arcades (50% of enrolled patients) in the Study Eye as determined by the Reading Centre.

Inclusion Criteria:

1) Patients with type 2 diabetes mellitus
2) Diabetes duration ≥ 5 years
3) Aged between 45-75 years-old
4) ETDRS level < 20 (MAs absent) (50% of enrolled patients)

   or

5) ETDRS levels 20 or 35 with presence of at least 1 MA in Field 2 between the superior and inferior arcades (50% of enrolled patients) in the study eye as determined by the Reading Centre
6) Informed Consent

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Exclusion Criteria:

1) Previous laser photocoagulation
2) Other diseases which may induce retinal degeneration (e.g. glaucoma)
3) Subject with a refractive error ≥ ± 5 diopter
4) Inadequate ocular media and/or pupil dilatation that did not permit good quality fundus photography
5) Renal failure (creatinine > 1.4 mg/dl)
6) HbA_{1C} > 10% in the previous 6 months and at screening
7) Subjects taking somatostatin or brimonidine, for any indication, in the previous 3 months
8) Subject had a condition or was in a situation which may put the subject at significant risk, may confound the study results or may interfere significantly with the patient's participation in the study
9) Pregnancy or nursing
10) Hypersensitivity to the active substances to be tested or to any of the excipients
11) Subject receiving systemic monoamine oxidase (MAO) inhibitor therapy or antidepressants which affect noradrenergic transmission (e.g. tricyclic antidepressants and mianserin)

TEST PRODUCTS, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

Somatostatin 0.1%, administered as eye drops of a sterile preserved solution. Batch number: G001 (expiry date: October 2014) / H001 (expiry date: October 2015).

Brimonidine tartrate 0.2%, administered as eye drops of a sterile preserved solution. Batch numbers: 120245, 120246 and 120247 (expiry date for all batches: January 2016).

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

Placebo (1.4% polyvinyl alcohol, 0.9% sodium chloride), administered as eye drops. Batch number: G001 (expiry date: October 2014) / H001 (expiry date: October 2015).

DURATION OF TREATMENT:

Patients were followed and treated during a 96-week period (24 months).

CRITERIA FOR EVALUATION:

DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS:

- Demographic characteristics: Age, gender, height, weight, body mass index (BMI)
- Medical History (including ocular history)
- Pregnancy test
- Ophthalmological examination
- Choice of study eye

EFFICACY:

The primary efficacy outcome measurement was the effectiveness of eye drugs in preventing or arresting abnormal mfERG.

For mfERG analyses, the study eye was divided into 103 hexagons, and IT and amplitude were measured in each hexagon. The normality of each hexagon was assessed with respect to the z-score, a measure of the mfERG change (IT or amplitude) in comparison to control mean and standard deviation values. An eye was considered abnormal, with respect to IT or amplitude, if it contained 6 or more abnormal hexagons.

Primary Efficacy Endpoint

- Change in total number of abnormal hexagons with respect to IT: success (no increase) versus failure (increase) at 24 months

Primary Efficacy-Related Endpoints

- Change in total number of abnormal hexagons with respect to IT between Baseline and 6 months, 12 months and 18 months: success versus failure
- Change in total number of abnormal hexagons with respect to amplitude between Baseline and 6 months, 12 months, 18 months and 24 months: success versus failure
- P1 IT, P1 IT Z score, P1 amplitude and P1 amplitude Z score by ring at Baseline, 6 months, 12 months, 18 months and 24 months
- Change in P1 IT, P1 IT Z score, P1 amplitude and P1 amplitude Z score by ring between Baseline and 6 months, 12 months, 18 months and 24 months
- Average P1 IT over rings, average P1 amplitude over rings, sum of P1 IT Z scores over rings and sum of P1 amplitude Z scores over rings at Baseline, 6 months, 12 months, 18 months and 24 months
- Primary Efficacy-Related Endpoint #1: Prevention (patient [eye] remained normal) at 6 months, 12 months, 18 months and 24 months in patients (eyes) identified as normal at Baseline - IT and amplitude
- Primary Efficacy-Related Endpoint #2: Progression arrest (number of abnormal hexagons did not increase) at 6 months, 12 months, 18 months and 24 months in patients (eyes) identified as abnormal at Baseline - IT and amplitude
- Primary Efficacy-Related Endpoint #3: Regression (patient [eye] changed to normal) at 6 months, 12 months, 18 months and 24 months in patients (eyes) identified as abnormal at Baseline - IT and amplitude
- Primary Efficacy-Related Endpoint #4: Change in total number of abnormal hexagons between Baseline and 6 months, 12 months, 18 months and 24 months - IT and amplitude
- Primary Efficacy-Related Endpoint #5: Prevention in patients (eyes) with normal status (<6 abnormal hexagons out of 103) at Baseline, and progression arrest in patients (eyes) with abnormal status (≥6 abnormal hexagons out of 103) at Baseline, between Baseline and 6 months, 12 months, 18 months and 24 months - IT and amplitude

Secondary Efficacy Endpoints

- CFP:
    - CFP 30°/35° - 7 fields classification at screening and 24 months and eye progression at 24 months (assessed by ETDRS)
    - CFP 45º/50º field 2 (inside the arcades): MA number at screening, 6 months, 12 months, 18 months and 24 months and change from screening, and MA formation, disappearance and turnover rates at 6 months and 12 months
- SD-OCT: RT, GCL thickness and RNFL thickness at Baseline, 6 months, 12 months, 18 months and 24 months

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- BCVA: BCVA score, count fingers, hand movements and light perception at Baseline, 6 months, 12 months, 18 months and 24 months
- The VF (assessed by VF test): global mean deviation and pattern deviation at Baseline and 24 months
- VFQ-25: sub-scale scores and composite scores at Baseline and 24 months

Efficacy Endpoints for the Complementary Analysis:

Raw data used was the same for main primary and secondary efficacy analysis and complementary analysis.

The selected endpoints for the complementary analysis were:

- CFP 45°/50° field 2: MA number at screening and 24 months and change from screening, and MA formation and disappearance rates at 24 months. MAs were counted in a fully automated way (reference document: MMO-21092016, dated 21 September 2016) in the whole area of the CFP 45°/50° field 2 image (inside and outside the arcades).
- mfERG: IT, amplitude and abnormal hexagons (segments) with respect to IT and amplitude at Baseline and 24 months. Raw mfERG data was filtered applying a 50 Hz filter (once) and a smooth filter (twice) using RETIscan software according to a procedure described in the Protocol for mfERG data filtering, dated 15 March 2017.
- SD-OCT: RT at Baseline and 24 months. A conversion factor (1.11) was applied to the OCT raw data obtained with Topcon to correct the differences between the two types of equipment used (Zeiss and Topcon).
- Blood biomarkers: laminin, ADMA and CML at screening and 12 months.

SAFETY:

Safety parameters were monitored by the investigators and any impairments were recorded and treated appropriately by endocrinologists or ophthalmologists. Safety was also monitored by the Adverse Events Sub-Committee and the Independent Data Monitoring Committee.

Safety Endpoints

- AEs and serious adverse events (SAEs) (assessed by inquiry and ophthalmological examination)
- Vital signs (systolic and diastolic blood pressure and heart rate)
- Intraocular pressure (IOP)
- Slit-lamp examination
- Ophthalmoscopy
- Overall drop discomfort
- Laboratory tests (haematology and biochemistry, including urinalysis [albumin excretion rate/albumin-creatinine ratio)
- Need for rescue treatment

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- Drug compliance

STATISTICAL METHODS:

A descriptive analysis was conducted for all study variables. Categorical variables are presented as counts and percentages. Continuous variables are presented as the mean, standard deviation, median, minimum and maximum.

DEFINITION OF POPULATIONS:

Efficacy:

All efficacy analyses were performed with the PE, with the exception of the complementary analyses, which were performed with the complementary efficacy population (CE) and the two subpopulations described below:

- PE: all randomised patients who received at least one dose of study medication and had a Baseline and at least one post-Baseline measurement for the primary outcome (mfERG), excluding patients with major protocol violations likely to affect the primary outcome. Number of patients per treatment arm: placebo 136, somatostatin 135 and brimonidine 139.
- CE: all randomised patients who completed the study (week 96/month 24), excluding patients with major protocol violations likely to affect the primary outcome. Number of patients per treatment arm: placebo 124, somatostatin 120 and brimonidine (97).
- MA>1 at screening subpopulation: subset of the CE with >1 MA at screening. Number of patients per treatment arm: placebo 21, somatostatin 23 and brimonidine 14.
- MA turnover>2 subpopulation: subset of the CE with an MA turnover rate of >2 between screening and 6 months. MA turnover is defined as sum of MA formation and MA disappearance rates. Number of patients per treatment arm: placebo 24, somatostatin 27 and brimonidine 17.

