EVALUATION OF THE THERAPEUTIC EQUIVALENCE OF TRAVOPROST PR AND TRAVATAN®. DOUBLE BLIND RANDOMIZED CLINICAL TRIAL IN SUBJECTS AFFECTED BY GLAUCOMA OR INTRAOCULAR HYPERTENSION.

This was a multi-center, prospective, randomized, double-blind, parallel-group comparison study in patients with known glaucoma or intraocular hypertension requiring a pharmacological treatment.

Name of Test Agent: TRAVOPROST PR (travoprost 40 µG)

Clinical Report No.: Travoprost 01/2011

EUDRACT No.: 2011-005419-10

Developmental Phase of Study: III

Study Initiation Date (first patient enrolled): 30 April 2012

Study Completion Date (last patient completed): 27 February 2013

Clinical Trial Report Date: FINAL Revised 30 June 2014

Sponsor:	**PH&T S.p.A.** Via Marostica, 1 20146 Milan (Italy) **RAFARM** 12 Korinthou Str., N. Psihiko GR 154 51 Athens (Greece)
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The study described in this report was performed in compliance with Good Clinical Practice (GCP).

2 SYNOPSIS

Name and Address of Company: PH&T S.p.A. Via Marostica, 1 20146 Milan, Italy RAFARM 12 Korinthou Str., N. Psihiko GR 154 51 Athens (Greece)	**(For PH&T/RAFARM Regulatory Affairs Use Only)** **Volume** **Page** **Item #:**	**(For National Authority Use only)**
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Title of Study: Evaluation of the therapeutic equivalence of Travoprost PR and Travatan®. Double blind randomized clinical trial in subjects affected by glaucoma or intraocular hypertension.

Investigators/Study Center(s): Prof. Alessandro Rossi, Milan; Prof. Luca Rossetti, Milan; Prof. Marco Centofanti, Rome; Prof. Carlo Sborgia, Bari; Prof. Carlo Emilio Campos, Bologna; Prof. Maurizio Fossarello, Cagliari; and Prof. Paolo Lanzetta, Udine.

Publication (reference, if any): None

Study Period: 30 April 2012 (first enrollment) 27 February 2013 (last completed)	**Phase of Development:** III

Objectives:

Primary objective: The main objective of the study was to assess the therapeutic equivalence of two different formulation of Travoprost (Travoprost PR versus Travatan®) in the treatment of subjects affected by primary angle glaucoma (POAG) or ocular hypertension (OH) treated for 12 weeks.
Primary end-point was the change in IOP from baseline in 2 study groups at 12 weeks.

Secondary objectives: Secondary end-points were:

- To assess local tolerability of the two formulations, in terms of local adverse events,
- To assess systemic tolerability of the two formulations in terms of changes in vital parameters (arterial blood pressure and heart rate will be registered at each visit), onset of systemic adverse events (registered at each visit) and changes in laboratory parameters (assessed at the entry and at the end of the 12-week treatment),
- To calculate the percentage change in IOP from start to end of 12-week treatment,
- To calculate the reduction in IOP by both formulation, at each time point at baseline and at the end of the 12-week treatment.

Study Design: This was a double blind, multi-center study. Subjects were treated according to a parallel group design following a computer generated randomization list balanced in block of 4. One hundred and thirty-two subjects were screened and one hundred and twenty randomized in the 8 investigational centers. The target to be reached, according to the sample size calculation (Protocol Amendment n.1), was one hundred and six completed subjects.

Patient Population:
Number of Patients Planned according to Study Protocol: 142 enrolled to reach 128 completed
Number of Patients Planned according to Protocol Amendment N.1: 120 enrolled to reach 106 completed
Number of Patient Screened: 132
Number of Patients Randomized: 120
Safety Population: 120
Intention-To-Treat Population: 113
Per protocol population: 101

Diagnosis and Main Criteria for Inclusion:
Patients of either sex and any race who were ≥ 18 years of age with known unilateral or bilateral POAG or IOH, and IOP > 21 mm Hg at Randomization visit.

Dose and Mode of Administration, Batch Number of Test Agent:
Travoprost PR (40 µG) was administered to patients in random sequence order. The subjects were instructed to instill, for 12 weeks, one drop of study medication in the affected eye(s) every evening at approximately 20.00 hours and to use the dropper bottles within 4 weeks of opening. Travoprost PR: Batch No.: 00020112, expiry date: February 2013

Dose and Mode of Administration, Batch Number of Comparative Agent: Travatan® (40 µG) was administered to patients in random sequence order. The subjects were instructed to instill, for 12 weeks, one drop of study medication in the affected eye(s) every evening at approximately 20.00 hours and to use the dropper bottles within 4 weeks of opening. Travatan®: Batch No.: 1BRF1A1, expiry date: April 2013.

Duration of Treatment: Twelve weeks

SYNOPSIS (continued)

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Evaluation Parameters:

Efficacy: The principal end-point of the study was the change in IOP comparing the values registered at the entry and at the end of the study. The mean values obtained in IOP assessment after 12-week treatment were compared.

It has been estimated that in order to show therapeutic equivalence between the two formulations, a maximum difference between mean values in the two treatment groups, at the end of the study is 1.5 mm Hg.

IOP was measured, with a Goldman applanation tonometer, for all subjects, at screening, randomization visits as well as after 2, 4, 6, 8 and 12 weeks of treatment at the same time (a deviation of 1 hour was accepted).

Three evaluations were done and registered. IOP assessment was performed in agreement with the European Vision Institute SOP .

The tonometric assessment was repeated at 13.00 and 17.00 at Randomization and final visits.

Local Tolerability: Local tolerability was assessed, at randomization and final visits by Slit lamp examination (to examine conjunctiva, eyelid, bulbi, cornea, iris, lens for opacities or other changes, anterior vitreous/vitreous membrane and anterior chamber with special emphasis on cells and flare). Gonioscopy was performed. Post-dilatation lens opacificities classification system was used to grade lens changes in the lens and detailed retinal and optic disc examination was performed. The skin and margins of upper and lower lids were examined and best-corrected visual acuity tested. Automated visual field testing was also performed. Photographs of the eye(s) were taken prior tonometry and prior to any drops being dispensed in the eye to depict conjunctival hyperemia (grades 0, 1, 2 or 3, where 0 signifies none or trace, 1 mild, 2 moderate, and 3 severe).

Safety: The methods used for safety assessment were based upon registration of local and systemic adverse events, possible changes detected in physical examination performed at V1, V2 and V7, vital parameters (blood pressure and heart rate) assessment. Blood tests (glucose, BUN, creatinine, Na+, K+, AST, ALT and uric acid) were scheduled only at the entry and at the end of the study to check safety, but should an adverse event occur, the Investigator was allowed to repeat them at the any time he/she considers them necessary.

Statistical Methods:

Demographics: Demographics and baseline characteristics were summarized for each treatment group by means of descriptive statistics (n, mean, standard deviation, minimum and maximum or frequency distributions, as appropriate). Baseline comparability of treatment groups was assessed using descriptive statistics. No hypothesis testing was planned for these comparisons.

Primary Efficacy: Changes in intraocular pressure between baseline and end of treatment value were submitted to an ANCOVA model with treatment as factor and baseline value as a covariate. The two treatments will be declared equivalent if the two-sided 95% CI for the difference between adjusted treatment means lie entirely within the interval –1.5 to 1.5 mmHg.

Secondary Efficacy: IOP, percentage change in IOP were summarized at each time point within each group by means of descriptive statistics. Mean changes and 95% CI on mean change from baseline were also calculated by means of an ANCOVA model with treatment as factor and baseline value as a covariate.

Safety: Adverse Events were coded using MedDRA dictionary. The System Organ Class (SOC) and Preferred Term (PT) was used for tabulation. Number of subjects experiencing adverse events, drug related adverse events, serious adverse events and adverse events leading to withdrawal were calculated as total and as number of event per patient. Difference between treatment groups on subjects who experienced adverse events, drug related adverse events, serious adverse events and adverse events leading to withdrawal was evaluated using Chi square test or two-tailed Fisher's exact test. Vital signs (systolic and diastolic blood pressure, heart rate) were analyzed within each group by means of descriptive statistics. Moreover mean change and 95% confidence interval on mean change from baseline was also calculated at any time point. Laboratory values were summarized using descriptive statistics.

Moreover shift table from baseline to end of treatment with regards to normal range, was provided for each treatment group and laboratory test.

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Summary and Conclusions:

Demographics: In all 132 patients were screened, following the wash-out period 120 patients were randomized to the two treatment groups: Travoprost PR (58) and Travatan® (62). Five patients (three in Travoprost PR and two in Travatan® group) received medication but had no post-baseline evaluation and were excluded from ITT analyses. The resulting ITT population comprised 113 patients of whom 53 (49.9 %) were males. Diagnoses included primary open-angle glaucoma in 86/113 (76.1 %) patients and ocular hypertension in 28/113 (23.9 %) patients. Study participants had a mean age of 63.2 years in the Travoprost PR group and 66.3 years in the Travatan® group. Mean weight and height were also well balanced between the two groups as follows: weight 74.2 kg in the Travoprost PR group and 70.7 kg in the Travatan® group; height: 166.9 cm in the Travoprost PR group and 165.5 cm in the Travatan® group. 98/113 patients (86.7 %) received assigned study medication in both eyes. The median duration of exposure was 58 days (range 7 – 96) in the Travoprost PR group and 62 days (range 5 – 100) in the Travatan® group.

Primary Efficacy Results: At baseline, mean IOP levels were similar across groups at each time point and for diurnal measurement. With regard to the primary efficacy variable, mean IOP level (9:00, 13:00 and 17:00) at baseline was 22.61 mm Hg in the Travoprost PR group and 23.04 mm Hg in the Travatan® group. By week 12 a reduction was observed in both treatment groups (- 7.79 mm Hg in the Travoprost PR group and - 8.84 mm Hg in the the Travatan® group). The LS mean (95% confidence interval) was -7.911 mm Hg (-8.722 - -7.099) for Travoprost PR treated patients and -8.725 mm Hg (-9.507 - -7.943) for the Travatan®-treated patients. Treatment difference was 0.814 mm Hg and 95 % confidence interval -0.3158 – + 1.943. Results of PP analyses of changes from baseline to week 12 in mean IOP levels (at the three times) showed drugs equivalence: the LS mean (95% confidence interval) was -8.400 mm Hg (-9.094 - -7.706) for Travoprost PR treated patients and -8.823 mm Hg (-9.457 - -8.189) for the Travatan®-treated patients. Treatment difference was 0.423 mm Hg and 95 % confidence interval -0.519 - +1.365.