Safety:

The safety analysis population consisted of patients who received at least one dose of the study treatment (placebo 152, somatostatin 145 and brimonidine 152).

Demographic and Other Baseline Characteristics:

The demographic and Baseline characteristics have been analysed using the safety population.

Data for demographic and other Baseline characteristics are presented using descriptive statistics.

EFFICACY ANALYSIS:

Primary Efficacy Analysis

The primary efficacy endpoint was evaluated through changes in abnormal hexagons with respect to IT, assessed by mfERG. Success was defined as no increase in the number of abnormal hexagons. Success rates for somatostatin and brimonidine were separately compared with the corresponding success rate for placebo by Chi-square test with a two-sided alpha of 0.05.

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Frequency distribution of patients for whom the number of pathological hexagons with respect to IT increased / decreased / remained the same, presented by treatment group and by patient status (normal / abnormal) at Baseline and overall.

Primary Efficacy-Related Analysis

Data for the primary efficacy-related endpoints are presented as descriptive statistics or frequency distributions. Results for somatostatin and brimonidine were separately compared with the corresponding results for placebo by Fisher's exact test (primary efficacy-related endpoints #1, #2 and #3), Wilcoxon test (primary efficacy-related endpoint #4) or Chi-square test (primary efficacy-related endpoint #5).

Secondary Efficacy Analysis

Data for the secondary efficacy endpoints are presented as descriptive statistics, frequency distributions and/or shift tables.

Regression analyses were carried out to assess the correlation between the presence and progression of neuronal and glial alterations (mfERG abnormalities and GCL thickness) and the appearance and progression of microvascular lesions (MA turnover and RT).

Colour Fundus Photography

CFP 30º/35º - 7 fields: Frequency distributions of ETDRS level classification and eye progression (defined as an increase of ETDRS level of at least two steps) are presented for both eyes by treatment group and by time point (Baseline and 6, 12, 18 and 24 months).

Frequency of eye progression at 24 months was compared between somatostatin and placebo and brimonidine and placebo by Fisher's exact test.

Eyes were classified into two groups:

- ETDRS at screening = 10
- ETDRS at screening = 20 or 35A to 35F

These two groups were compared with respect to different primary efficacy-related endpoints and secondary endpoints.

Regression models were created to test associations with ETDRS (independent variable). Dependent variables included in the model were GCL thickness, RNFL thickness, BCVA, IT, amplitude, number of abnormal hexagons and the VF.

Fisher's exact tests were used to test the association between ETDRS group and percentage of abnormal eyes with respect to IT and amplitude.

CFP 45º/50º field 2: Descriptive statistics for MA number and change from screening, and MA formation rate (number of new MAs/year), disappearance rate (number of lost MAs/year) and turnover rate ([number of new MAs + number of lost MAs]/year), are presented for both eyes by treatment group and time point.

Spectral Domain Optical Coherence Tomography

The following are presented for both eyes by treatment group and time point (Baseline, 6, 12, 18 and 24 months).

- Descriptive statistics for RT, GCL thickness and RNFL thickness

Moreover, eyes were classified into three groups:

- Normal RT at Baseline (Normal)
- Decreased RT at Baseline (Thinning)
- Increased RT at Baseline (Thickening)

These three groups were compared with respect to different primary efficacy-related endpoints and secondary endpoints.

Regression models were created to test associations with RT (independent variable). Dependent variables included in the model were GCL thickness, RNFL thickness, BCVA, IT, amplitude, number of abnormal hexagons and the VF.

Fisher's exact tests were used to test the association between RT (central subfield [CSF], IR [nasal, superior, temporal, inferior], OR [nasal, superior, temporal, inferior] and average GCL) and percentage of abnormal eyes with respect to IT and amplitude.

Visual Function Questionnaire (VFQ-25)

Descriptive statistics for VFQ-25 sub-scales scores and a composite score are presented by treatment arm and Baseline ETDRS level (< 20 vs. 20 or 35) at Baseline and 24 months.

Best Corrected Visual Acuity (BCVA)

The following are presented for both eyes by treatment group and time point (Baseline and 6, 12, 18 and 24 months):

- Descriptive statistics for BCVA score
- Change from Baseline in BCVA score
- Frequency distribution for:
    - Count fingers
    - Hand movements
    - Light perception

Visual Field (VF) Test

The following are presented for both eyes by treatment group and time point (Baseline and 24 months):

- Descriptive statistics for:
    - Global mean deviation (absolute values and change from Baseline)
    - Pattern deviation (absolute values and change from Baseline)

Complementary Efficacy Analyses

Complementary efficacy analyses were planned after finalisation of the original Statistical Analysis Plan. Following the advice of the AEMPS, these complementary efficacy analyses were focused on retinal MAs, a classical macroscopic parameter commonly used for diagnosis of DR.

The aim was to assess whether somatostatin and brimonidine were able to arrest the progression of microvascular and neurodegenerative changes in patients with early retinal microvascular effects associated with DR, i.e. the MA>1 at screening subpopulation.

Additionally, three blood biomarkers of DR progression (laminin, ADMA and CML) were analysed.

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Differences in mean values and number and percentage of patients who fulfilled the relevant definition of success were analysed. For each treatment group, changes over time were compared statistically. In addition, data for somatostatin and brimonidine were statistically compared with data for placebo.

SAFETY ANALYSIS:

AEs and SAEs are presented as frequency distributions. Vital signs and IOP are presented as descriptive statistics for actual values and change from Baseline. Slit-lamp examination and ophthalmoscopy data are presented as frequency distributions and shift tables. Overall drop discomfort is presented as frequency distributions. Laboratory test data are presented as frequency distributions and shift tables. Drug compliance is presented as descriptive statistics.

RESULTS AND CONCLUSIONS:

STUDY PATIENTS

A total of 450 patients were randomised to one of the treatment arms: 152 patients to placebo, 146 to somatostatin 0.1% and 152 to brimonidine tartrate 0.2%. However, only 449 patients started study treatment and were included in the safety population, because one patient randomised to somatostatin did not initiate the assigned treatment. A total of 39 patients in the safety population (8.7%) were excluded from the PE. Thus, the PE included 410 patients (91.1%): 136 patients in the placebo arm, 135 patients in the somatostatin arm and 139 patients in the brimonidine arm. Of the randomised patients, 341 (75.8%) completed the study: 124 patients in placebo arm, 120 patients in somatostatin arm and 97 patients in the brimonidine arm. The main reason for early withdrawal from the study in the placebo and somatostatin arms was withdrawal of informed consent (7.2% and 9.0% of the safety analysis population, respectively). The main reasons for early withdrawal in the brimonidine arm were the development of allergic reactions to the study drug (9.9% of the safety population), interruption of the study medication for more than 1 month or repetition of the same AEs after reintroduction of the drug (7.9% of the safety population) and occurrence of AEs whose toxicity forced permanent interruption according to the Investigator's criteria (5.9% of the safety population).

DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS: SOMATOSTATIN

Most patients were male: 64.1% for somatostatin and 68.4% for placebo (safety population). The treatment arms were similar in terms of mean age (63.2 years for both treatment arms) and body mass index (31.0 kg/m^2 for somatostatin and 30.6 kg/m^2 for placebo). The most common comorbidities were hypertension (73.8% for somatostatin and 74.3% for placebo) and dyslipidaemia (69.0% for somatostatin and 71.7% for placebo).

At Baseline, most patients had a positive value for sphere power (indicating hyperopia) in the study eye (77.9% for somatostatin and 69.1% for placebo), with a mean (standard deviation) value of 1.2 (1.2) degrees for somatostatin and 1.4 (1.2) degrees for placebo. A minority of patients had a positive value for cylinder power (indicating hyperopic astigmatism) in the study eye (39.3% for somatostatin and 36.2% for placebo), with a mean (standard deviation) value of 1.0 (4.2) degrees for somatostatin and 0.6 (0.7) degrees for placebo. The mean (standard deviation) axis was 74.3 (60.9) degrees for somatostatin and 65.9 (56.3) degrees for placebo. For each slit-lamp and ophthalmoscopy parameter, clinically significant abnormalities in the study eye were present in a maximum of 2% of patients. Mean (standard deviation) intraocular pressure in the study eye was similar for the treatment arms: 15.9 (3.1) mmHg for somatostatin and 15.4 (3.0) mmHg for placebo. The right eye was chosen as the study eye in 50.3% of patients in the somatostatin arm and 44.1% of patients in the placebo arm.