Secondary Efficacy Results:

Change and percent change in IOP

The mean change from baseline in IOP measured at 9.00 was significant from Visit 3 on in both groups, with a relevant reduction from Visit 2 to Visit 3, followed by a slow decrease until Visit 7 (or End of Study). At Visits 3, 5 and 7 (or End of Study) the mean change from baseline was -7.79 mmHg (range -15.0 - +4.0), -8.28 mmHg (range -13.0 - +5.0) and -7.83 mmHg (range -20.0 - +11.7), respectively, in the Travoprost PR group, and -8.33 mmHg (range -22.0 - -2.0), -8.60 mmHg (range -16.0 – 0.0) and -8.93 mmHg (range -19.0 - +3.0), respectively, in the Travatan® group.

A similar trend was observed for mean percent change from baseline in IOP measured at 9.00. At Visits 3, 5 and 7 (or End of Study) the mean percent change from baseline was -33.92% (range -54.5 - +18.5), -36.06% (range -56.5 - +23.1) and -33.76 (range -66.7 - +53.8), respectively, in the Travoprost PR group, and -35.33% (range -64.7 - -7.7), -36.57% (range -62.0 – 0.0) and -37.7% (range -60.6 - +22.0), respectively, in the Travatan® group.

The estimation of the ANCOVA model was based on all 113 patients included in the ITT population. The LS means of percent change in IOP from baseline to end of treatment were -34.611% (95% CI: -38.139, -31.084) in the Travoprost PR group and -38.061% (-41.460, -34.663) in the Travatan® group.

The estimate of the difference between treatments (Travoprost PR - Travatan®) was 3.450 (95% CI: -1.456, 8.356, p-value = 0.166).

Safety Results (assessed on Safety population):

Local and systemic adverse events:

The total number of adverse events during the treatment period was 57 in the Travoprost PR group and 73 in the Travatan® group.

The number of patients with at least one AE was 22 (37.9%) in the Travoprost PR group and 27 (43.5%) in the Travatan® group. The difference between groups was not significant (chi-square test p-value = 0.532).

The total number of drug-related adverse events was 38 in the Travoprost PR group and 41 in the Travatan® group. The number of patients with at least one drug-related AE was 19 (32.8%) in the Travoprost PR group and 22 (35.5%) in the Travatan® group. The difference between groups was not significant (chi-square test p-value = 0.753).

SYNOPSIS (continued)

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The most commonly involved SOCs were: eye disorders, with 16 patients (27.6%) in the Travoprost PR group and 17 (27.4%) in the Travatan® group; infections and infestations, with 2 patients (3.4%) in the Travoprost PR group and 9 (14.5%) in the Travatan® group; musculoskeletal and connective tissue disorders, with 2 patients (3.4%) in the Travoprost PR group and 5 (8.1%) in the Travatan® group; skin and subcutaneous tissue disorders, with 4 patients (6.9%) in the Travoprost PR group and 3 (4.8%) in the Travatan® group; vascular disorders, with 4 patients (6.9%) in the Travoprost PR group and 3 (4.8%) in the Travatan® group; respiratory, thoracic and mediastinal disorders, with 2 patients (3.4%) in the Travoprost PR group and 4 (6.5%) in the Travatan® group; gastrointestinal disorders, with 1 patient (1.7%) in the Travoprost PR group and 4 (6.5%) in the Travatan® group; nervous system disorders, with 2 patients (3.4%) in the Travoprost PR group and 3 (4.8%) in the Travatan® group.

The most commonly reported drug-related AEs by PT (i.e. those reported by at least 3% of patients in either group) were: conjuctival hyperaemia, with 6 patients (10.3%) in the Travoprost PR group and 5 (8.1%) in the Travatan® group; dry eye, with 1 patient (1.7%) in the Travoprost PR group and 2 (3.2%) in the Travatan® group; eye irritation, with 3 patients (5.2%) in the Travoprost PR group and 7 (11.3%) in the Travatan® group; eye pruritus, with 1 patient (1.7%) in the Travoprost PR group and 3 (4.8%) in the Travatan® group; eyelid oedema, with 2 patients (3.4%) in the Travoprost PR group and 0 (0%) in the Travatan® group; ocular hyperaemia, with 3 patients (5.2%) in the Travoprost PR group and 2 (3.2%) in the Travatan® group; headache, with 2 patients (3.4%) in the Travoprost PR group and 0 (0%) in the Travatan® group; dyspnoea, with 2 patients (3.4%) in the Travoprost PR group and 0 (0%) in the Travatan® group; pruritus, with 2 patients (3.4%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group; hyperaemia, with 2 patients (3.4%) in the Travoprost PR group and 3 (4.8%) in the Travatan® group; hypertension, with 2 patients (3.4%) in the Travoprost PR group and 0 (0%) in the Travatan® group.

Changes in physical examination

The number of patients with at least one abnormal condition was 11 (20.0%) in the Travoprost PR group and 12 (20.0%) in the Travatan® group. Shifts from normal baseline to abnormality were observed in the following systems: eyes, ears, nose, with 4 patient (6.9%) in the Travoprost PR group; mouth and throat, with 1 patient (1.7%) in the Travoprost PR; neck, with 1 patient (1.6%) in the Travatan® group; chest, with 1 patient (1.7%) in the Travoprost PR group and 1 patient (1.6%) in the Travatan® group; heart, with 1 patient (1.6%) in the Travoprost PR group and 2 patients (3.2%) in the Travatan® group; abdomen with 2 patients (3.4%) in the Travoprost PR group and 1 patient (1.6%) in the Travatan® group; neurological, with 1 patient (1.6%) in the Travatan® group; skin, with 1 patient (1.6%) in the Travatan® group; limbs, with 1 patient (1.6%) in the Travatan® group.

Changes in vital parameters

No significant change from baseline were observed.

Changes in lab tests

With regards to laboratory, shifts to clinically significant abnormalities were observed in the following tests: glucose, with 1 patient (1.6%) in the Travatan® group; BUN, with 1 patient (1.7%) in the Travoprost PR group (below the lower limit).

Local tolerability

The following shifts of conjunctival hyperemia were observed: from none or trace at baseline to mild at the end of treatment, with 10 patients (17.2%) in the Travoprost PR group and 10 (16.1%) in the Travatan® group; from none or trace at baseline to moderate at the end of treatment, with 4 patients (6.9%) in the Travoprost PR group and 5 patients (8.1) in the Travatan® group; from none or trace at baseline to severe at the end of treatment, with 1 patient (1.7%) in the Travoprost PR group; from mild at baseline to moderate at the end of treatment, with 7 patients (12.1%) in the Travatan® group and 8 patients (12.9%) in the Travatan® group; from mild at baseline to severe at the end of treatment, with 2 patients (3.2%) in the Travatan®. Furthermore two subjects in the Travoprost PR group and two in the Travatan® group had an improvement from mild to none.

Shifts, in lids examination, from normal at baseline to abnormality were observed in the following parts of the eye: skin, with 1 patient (1.7%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group; margin of lower lids, with 1 patient (1.7%) in the Travatan® group; margin of upper lids, with 2 patients (3.4%) in the Travoprost PR group and 2

(3.2%) in the Travatan® group.
Shifts in slit lamp examination from normal baseline to abnormality were observed in: conjunctiva, with 10 patients (17.2%) in the Travoprost PR group and 14 (22.6%) in the Travatan® group; palpebra, with 2 patients (3.4%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group; len, with 1 patient (1.6%) in the Travatan® group; vitreous membrane, with 1 patient (1.6%) in the Travatan® group.
The shifts of anterior chamber angle were observed in 4 patients (6.9%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group (from 35-20 at baseline to 45-35 at the end of treatment) and in 1 patient (1.7%) in the Travoprost PR group and 2 (3.2%) in the Travatan® group (from 45-35 at baseline to 35-20 at the end of treatment).
The following shifts, in visual field, were observed: from normal at baseline to abnormal at the end of treatment, with 4 patients (6.9%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group; from abnormal at baseline to normal at the end of treatment, with 1 patient (1.7%) in the Travoprost PR group and 5 (8.1) in the Travatan® group.
The following shifts were observed in cortical cataract: from: from C1 at baseline to C2 at the end of treatment in 1 patient (1.7 %) in the Travoprost PR and 2 (3.2%) in the Travatan® group; from C1 at baseline to C3 at the end of treatment in 1 patient (1.6%) in the Travatan® group; and from C2 to C1 in 1 patient (1.7 %) in the Travoprost PR group and 2 (3.2%) in the Travatan® group.
The following shifts, in nuclear color, were observed: from NC2 at baseline to NC3 at the end of treatment in 2 patients (3.4%) in the Travoprost PR group; from NC3 at baseline to NC4 at the end of treatment in 1 patient (1.7%) in the Travoprost PR group; from NC2 at baseline to NC4 at the end of treaement in 1 patient (1.6%) in the Travatan® group.
The following shifts, in nuclear opalescence were observed: The following shifts were observed: from NO2 at baseline to NO3 at the end of treatment, with 3 patients (5.2%) in the Travoprost PR group and 2 (3.2%) in the Travatan® group; from NO3 at baseline to NO4 at the end of treatment, with 1 patient (1.1%) in the Travatan® group; from NO3 at baseline to NO2 at the end of treatment, with 1 patient (1.1%) in the Travatan® group.
Only one shift was observed in posterior subcapsular cataract, from P3 at baseline to P2 at the end of treatment in 1 patient (1.6%) in the Travatan® group.
No significant changes from baseline were observed in visual acuity.
The only shift, from normal baseline to abnormality, in the detailed retinal examination was observed in one patient (1.7%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group.
The only shift, from abnormal baseline to normality, in the detailed optic disk examination was observed in 4 patients (6.5%) in the Travatan® group.
Conclusions: The primary objective of the study was to assess the therapeutic equivalence of two different formulations of Travoprost (Travoprost PR versus Travatan®) in the treatment of subjects affected by primary angle glaucoma (POAG) or ocular hypertension (OH) in terms of intra-ocular pressure (change from baseline to Week 12 or End of Study Visit). A total of 120 patients were included in the Safety population, 58 in the Travoprost PR group and 62 in the Travatan® group. A total of 113 patients were included in the intent-to-treat population (ITT), 54 in the Travoprost PR group and 59 in the Travatan® group. A total of 101 patients were included in per protocol population (PP), 46 in the Travoprost PR group and 55 in the Travatan® group.
With respect to the primary endpoint of the study, equivalence of Travoprost PR and Travatan® was demonstrated for both ITT and PP populations. The estimate of the difference between treatments (Travoprost PR - Travatan®) in change in IOP from baseline to end of treatment (Week 12 or End of Study) was 0.814 mmHg (95% CI: -0.315, 1.943) in the ITT population and 0.423 mmHg (95% CI: -0.519, 1.365) in the PP population.
The mean change from baseline in IOP measured at 9.00 was significant from Visit 3 on in both groups, with a relevant reduction from Visit 2 to Visit 3, followed by a slow decrease until Visit 7 (or End of Study).
The estimate of the difference between treatments (Travoprost PR - TRavatan®) in percent change in IOP from baseline to end of treatment (Week 12 or End of Study) was 3.45% (95% CI: -1456, 8.356).
The median duration of exposure was 58 days (range 7 – 96) in the Travoprost PR group and 62 days (range 5 – 100) in the Travatan® group.
The total number of adverse events during the treatment period was 57 in the Travoprost PR group and 73 in the Travatan® group. The number of patients with at least one AE during the treatment period was 22 (37.9%) in the Travoprost PR group and 27 (43.5%) in the Travatan® group. The difference between groups was not significant (chi-square test p-value = 0.532).
The total number of drug-related adverse events was 38 in the Travoprost PR group and 41 in the Travatan® group. The number of patients with at least one drug-related AE was 19 (32.8%) in the Travoprost PR group and 22 (35.5%) in the Travatan® group. The difference between groups was not significant (chi-square test p-value = 0.753).
The total number of serious adverse events during the treatment period was 2, reported by one patient in each treatment group.
The total number of adverse events leading to withdrawal during the treatment period was 14 in the Travoprost PR group and 5 in the Travatan® group. The number of patients with at least one AE leading to withdrawal during the treatment period was 5 (8.6%) in the Travoprost PR group and 3 (4.8%) in the Travatan® group. The difference between groups was not significant (Fisher exact test p-value = 0.481).
There were no substantial differences between groups in the results of the other safety endpoints (laboratory tests, physical examination findings, vital signs and local tolerability variables).