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EFFICACY RESULTS: SOMATOSTATIN

Primary Endpoint

Efficacy in preventing or arresting neurodysfunction, i.e. success for the primary endpoint, was defined as no increase in the number of abnormal hexagons with respect to IT at 24 months compared to Baseline. A Chi-square test found no significant difference in the rate of success between the somatostatin and placebo arms (p=0.110). Specifically, 45.8% of somatostatin-treated patients and 56.1% of placebo-treated patients showed no change or a reduction in the number of abnormal hexagons with respect to IT at 24 months compared to Baseline.

Primary Efficacy-Related Endpoints

Evaluating success for the primary endpoint with respect to amplitude, i.e. efficacy in terms of no increase in the number of abnormal hexagons, a Chi-square test found no significant difference in the rate of success at 24 months between the somatostatin and placebo arms (p=0.634). Specifically, 57.5% of somatostatin-treated patients and 54.5% of placebo-treated patients showed no change or a reduction in the number of abnormal hexagons with respect to amplitude at 24 months compared to Baseline.

Chi-square tests found no evidence that the proportion of patients who did not show an increase in the number of abnormal hexagons with respect to IT or amplitude was different for somatostatin compared with placebo at the other time points analysed (6 months, 12 months and 18 months).

Primary Efficacy-Related Endpoint #1: Prevention

Fisher's exact tests show no evidence that prevention rates with respect to IT and amplitude were different for somatostatin compared with placebo.

Primary Efficacy-Related Endpoint #2: Progression Arrest

Fisher's exact tests show no evidence that the rate of progression arrest with respect to IT and amplitude was consistently different for somatostatin compared with placebo.

Primary Efficacy-Related Endpoint #3: Regression

Fisher's exact tests show no evidence that the rate of regression with respect to IT and amplitude was consistently different for somatostatin compared with placebo.

Primary Efficacy-Related Endpoint #4: Change in Total Number of Abnormal Hexagons

Wilcoxon tests show no evidence that change in the total number of abnormal hexagons with respect to IT and amplitude was consistently different for somatostatin compared with placebo.

Primary Efficacy-Related Endpoint #5: Prevention in Patients with Normal Status at Baseline and Progression Arrest in Patients with Abnormal Status at Baseline

Chi-square tests show no evidence that the success rate with respect to IT and amplitude was consistently different for somatostatin compared with placebo.

Secondary Efficacy Endpoints

Colour Fundus Photography

For the study eye, the rate of ETDRS level progression at 24 months, obtained by analysing CFP 30°/35° - 7 fields, was 3.4% for somatostatin and 4.9% for placebo. The difference between somatostatin and placebo was not statistically significant.

A descriptive analysis for MA number, obtained inside the arcades of the CFP 45°/50° field 2 image, showed that mean MA number decreased from 0.8 at screening to 0.4 at 24 months in the somatostatin arm. In the placebo arm, mean MA number was 0.6 at screening and 0.5 at 24 months.

Spectral Domain Optical Coherence Tomography

In SD-OCT analyses, RT, GCL thickness and RNFL thickness showed no noteworthy time trends in the somatostatin and placebo arms.

Best Corrected Visual Acuity

Mean BCVA score for the study eye showed no consistent differences between the somatostatin and placebo arms. Mean BCVA score for the study eye was 86.0 at Baseline and 86.2 at 24 months for somatostatin and 86.2 at Baseline and 86.7 at 24 months for placebo.

The Visual Field

VF parameters (global mean deviation and pattern deviation) showed no noteworthy differences between the somatostatin and placebo arms during the study.

Visual Function Questionnaire

For VFQ-25, there were no noteworthy differences between mean sub-scale and composite scores at Baseline and at 24 months in the somatostatin arm or the placebo arm.

It should be noted that placebo-treated patients did not show disease progression during the 2 years of the clinical trial based on the different efficacy variables analysed for primary and secondary endpoints, making it unfeasible to evaluate the neuroprotective role of somatostatin eye drops in the PE.

As explained above, following the recommendation of the AEMPS, efficacy was evaluated from a macroscopic point of view in a new set of complementary analyses. Specifically, the efficacy of somatostatin eye drops was evaluated in a subpopulation of the CE more affected by DR in terms of retinal MAs. Results obtained in the complementary analyses of the MA>1 at screening subpopulation are presented below.

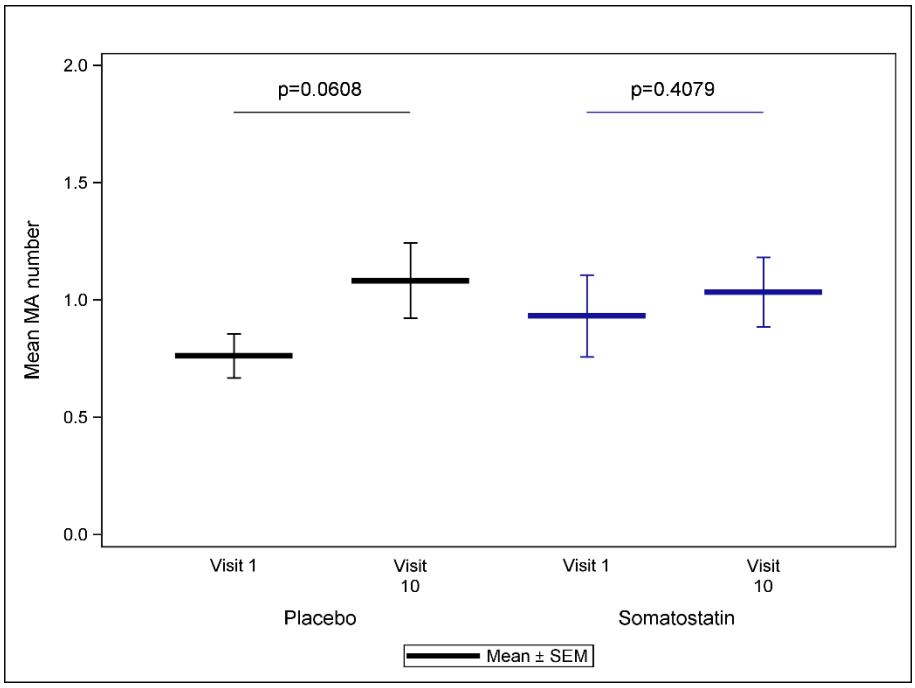
Complementary Efficacy Analyses

Colour Fundus Photography 45°/50° field 2

The complementary analysis was focused on the automated evaluation of microvascular retinal damage in the whole area of the CFP field 2 image.

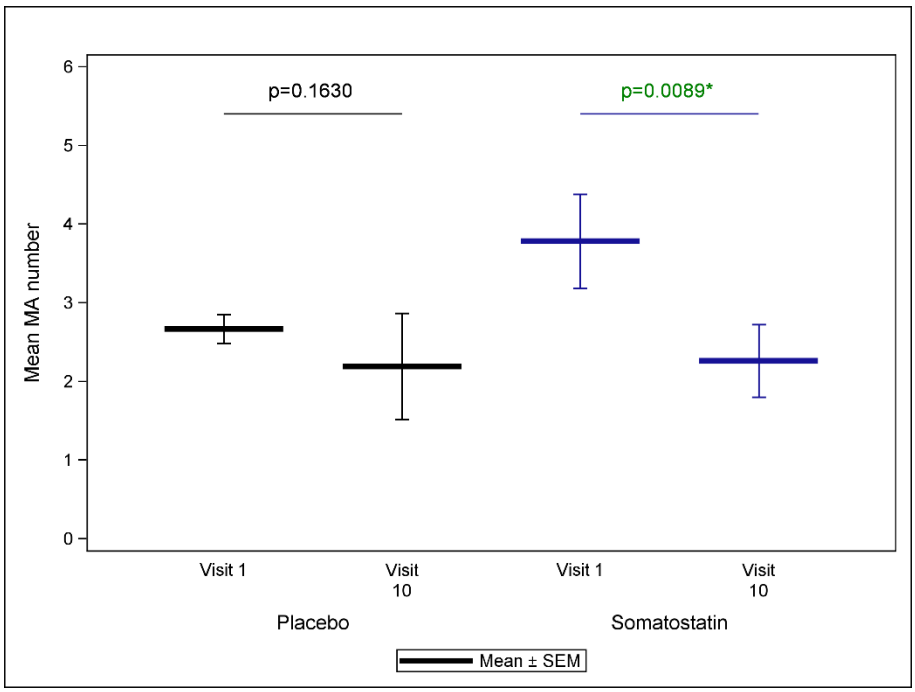
Whereas patients in the CE treated with placebo showed an increase in MA number between screening and 24 months (change +0.3, p=0.0608), an arrest in the appearance of microvascular lesions was observed in somatostatin-treated patients (change +0.1, p=0.4079) (Figure 1).