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADR	Adverse Drug Reaction
AE	Adverse Event
ANCOVA	Analysis of Covariance
AST	Aspartate Amino Transferase
ALT	Alanine Amino Transferase
BMI	Body Max Index
BPM	Beat per Minute
BUN	Blood Urea Nitrogen
cm	Centimeter
COSTART	Coding Symbols for a Thesaurus of Adverse Reaction Terms
CRO	Contract Research Organization
Cronos	Cronos Ricerche Cliniche Srl
CRF	Case report form
CSR	Clinical study report
DDP	Drug dispensing person
DEC	Data Entry Clerk
DM	Data Manager
DVG	Discrete Value Group
EU	European Union
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IOP	Intra-ocular pressure
IRB	Institutional Review Board
ITT	Intention-to-treat Population
LS	Least Squares
kg	Kilogram
mg	Milligram
mL	Milliliter
mm	Millimeter
N/No./n	Number
OC	Oracle Clinical
OH	Ocular hypertension
POAG	Open-angle-glaucoma
PP	Per Protocol Population
PT	Preferred Term
SAE	Serious Adverse Event

SAER	Serious Adverse Event Report
SD	Standard deviation
SOC	System Organ Class
Study agent	Any test agent, comparative agent, or control agent administered to subject during the study
TEAEs	Treatment Adverse Events
WHO	World Health Organization

5 ETHICS

5.1 INDEPENDENT ETHICS COMMITTEE (IEC)

Before commencing the study, the protocol (Appendix I) was submitted by Sponsor or Investigator (according to local procedures) to all IECs for approval. The coordinating center IEC (Milan Policlinic) approved the study on 24 January 2012. A copy of the written approval forms duly signed by the Chairman of each local IEC were remitted to the Sponsor together with a list of the members of the IEC before the beginning of the study (and archived in the trial master file). A protocol amendment (Appendix II) was issued on 22 November and it was submitted to all the local IECs for approval. The coordinating center IEC (Milan Policlinic) approved the protocol amendment on 22 January 2013. A copy of the written approval forms duly signed by the Chairman of each local IEC were remitted to the Sponsor together with a list of the members of the IEC (and archived in the trial master file). A list of the IECs consulted is provided in Appendix III.

5.2 ETHICAL CONDUCT OF STUDY

The study was performed in accordance with the Declaration of Helsinki approved by the 18th World Medical Assembly in Helsinki, Finland, June 1964, and amended at the 29th World Medical Assembly in Tokyo, Japan, October 1975, at the 35th World Medical Assembly in Venice, Italy, October 1983, at the 41st World Medical Assembly in Hong Kong, September 1989, at the 48th World Medical Assembly in Somerset West, South Africa, October 1996, at the 52nd World Medical Assembly in Edinburgh, Scotland, October 2000, and at the 59th World Medical Assembly in Seoul, Korea, October 2008.

It was mandatory that all considerations about the protection of human subjects were carried out in accordance with the Declaration of Helsinki.

5.3 PATIENT INFORMATION AND CONSENT

Before entry, the patients were requested to give their written informed consent to participate in the study. All patients signed and almost all personally dated an approved informed consent form after receiving detailed written and verbal information about the reason, the nature, and the possible risks associated with the administration of the study agents, according to the guidelines provided in the Declaration of Helsinki (Appendix 5 of the protocol).
A copy of the approved patient consent form used by each Investigator was provided to the Sponsor for archiving in the trial master file.

The obtainment of patient's written consent was certified by the Investigator in the CRF (Appendix IV). The patient was aware and consented that personal information would be made available to the Sponsor, their representatives, and to the competent authorities.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The study was conducted at eight Italian ophtalmological centers that routinely visit patients affected by unilateral or bilateral POAG or IOH. A designated Investigator at each study site was responsible for the management of the study.

The complete name, address, and qualifications of the Investigators can be found in Appendix V along with Principal Investigators CVs. CVs of the whole study staff in the eight centers are available for Inspection and filed in TMF. In addition, the appendix includes a list of the author(s) of the report and the responsible biostatistician(s).

All monitoring activities were conducted on behalf of PH&T S.p.A and Rafarm by Dr. Michela Cassinotti, Dr. Sonia Sarnataro, Dr. Paola Minguzzi and Mrs. Cinzia Lamperti, CRONOS, Milan, Italy.

Data management and biometric activities were conducted by CROS-NT, Verona, Italy.

The study was conducted under the supervision of Dr. Diana Scatozza, PH&T S.p.A.

The signature of the Sponsor's Responsible Medical Officer is included in Appendix VI.

7 INTRODUCTION

Glaucoma is a condition characterized by a loss of peripheral visual field associated with optic nerve damage (1). This disease, generally associated with raised intraocular pressure (IOP), i.e. values higher than about 21 mm Hg, can lead to blindness if left untreated and occurs in approximately 1 to 2 % of the population over 40, rising to 5 % at 70 years. Primary open-angle-glaucoma (POAG) is the most prevalent form. It is caused by chronic obstruction of the outflow of aqueous humour within the trabecular meshwork. IOP is currently the only proven modifiable risk factor in the management of POAG. Either medical or surgical management can achieve the control of IOP. Ocular Hypertension (OH) is defined as a raised IOP that has not resulted in demonstrable peripheral visual defects. Lowering IOP has been proven effective in slowing the progression of POAG and reducing the progression from OH to POAG.

Current treatments for POAG are designed to lower IOP in order to prevent further damage to nerve fibres and arrest progression of visual field loss (2). Prostaglandin analogues are a newer class of drugs among various topical ocular hypotensive medications with a proven safety and efficacy for controlling IOP. Their potency, once a day dosing and lower incidence of systemic adverse events have made them popular for use as monotherapeutic and first-line agents (3). They include Travoprost, bimaprost, latanoprost and unoprostone. All of them have a similar molecular structure and they work by increasing the aqueous drainage via trabecular meshwork and the uveo-scleral pathway.
Travoprost is absorbed through the cornea where the isopropyl ester pro-drug is hydrolyzed to the acid form to become biologically active. Studies in humans indicate that the peak concentration in the aqueous humor is reached about 2 hours after topical administration (4, 5, 6, 7, 8, 9, 10, 11). The active acid of Travoprost reaching the systemic circulation is primarily metabolized by the liver and the metabolites are mainly eliminated by the kidneys.

No data is actually available showing that the formulation of Travoprost PR ensures equivalent therapeutic activity to Travatan® in terms of IOP control with its recommended one drop dosage.
The demonstration of identical IOP reduction at the end of 12-week treatment compared to basal values in both treatment groups is the aim of the present trial.

8 STUDY OBJECTIVE(S)

Primary objective:
The objective of the study was to assess the therapeutic equivalence of two different formulations of Travoprost (Travoprost PR versus Travatan®) in the treatment of subjects affected by POAG or OH treated for 12 weeks. Primary outcome was the change in IOP from baseline in the 2 study groups at 12 weeks.

Secondary objectives:
Secondary end-points were:

- To assess local tolerability of the two formulations, in terms of local adverse events,
- To assess systemic tolerability of the two formulations in terms of changes in vital parameters (arterial blood pressure and heart rate will be registered at each visit), onset of systemic adverse events (registered at each visit) and changes in laboratory parameters (assessed at the entry and at the end of the 12-week treatment),
- To calculate the percentage change in IOP from start to end of 12-week treatment,
- To calculate the reduction in IOP by both formulations, at each time point recorded at baseline and at the end of the 12-week treatment.

9 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN DESCRIPTION

This was a Phase III, multi-centre, prospective, randomized, double-blind, parallel-group comparison study. One hundred and thirty-two subjects, affected by POAG or OH were screened and one hundred and twenty randomized in the 8 investigational centres. The target to be reached, according to the sample size calculation described into protocol amendment (Version 1), modified according to published data (12, 13), was one hundred six completed subjects.

9.2 DISCUSSION OF STUDY DESIGN

This study was a randomized, double-blind, parallel-group comparison of Travoprost PR and Travatan®. The actual protocol is included as Appendix I and a sample CRF as Appendix IV. A flow chart of the study design is shown in Fig. 1 below.

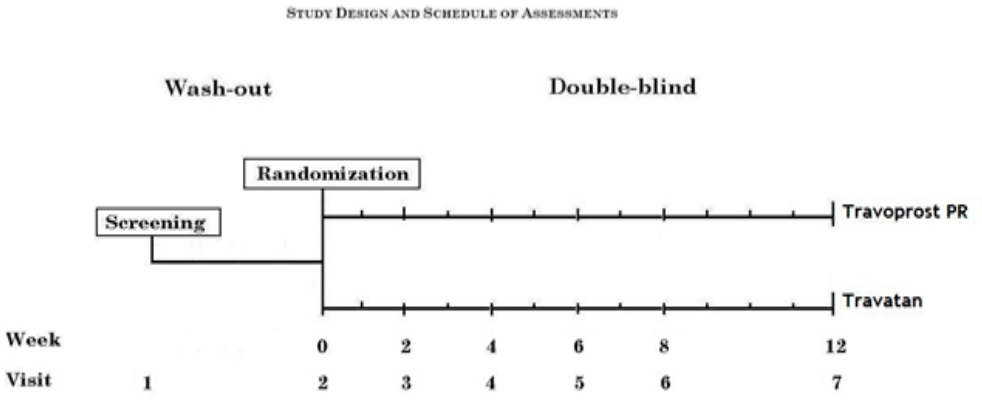

Fig 1

Randomization smoothes out differences between treatment groups with respect to their baseline characteristics. Even if more complicated to conduct, double-blind design is generally considered to provide the most reliable data from a clinical trial. On the other hand, the parallel-group design was chosen for ethical considerations, to minimize the discomfort and risk to the patients.