Figure 1 Mean Number of Microaneurysms (Complementary Efficacy Population)



In the MA>1 at screening subpopulation, treatment with somatostatin for 24 months significantly reduced the number of MAs (change -1.5, p=0.0089); patients treated with placebo did not show a significant reduction in number of MAs (change -0.5, p=0.1630) (Figure 2).

Figure 2 Mean Number of Microaneurysms (MA>1 at Screening Subpopulation)



Moreover, in the MA>1 at screening subpopulation, the MA formation rate at 24 months tended to be lower (0.23 vs. 0.51, p=0.4413) and the MA disappearance rate at 24 months tended to be higher (1.17 vs. 0.89, p=0.8151) in somatostatin-treated patients compared to the placebo group.

In the MA turnover>2 subpopulation, the MA formation rate at 24 months tended to be higher in the placebo arm than in the somatostatin arm (0.53 vs. 0.35, p=0.7903) and the MA disappearance rate at 24 months tended to be lower for placebo than for somatostatin (0.63 vs. 1.01, p=0.5791). Moreover, after 24 months of treatment, MA number tended to decrease in the somatostatin group

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(change -0.8, p=0.2108), but remained practically constant in the placebo group (change +0.2, p=0.8953). Furthermore, compared to the placebo group, a higher percentage of patients in the somatostatin group showed a reduction in MA number between screening and 24 months (57.7% vs. 37.5%, p=0.1713).

mfERG (Amplitude and IT)

Somatostatin treatment for 24 months significantly improved amplitude in the MA>1 at screening subpopulation (change +2.84 nV/deg^2, p=0.0203) but not in placebo-treated patients (change +0.33 nV/deg^2, p=0.8178) (Figure 3). Moreover, the percentage of patients who showed no change or an increase in amplitude between Baseline and 24 months was higher in the somatostatin group compared to the placebo group (69.6% vs. 42.9%, p=0.1271). Further analysis by rings indicated that the increase in amplitude in the somatostatin arm corresponded to the OR (change +7.91 nV/deg^2, p=0.0179) (Figure 4). No significant changes in IT were observed after 24 months of somatostatin treatment (change +0.13 ms, p=0.5642) (Figure 5).

Figure 3 Mean Amplitude (MA>1 at Screening Subpopulation)

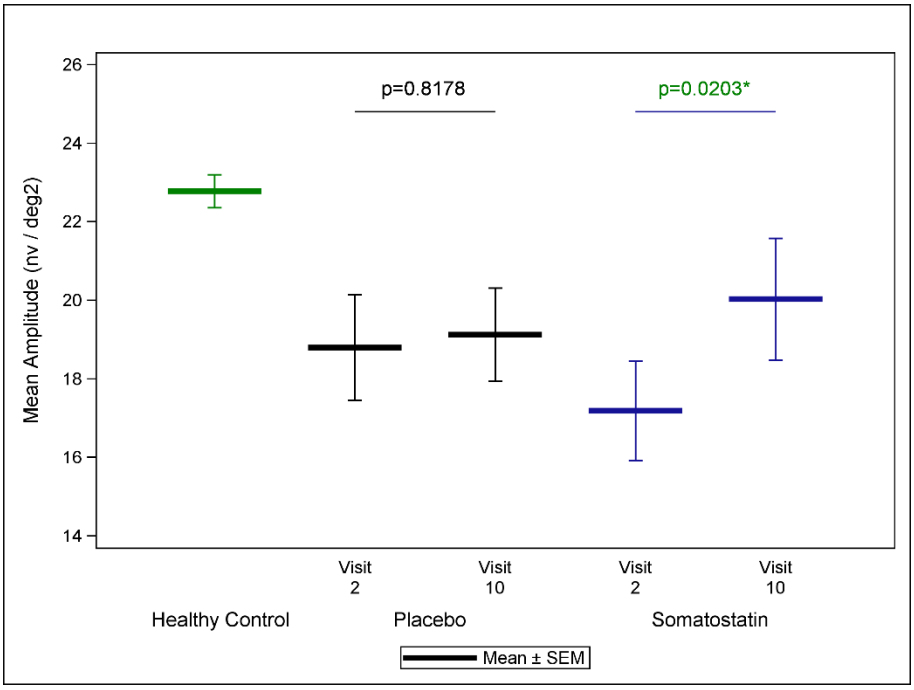


Figure 4 Mean Amplitude in the Outer Ring (MA>1 at Screening Subpopulation)

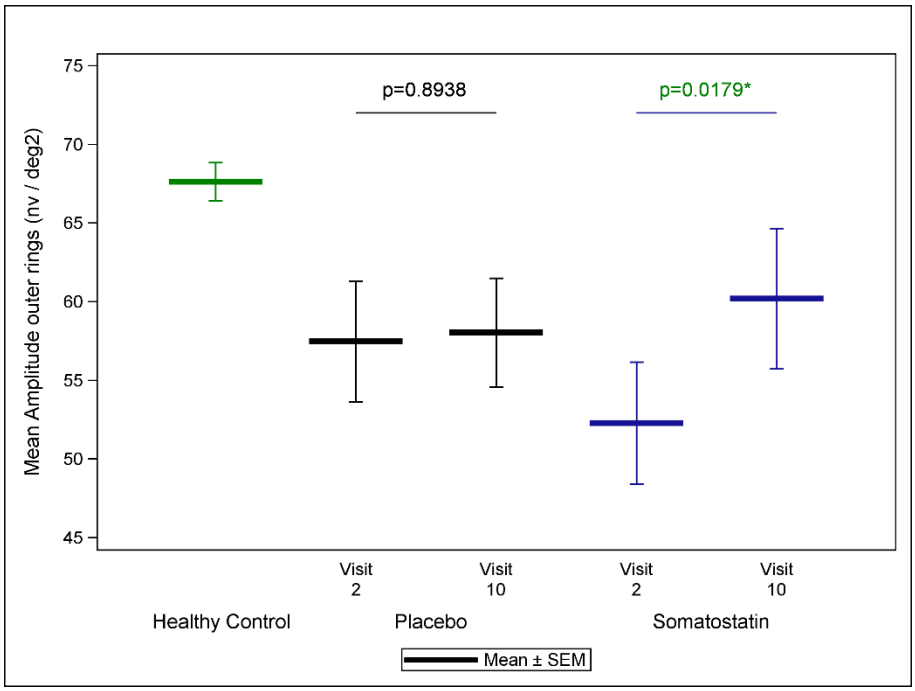
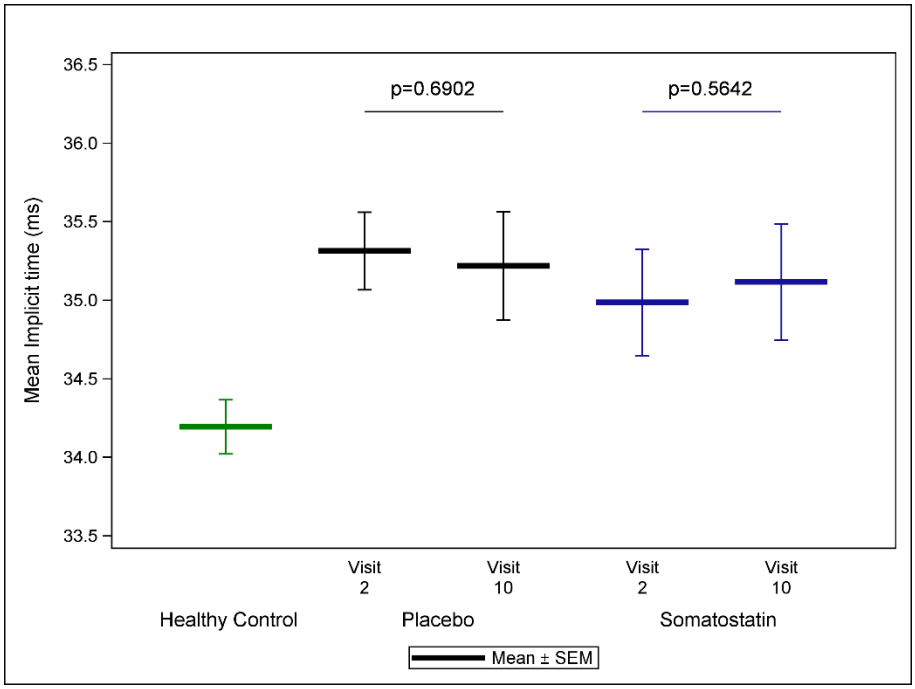


Figure 5 Mean Implicit Time (MA>1 at Screening Subpopulation)



Efficacy in preventing or arresting abnormal mfERG, i.e. maintaining or reducing the number of abnormal hexagons with respect to IT at 24 months compared to Baseline, was analysed in order to evaluate the primary efficacy endpoint in the MA>1 at screening subpopulation. In this subpopulation, a higher percentage of patients who showed no change or a reduction in the number of abnormal hexagons with respect to IT between Baseline and 24 months was observed in the somatostatin group compared to the placebo group (56.5% vs. 38.1%, p=0.2457) (Figure 6). Similar results were obtained when analysing the change in the number of abnormal hexagons between Baseline and 24 months with respect to amplitude (rate of success 73.9% for somatostatin-treated patients vs. 52.4% for placebo-treated patients, p=0.2106) (Figure 7), although the observed differences between the somatostatin and placebo arms were not statistically significant.

Figure 6 Percentage of Patients with Success (No Change or a Reduction) for Number of Abnormal Hexagons with Respect to Implicit Time (MA>1 at Screening Subpopulation)

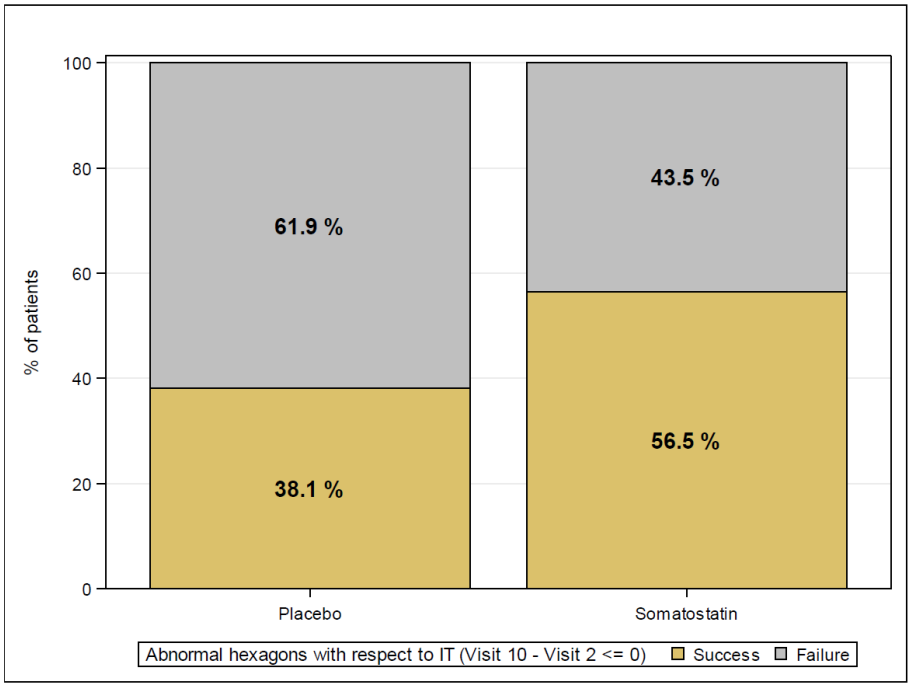
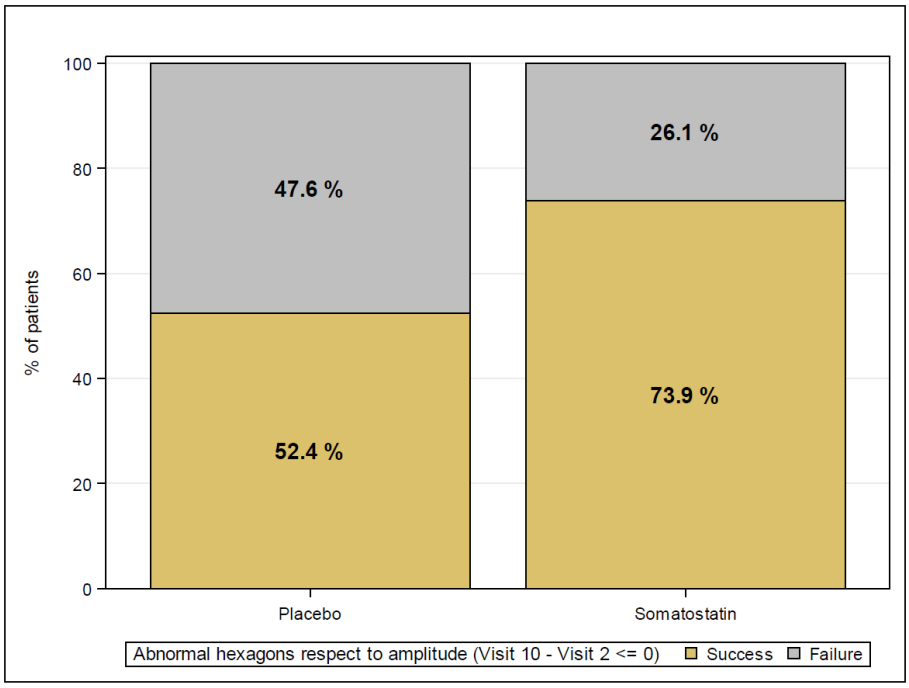


Figure 7 Percentage of Patients with Success (No Change or a Reduction) for Number of Abnormal Hexagons with Respect to Amplitude (MA>1 at Screening Subpopulation)



Spectral Domain Optical Coherence Tomography

SD-OCT analysis in the MA>1 at screening subpopulation revealed significant thinning of the retina in the IR (change -1.93 µm, p=0.0477) and OR (change -2.03 µm, p=0.0349) between Baseline and 24 months in the placebo group, indicating DR progression in this group (Figure 8 and Figure 9). No such thinning of the retina in the IR (change -0.57 µm, p=0.6295) or OR (change -0.58 µm, p=0.5189) was observed in patients who received somatostatin eye drops for 24 months (Figure 8 and Figure 9). Significant differences in CSF RT between Baseline and 24 months were not observed in the placebo group (change -0.36 µm, p=0.8060) or the somatostatin group (change +1.43 µm, p=0.2773).

Figure 8 Mean Retinal Thickness in the Inner Ring (MA>1 at Screening Subpopulation)