The dosage used, for both drugs, in this trial is the one approved for Travatan® which is on the market since 2001.

9.3 SELECTION OF STUDY POPULATION

9.3.1 Inclusion Criteria

Patients of either sex and any race were enrolled in the study if the following inclusion criteria were met:

- were 18 years or older;
- were affected by unilateral or bilateral POAG or IOH,
- had a IOP > 21 mm Hg at Randomization visit,
- gave written informed consent to participate in the study.

9.3.2 Exclusion Criteria

Patients were excluded from the study if they did not fulfill the inclusion criteria or if any of the following conditions were observed:

- were affected by closed or slit like anterior chamber angle,
- had a positive history for acute angle closure,
- had a positive history of argon laser trabeculoplasty within 3 months prior screening (the un-lasered eye could be enrolled in the study) or of any ocular filtering surgical intervention (the un-operated eye could be enrolled in the study),
- had ocular surgery or ocular inflammation/infection in either eye within 3 months prior to screening,
- were currently using contact lenses,

- had a best corrected visual acuity < 20/200,
- had been previously treated with Travatan®,
- were concomitantly treated with hypotonic agents,
- had a known cardiac conduction defects,
- had a decompensate heart failure,
- had reactive airway disease,
- had liver impairment with transaminase levels >3x the upper limit of normal range,
- had hypersensitivity to any of the components of the treatment medication,
- were female subjects of child-bearing potential with a positive pregnancy test;
- were female subjects who are nursing;
- were not able to attend all the planned visits and/or to have all the tests foreseen by the protocol performed,
- had a history of non-compliance, alcoholism or drug abuse,
- had previously participated in this study or in a clinical trial of an investigational drug within the last 30 days prior to the Screening visit,
- had any condition which, in the opinion of the investigator, could interfere with the study results or be considered detrimental to the subject's welfare.

9.3.3 Removal of Patient from Therapy or Assessment

Subjects were free to withdraw from the study at any time without explaining the reason.
The Investigator was also free to withdraw a subject at any time due to medical reasons. Should this decision is taken, the Investigator informed Cronos by phone or fax. All the subjects withdrawn before the end of the study were followed for 30 days in order to register possible serious adverse events.

Subjects who withdrew due to an Adverse Event (worsening in clinical or laboratory parameters) were followed until the baseline condition was reached. All the information collected during that time was recorded in the CRF. In the event of an early termination due to death or Serious Adverse Event, it was mandatory to provide a clear description of the events, which induced to the withdrawal.
Subjects were withdrawn from the study by the investigator for any of the following reasons:
a) Withdrawal of consent
b) Experience of any adverse event, which in the opinion of the investigator precluded the continuation of the study.
c) Non-compliance with the requirements of the study
d) Pregnancy started during the study
e) Subject lost at follow-up
f) PH&T/RAFARM or Health Authorities requested to have this study interrupted,
g) Subject required a pharmacological treatment forbidden in this study

Subjects who were withdrawn due to adverse events have not been replaced.

Replacement of subjects was allowed if:
a) Subjects were entered into the study even if they did not meet entry criteria;
b) Screening failures
c) A subject eligible who gave his/her signed consent withdrew from the study before investigational treatment administration;

d) Subjects withdrew from the study immediately after the first administration for reasons not related to safety/tolerability of the test compound and did not complete study follow-up procedures;
e) A subject was administered study drug incompletely or inadequately;
f) Lost to follow-up
g) Forbidden concomitant therapies were administered concomitantly;
h) Technical problems with equipment causing incomplete or inadequate IOP assessment at the end of the treatment period;
i) The investigator failed to maintain a standard of compliance with the indication of the present protocol in a way, which was considered to affect the interpretation of the study results.

9.4 TREATMENTS

9.4.1 Treatments Administered

Travoprost PR (travoprost 40 µg) and Travatan® (travoprost 40 µg) were supplied in bottles, each containing 2.5 mL of ready to use solution.
All the subjects already under topic anti-hypertensive treatment underwent a wash-out period in order to reach an IOP > 21 mm Hg. Subjects without a previous history of PAOG or OH who met the IOP inclusion value were entered into the study without undergoing the wash-out period. The study medication was supplied at Randomization visit and collected back during the visit after 4 weeks (V4), when a new bottle was dispensed.
This second bottle was then collected during the visit at week 8 (V6) when a third bottle was supplied. At the end of the study (V7) the third bottle was collected.
The subjects were instructed to instill one drop of study medication in the affected eye(s) every evening at approximately 20.00 hours, during the 12 week treatment period, to use the dropper bottles within 4 weeks of opening and to protect them by light.

9.4.2 Identity of Investigational Products

Each Travoprost PR bottle contained:

	Quantity per ml
Travoprost	**40 µg**
Excipients	
Benzalkonium chloride	0.15 mg
Macrogol 15 Hydroxystearate	5.00 mg
Trometamol	1.20 mg
Boric acid	3.00 mg
EDTA disodium	0.10 mg
Mannitol	46 mg
HCl 1 N/ NaOH 1 N	q.s. pH 6.0
Water for injection	q.s. 1 ml

Only one batch had been used: No.: 00020112, expiry date: February 2013

Each Travatan® 40 µg/ml Drops bottle contained::

	Quantity per ml
Travoprost	**40 µg**
Excipients	
Polyquaternium-1	Not reported in SPC
Polyoxyethylene hydrogenated castor oil 40 (HCO-40)	Not reported in SPC
Boric Acid (E284)	Not reported in SPC
Mannitol (E421)	Not reported in SPC
Sodium Chloride	Not reported in SPC
Propylene glycol (E1520)	Not reported in SPC
Sodium hydroxide and/or hydrochloric acid (to adjust pH)	Not reported in SPC
Purified water	q.s. 1 ml

Only one batch had been used: No.: 1BRF1A1, expiry date: April 2013

No special storage conditions were required for the boxes containing the bottles (open and unopened). The bottles had to be used within 4 weeks after opening and be protected by light.
The Drug Dispensing Person (DDP) or the hospital pharmacist was responsible for drug storage. The study monitor checked the drug storage conditions during site visits without opening the boxes or performing any drug accountability.