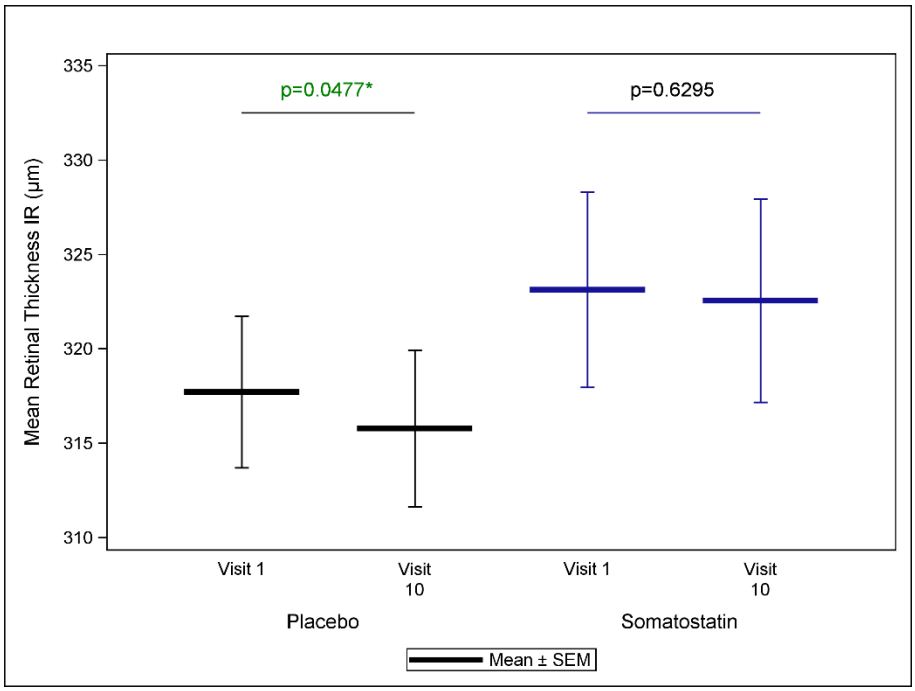
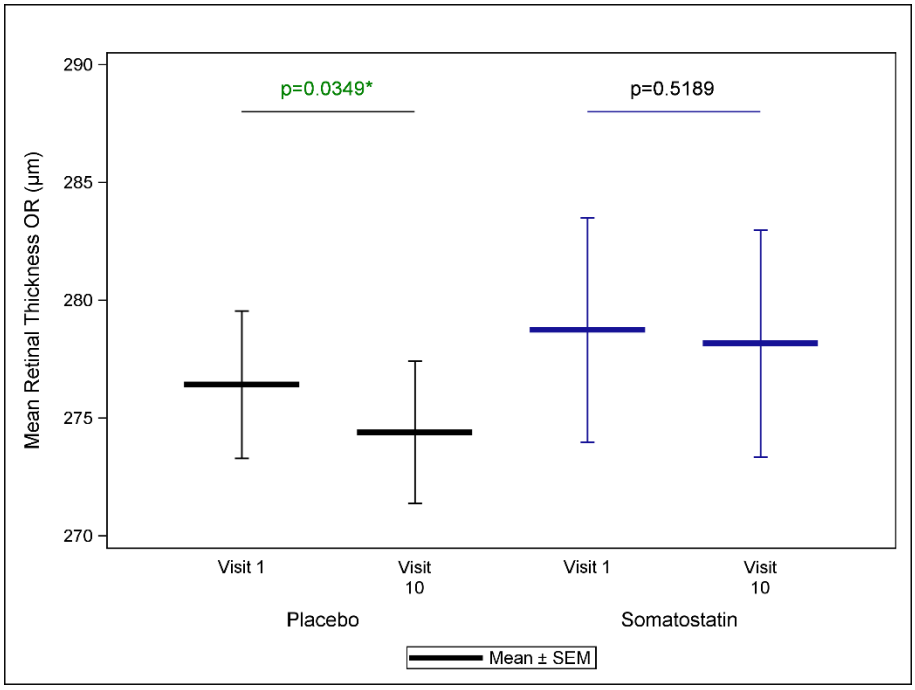


Figure 9 Mean Retinal Thickness in the Outer Ring (MA>1 at Screening Subpopulation)



Blood Biomarkers

Levels of laminin, ADMA and CML in serum samples collected at screening, 6 months (Visit 1) and 12 months (Visit 6) were determined in order to monitor the progression of DR, since elevated serum levels of these blood biomarkers has been associated with this disease.

In the MA>1 at screening subpopulation, a tendency of reduced laminin levels at 12 months compared to screening was observed in the somatostatin group (change -78.91 ng/mL, p=0.2935), whereas a tendency of increased laminin levels was observed in the placebo arm (change +29.75 ng/mL, p=0.3339), indicating DR progression in this group (Figure 10). Compared to the placebo group, a

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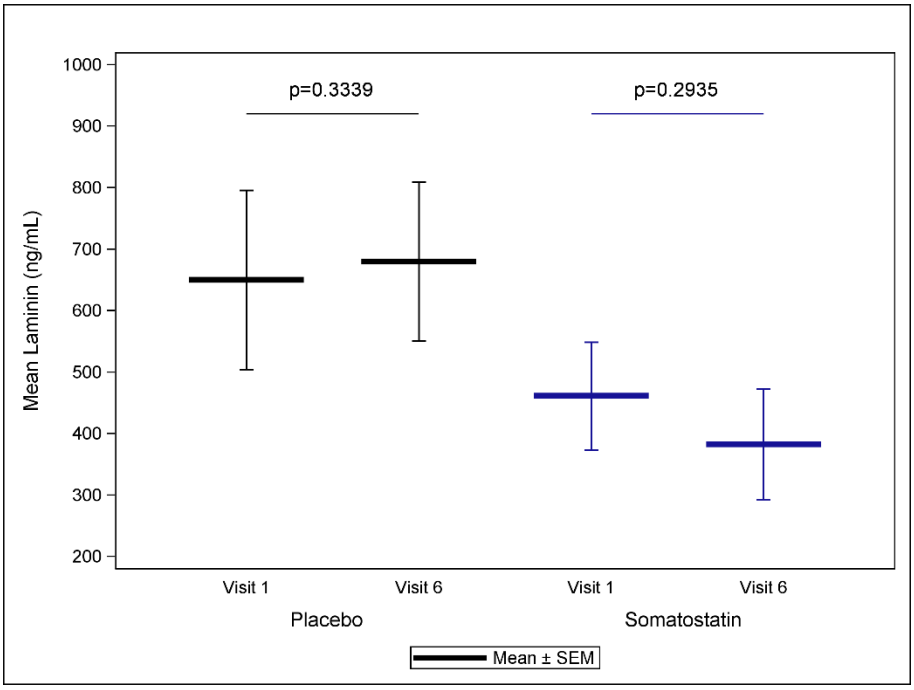
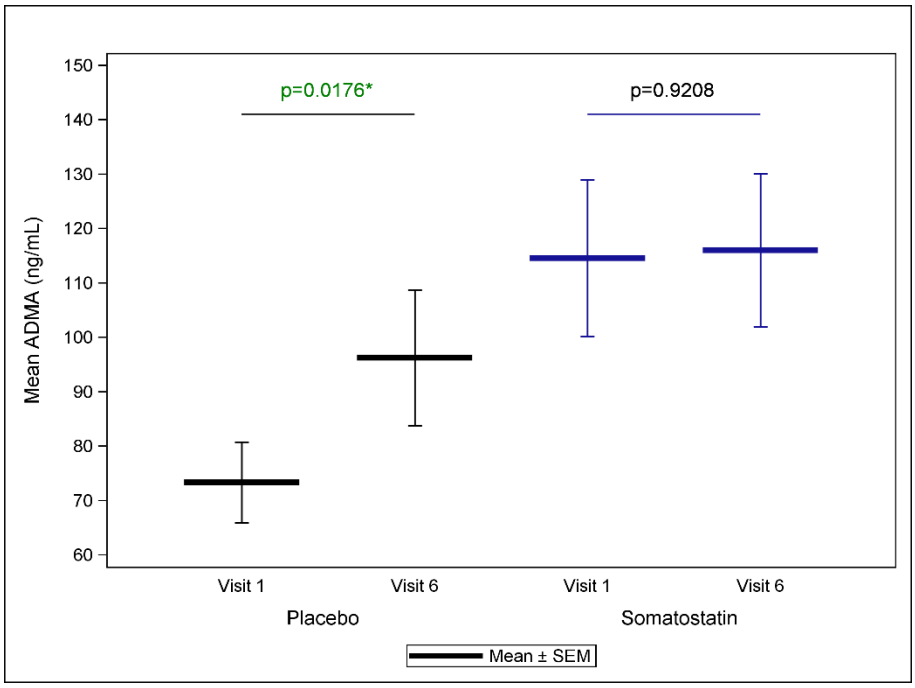
higher percentage of somatostatin-treated patients showed no change or a reduction in laminin (68.4% vs. 42.9%, p=0.1253).

Figure 10 Mean Laminin Level (MA>1 at Screening Subpopulation)



Serum levels of ADMA were significantly elevated in placebo-treated patients at 12 months (change +22.91 ng/mL, p=0.0176), indicating DR progression in this group. In contrast, somatostatin-treated patients showed practically constant levels of ADMA (change +1.46 ng/mL, p=0.9208) (Figure 11). Levels of CML showed no significant change in either the placebo group (change -10.80 ng/mL, p=0.6848) or the somatostatin group (change -10.43 ng/mL, p=0.5705).

Figure 11 Mean ADMA Level (MA>1 at Screening Subpopulation)



SAFETY RESULTS: SOMATOSTATIN

During the study, 107 patients (74%) in the somatostatin arm and 120 patients (79%) in the placebo arm had at least one AE. SAEs were recorded in 12 patients (8%) in the somatostatin arm and 23 patients (15%) in the placebo arm.

In the somatostatin arm, 506 AEs were reported, of which 89 AEs (18%) were considered to be related to study drug (related, probably related or possibly related); 332 AEs (66%) were not eye related and 490 AEs (97%) were mild or moderate in severity. In the placebo arm, 563 AEs were reported, of which 85 AEs (15%) were considered to be related to study drug; 396 AEs (70%) were not eye related and 539 AEs (96%) were mild or moderate in severity.

Twelve (12) patients (8%) in the somatostatin arm and 23 patients (15%) in the placebo arm reported at least one SAE. A total of 19 SAEs were reported in the somatostatin arm and 34 SAEs in the placebo arm. One SAE in the somatostatin arm (Visual impairment) was eye related, but none of the SAEs were considered to be related to study drug.

There were 2 fatal AEs in the placebo arm: Cardiac failure and Metastases to bone. Both fatal AEs were SAEs and were graded as severe, but were considered to be unrelated to placebo treatment. There were no suspected unexpected serious adverse reactions (SUSARs) or other serious adverse reactions (SARs).

In the somatostatin arm, 6 AEs in 6 patients (4.1%) led to permanent discontinuation of study drug: Ocular hyperaemia, Schizophrenia, Myalgia, Cystoid macular oedema, Viral infection and Nasopharyngitis. In the placebo arm, 17 AEs in 13 patients (8.6%) led to permanent discontinuation of study drug: Benign prostatic hyperplasia, Blepharitis, Cardiac failure, Coma, Cornel abrasion, Dyspnoea, Headache, Keratitis, Metastases to bone, Myocardial infarction, Ocular discomfort, Photopsia, Pigmentary glaucoma, Punctate keratitis, Rectal adenocarcinoma, Tachycardia and Tongue neoplasm malignant stage unspecified.

CONCLUSIONS: SOMATOSTATIN

Based on the results of this study it can be concluded that somatostatin 0.1% has a favourable safety and tolerability profile. The percentage of patients who suffered AEs was similar in the somatostatin and placebo arms: 74% and 79%, respectively. The percentage of patients who suffered SAEs was lower for somatostatin (8%) than for placebo (15%), as was the percentage of patients with AEs that led to permanent discontinuation of study drug (4.1% vs. 8.6%). Most AEs in patients receiving somatostatin were mild or moderate in severity (97%). Less than a fifth of AEs in the somatostatin arm were related to study drug. There were no SUSARs or other SARs.

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In the evaluation of success for the primary endpoint, i.e. efficacy in preventing or arresting neurodysfunction in terms of no increase in the number of abnormal hexagons with respect to IT, there was no difference between the somatostatin and placebo arms. Results for the primary efficacy-related and secondary efficacy endpoints show no consistent differences between the somatostatin and placebo arms. RT, GCL thickness, RNFL thickness, BCVA score, VF parameters (global mean deviation and pattern deviation) and VFQ-25 showed no noteworthy changes between Baseline and 24 months in the somatostatin arm or the placebo arm. Moreover, these results reveal that placebo-treated patients did not show DR progression during the 2 years of the clinical trial, making it unfeasible to evaluate the neuroprotective role of somatostatin eye drops in the PE.

For this reason, and following the recommendation of the AEMPS, complementary analyses focused on retinal MAs, a classical macroscopic parameter commonly used for diagnosis of DR, were performed. Specifically, the efficacy of somatostatin eye drops in a subpopulation of the PE with early microvascular effects, i.e. >1 MA at screening, was evaluated.

Collectively, the results of the complementary efficacy analyses demonstrate that treatment with somatostatin eye drops for 2 years reduces microvascular lesions and arrests neurodegeneration of the inner and outer retina in patients with early DR who have a higher number of MAs at screening, thereby arresting the progression of 2 of the main macroscopic hallmarks of the disease. Moreover, mfERG analysis based on changes in amplitude values confirmed that neurodysfunction, observed in retinal cells of patients with early microvascular effects associated with DR, was improved after somatostatin eye drop administration for 2 years, demonstrating the neuroprotective role of somatostatin eye drops in these patients. Finally, the DR biomarker results support the conclusion that somatostatin eye drops may reduce the progression of DR. In summary, the complementary efficacy analyses have demonstrated the efficacy of somatostatin eye drops in the arrest of DR progression in diabetes patients with early microvascular effects.

In conclusion, somatostatin 0.1% eye drops appear to be an attractive non-invasive therapeutic approach for DR arrest in diabetes patients with early microvascular disease, for whom no treatment has so far been approved.

DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS: BRIMONIDINE

Most patients were male: 65.1% for brimonidine and 68.4% for placebo (safety population). The treatment arms were similar in terms of mean age (63.5 years for brimonidine and 63.2 years for placebo) and body mass index (30.7 kg/m^2 for brimonidine and 30.6 kg/m^2 for placebo). The most common comorbidities were hypertension (71.1% for brimonidine and 74.3% for placebo) and dyslipidaemia (72.4% for brimonidine and 71.7% for placebo).

At Baseline, most patients had a positive value for sphere power (indicating hyperopia) in the study eye (69.7% for brimonidine and 69.1% for placebo), with a mean (standard deviation) value of 1.2 (1.1) degrees for brimonidine and 1.4 (1.2) degrees for placebo. Hyperopia is commonly observed in patients with DR, because high glucose levels can affect the shape of the lens, causing or exacerbating refractive errors. A minority of patients had a positive value for cylinder power (indicating hyperopic astigmatism) in the study eye (42.8% for brimonidine and 36.2% for placebo), with a mean (standard deviation) value of 0.7 (0.8) degrees for brimonidine and 0.6 (0.7) degrees for placebo. The mean (standard deviation) axis was 75.1 (63.1) degrees for brimonidine and 65.9 (56.3) degrees for placebo. For each slit-lamp and ophthalmoscopy parameter, clinically significant abnormalities in the study eye were present in a maximum of 2% of patients. Mean (standard deviation) intraocular pressure in the study eye was similar for the treatment arms: 15.8 (3.0) mmHg for brimonidine and

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15.4 (3.0) mmHg for placebo. The right eye was chosen as the study eye in 55.9% of patients in the brimonidine arm and 44.1% of patients in the placebo arm.

EFFICACY RESULTS: BRIMONIDINE

Primary Efficacy Endpoint

Efficacy in preventing or arresting neurodysfunction, i.e. success for the primary endpoint, was defined as no increase in the number of abnormal hexagons with respect to IT at 24 months compared to Baseline. A Chi-square test found no statistically significant difference in the rate of success between the brimonidine and placebo arms (p=0.294). Specifically, 49.0% of patients in the brimonidine arm and 56.1% of patients in the placebo arm had success for the primary endpoint.

Primary Efficacy-Related Endpoints

Evaluating success for the primary endpoint with respect to amplitude, i.e. efficacy in terms of no increase in the number of abnormal hexagons, a Chi-square test found no statistically significant difference in the rate of success at 24 months between the brimonidine and placebo arms (p=0.177) Specifically, 63.5% of patients in the brimonidine arm and 54.5% of patients in the placebo arm had success for the primary efficacy endpoint with respect to amplitude at 24 months.

Primary Efficacy-Related Endpoint #1: Prevention

Fisher's exact tests show no evidence that prevention rates with respect to IT and amplitude were different for brimonidine compared with placebo.

Primary Efficacy-Related Endpoint #2: Progression Arrest

Fisher's exact tests show no evidence that rates of progression with respect to IT and amplitude were different for brimonidine compared with placebo.

Primary Efficacy-Related Endpoint #3: Regression

Fisher's exact tests show no evidence that prevention rates with respect to IT and amplitude were consistently different for brimonidine compared with placebo.

Primary Efficacy-Related Endpoint #4: Change in Total Number of Abnormal Hexagons

Wilcoxon tests show no evidence that change in the total number of abnormal hexagons with respect to IT and amplitude was different for brimonidine compared with placebo.

Primary Efficacy-Related Endpoint #5: Prevention in Patients with Normal Status at Baseline and Progression Arrest in Patients with Abnormal Status at Baseline

Chi-square tests show no evidence that success rates with respect to IT and amplitude were different for brimonidine compared with placebo.

Secondary Efficacy Endpoints

Colour Fundus Photography

For the study eye, the rate of ETDRS level progression at 24 months, obtained by analysing CFP 30°/35° - 7 fields, was 6.3% for brimonidine and 4.9% for placebo.

A descriptive analysis of MA number, obtained inside the arcades of the CFP 45°/50° field 2 image, showed that mean MA number remained at 0.6 in the brimonidine arm. In the placebo arm, mean MA number was 0.6 at screening and 0.5 at 24 months.

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Spectral Domain Optical Coherence Tomography

In SD-OCT analyses, RT, GCL thickness and RNFL thickness showed no noteworthy time trends in the brimonidine and placebo arms.

Best Corrected Visual Acuity

Mean BCVA score for the study eye showed no noteworthy differences between the brimonidine and placebo arms. Mean BCVA score for the study eye was 86.2 at Baseline and 85.7 at 24 months for brimonidine and 86.2 at Baseline and 86.7 at 24 months for placebo.

The Visual Field

VF parameters (global mean deviation and pattern deviation) showed no noteworthy differences between the brimonidine and placebo arms during the study

Visual Function Questionnaire

For VFQ-25, there were no noteworthy differences between mean sub-scale and composite scores at Baseline and at 24 months in the brimonidine arm or the placebo arm.

It should be noted that placebo-treated patients did not show disease progression during the 2 years of the clinical trial based on the different efficacy variables analysed for primary and secondary endpoints, making it unfeasible to evaluate the neuroprotective role of brimonidine eye drops in the PE.

As explained above, following the recommendation of the AEMPS, efficacy was evaluated from a macroscopic point of view in a new set of complementary analyses. Specifically, the efficacy of brimonidine eye drops was evaluated in a subpopulation of the CE more affected by DR in terms of retinal MAs. Results obtained in the complementary analyses of the MA>1 at screening subpopulation are presented below.

Complementary Efficacy Analyses

The complementary analysis was focused on the automated evaluation of microvascular retinal damage in the whole eye area of the CFP40˚/45˚ field 2 image. A comparison of number of MAs between screening and 24 months in patients who completed the study (CE) revealed disease progression in patients treated with brimonidine (change in MA number +0.4, p=0.0158).

In accordance with these results, brimonidine did not show efficacy in patients with early microvascular effects. In the MA>1 at screening subpopulation, there were no significant differences between brimonidine and placebo for microvascular variables, mfERG variables, RT assessed by SD-OCT or blood biomarkers of DR. Moreover, no significant changes between screening and 24 months in MA number (change -0.6, p=0.5852), IT (change 0.00 ms, p=0.5313) or amplitude (change -1.16 nV/deg^2, p=0.4079) were observed in the brimonidine group. Furthermore, compared to Baseline, number of abnormal hexagons with respect to amplitude showed a significant increase at 24 months in the brimonidine group (change +4.29, p=0.0498) but not in the placebo group (change -2.86, p=0.8386).

SD-OCT in the MA>1 at screening subpopulation revealed significant thinning of the retina in the IR (change -1.93 µm, p=0.0477) and OR (change -2.03 µm, p=0.0349) between Baseline and 24 months in the placebo group, and a tendency of reduced thickness of these retinal zones in the brimonidine group (IR: change -2.50 µm, p=0.0587; OR: change -1.41 µm, p=0.1337), indicating DR-associated retinal neurodegeneration in both groups. Moreover, near-significant thinning of the CSF retinal zone

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between Baseline and 24 months was observed in brimonidine-treated patients (change -3.41 µm, p=0.0601), but not in placebo-treated patients (change -0.36 µm, p=0.8060).

Regarding DR biomarker evolution in this subpopulation of patients, placebo-treated patients showed a tendency of increased laminin levels (change +29.75 ng/mL, p=0.3339) and a significant increase in ADMA levels (change +22.91 ng/mL, p=0.0176) between screening and 12 months, indicating DR progression. No significant differences between screening and 12 months were observed in brimonidine-treated patients (laminin: change +113.48 ng/mL, p=0.7148; ADMA: change +7.74 ng/mL, p=0.4803). CML levels showed no meaningful change between screening and 12 months in either treatment group.

In the MA turnover>2 subpopulation, brimonidine-treated patients showed a significant increase in MA number between screening and 24 months (change +1.1, p=0.0484); MA number remained practically constant in placebo-treated patients (change +0.2, p=0.8953). Moreover, the percentage of patients who showed a decrease or no change in MA number between screening and 24 months was significant lower in the brimonidine group compared to the placebo group (35.3% vs 70.8%, p=0.0308).

SAFETY RESULTS: BRIMONIDINE

During the study, 133 patients (88%) in the brimonidine arm and 120 patients (79%) in the placebo arm had at least one AE. SAEs were recorded in 21 patients (14%) in the brimonidine arm and 23 patients (15%) in the placebo arm.

In the brimonidine arm, 640 AEs were reported, of which 231 AEs (36%) were considered to be related (related, probably related or possibly related) to study drug; 311 AEs (49%) were eye related and 610 AEs (95%) were mild or moderate in severity. In the placebo arm, 563 AEs were reported, of which 85 AEs (15%) were considered to be related to study drug; 396 AEs (70%) were not eye related and 539 AEs (96%) were mild or moderate in severity.

A total of 26 SAEs were reported in the brimonidine arm and 34 in the placebo arm. Two SAEs in the brimonidine arm (Ocular hyperaemia and Cardiac arrest) were considered to be related to study drug; two SAEs in the brimonidine arm (Glaucoma and Ocular hyperaemia) were eye related.

There were 2 fatal AEs in the placebo arm: Cardiac failure and Metastases to bone. Both fatal AEs were SAEs and were graded as severe. The event of Cardiac failure was judged to have an unlikely relationship to study drug and the event of Metastases to bone was judged to be unrelated to study drug. There was also 1 fatal AE in the brimonidine arm: Cardiac arrest. It was an SAE, was graded as severe, was considered to have a possible relationship to study treatment and was assessed as a SUSAR.

In addition to the SUSAR, there was 1 other SAR: Ocular hyperaemia in a patient in the brimonidine arm. It was graded as moderate and led to permanent discontinuation of study drug.

In the brimonidine arm, 59 AEs in 33 patients (21.7%) led to permanent discontinuation of study drug (when each preferred term was counted only once per patient). The most frequent AE leading to permanent discontinuation of study drug was Ocular hyperaemia (16 patients, 10.5%), followed by Conjunctival follicles (6 patients, 3.9%), Lacrimation increased (4 patients, 2.6%), Eye pain (3 patients, 2.0%), Eyelid oedema (3 patients, 2.0%), Eye pruritus (3 patients, 2.0%) and Foreign body sensation in eyes (3 patients, 2.0%). Of the AEs leading to permanent discontinuation of study drug, 53 (89.8%) were eye related. In the placebo arm, 17 AEs in 13 patients (8.6%) led to permanent discontinuation of study drug: Benign prostatic hyperplasia, Blepharitis, Cardiac failure, Coma, Cornel abrasion, Dyspnoea, Headache, Keratitis, Metastases to bone, Myocardial infarction, Ocular

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discomfort, Photopsia, Pigmentary glaucoma, Punctate keratitis, Rectal adenocarcinoma, Tachycardia and Tongue neoplasm malignant stage unspecified.

CONCLUSIONS: BRIMONIDINE

While the percentage of patients who suffered SAEs was similar for brimonidine (14%) and placebo (15%), the percentage of patients who suffered AEs was slightly higher for brimonidine (88%) than for placebo (79%). Moreover, the percentage of patients with AEs that led to permanent discontinuation of study drug was higher for brimonidine (21.7%) than for placebo (8.6%). Of the AEs leading to permanent discontinuation of brimonidine, 53 (89.8%) were eye related. And while most AEs in patients receiving brimonidine were mild or moderate in severity, over a third of AEs in the brimonidine arm were related to study drug. Moreover, there was 1 fatal SUSAR and 1 other SAR in the brimonidine arm. Thus, brimonidine tartrate 0.2% has an unfavourable safety and tolerability profile in the target patient population.

In the evaluation of success for the primary endpoint, i.e. efficacy in preventing or arresting neurodysfunction in terms of no increase in the number of abnormal hexagons with respect to IT, there was no difference between brimonidine and placebo arms. Results for the primary efficacy-related and secondary efficacy endpoints show no consistent differences between the brimonidine and placebo arms. RT, GCL thickness, RNFL thickness, BCVA score, VF parameters (global mean deviation and pattern deviation) and VFQ-25 showed no noteworthy changes between Baseline and 24 months in the brimonidine arm or the placebo arm. Moreover, these results reveal that placebo-treated patients did not show DR progression during the 2 years of the clinical trial, making it unfeasible to evaluate the protective role of brimonidine eye drops in the PE.

For this reason, and following the recommendation of the AEMPS, complementary analyses focused on retinal MAs were performed. Specifically, the efficacy of brimonidine eye drops in a subpopulation of the PE with early microvascular effects, i.e. >1 MA at screening, was evaluated.

Results from the complementary efficacy analyses do not indicate positive effects of brimonidine on the arrest of DR progression. The number of MAs increased between screening and 24 months in patients treated with brimonidine, indicating disease progression. In addition, brimonidine eye drops did not show positive effects on any of the efficacy variables analysed in patients with early microvascular effects associated with DR. This, together with the unfavourable safety and tolerability profile, excludes brimonidine tartrate 0.2% eye drops as a therapeutic option for DR arrest in diabetes patients with early microvascular disease.