The preparation, packaging, storage, and subsequent distribution of Travoprost PR were carried out by Depo Pack snc.
Travatan® was purchased from the market while its packaging, storage, and subsequent distribution of were carried out by Depo Pack snc.

Each trial center was supplied with a sufficient number of medication sets to treat the assigned patients. Each medication set of Travoprost PR and Travatan®, containing the 3 Treatment boxes, carried a label containing the following core information:

- Sponsor's name and address
- description of the content
- protocol number
- subject number
- batch number (Masking code)
- re-assay date
- storage conditions
- caution statement ('New drug limited to investigational use only - keep out of reach of children")

Each Treatment box bored a two parts label, each part containing the same information:

- Product name and formulation
- protocol number

- subject number
- batch number (masking Code)
- re-assay date
- Date of assignment to the patient.

9.4.3 Method of Assigning patients to Treatment Groups

Patients received either Travoprost PR or Travatan® according to a computer-generated randomization list balanced in block of four (Appendix VII) prepared by "CROS NT", Via Germania, 2 - 37135 Verona (Italy). Drug was assigned at Randomization visit to the patients with IOP > 21 mm Hg.

For each patient, the randomization list also indicated the eye (left or right) to be treated and analyzed. In case of bilateral disease, both the eyes were treated but only the eye specified in the list was considered in the analysis. In case of mono-lateral disease, only the diseased eye was treated and analyzed, ignoring the indication reported in the randomization list.

Upon finalization of the database, the study was un-blinded.

9.4.4 Selection of Doses in the Study

The dose used in the study (1 drop every evening in each affected eye) is the one approved for Travatan®.

9.4.5 Selection and Timing of dose for each Patient

All the patients have been requested to apply, in the affected eye(s), once daily in the evening one drop. They have been requested not to use this medication more frequently than prescribed; using more could decrease effectiveness.

Before applying eye drops, patients washed their hands. To avoid contamination, they did not touch the dropper tip or let it touch their eye or any other surface.

The following instructions have been given: tilt your head back, look upward and pull down the lower eyelid to make a pouch. Hold the dropper directly over your eye and apply the prescribed number of drops. Look downward and gently close your eye for 1 to 2 minutes. Place one finger at the inside corner of your eye near the nose and apply gentle pressure. This will prevent the medication from draining out. Try not to blink and do not rub your eye. Do not rinse the dropper. Replace the dropper cap after each use.

Patients have been reminded to apply this medication regularly at the same time each day (in the evening). Should the patient use another kind of eye medication (e.g., drops or ointments), he/she has been requested to wait at least 5 minutes before applying other products and to use eye drops before eye ointments to allow the eye drops to enter the eye.

9.4.6 Blinding

Each medication set of Travoprost PR and Travatan®, contained 3 Treatment boxes. Each Treatment box contained only one bottle, which was identified with one-part label. The tear-off part of each vial label used was stuck on the appropriate space of the Drug Log Book at the time of administration.

Travoprost PR and Travatan® bottles were different and therefore a DDP was selected by the Investigator for the duration of the study and was responsible for dispensing the different study drugs according to the randomization code. The DDP was not involved in either safety or efficacy assessments. It was the responsibility of the DDP to ensure that the Investigator and other study personnel were unaware of the study agent administered. Additionally, the DDP was responsible for drug accountability and maintaining the Drug Log Book. Upon completion of the study, the DDP was asked to sign a statement confirming that the double-blinded nature of the study was maintained throughout. In order to avoid that the patient recognized Travatan® bottles due to a previous use, no patients previously treated with this drug were allowed to be entered into the study (see Exclusion criteria).
The randomization code might be broken only on an individual subject basis, in case of a serious adverse event (SAE), for which the Investigator must know the investigational product that was administered in order to initiate appropriate treatment. For this purpose, the Investigator was allowed to obtain this information from the randomization code list maintained by the DDP. If this information was revealed by the DDP to the Investigator, a memo of explanation was provided to include the subject number, date and declaration of the reason for breaking the study blind.

9.4.7 Prior and concomitant Therapy

If, for medical reasons, any drug other than the test drug was administered during the study, Investigator and/or study physician recorded all pertinent information on the case record form.
The subjects were informed not to take any new drug without prior asking permission to the Investigator.
In vitro studies have shown that precipitation occurs when eye drops containing thiomersal are mixed with Travoprost. If such drugs were used the eye drops were administered with an interval of at least five minutes.
Concomitant therapies with topical hypotonic agents were not allowed because of possible differences between treatment groups.

9.4.8 Treatment Compliance

Given the impossibility to count the exact number of drops administered, Travoprost PR or Travatan® compliance was checked by patient interview during the visit and on the left volume of the returned bottled by the DDP. In accordance with International Conference on Harmonization (ICH) requirements, the DDP had to be able to account for all study drugs furnished to the institution. The use of the study drugs was recorded, by the DDP, in each patient Drug Log Book. No study drug was to be used outside of this study. All study drugs were accounted for and returned, whether used or unused, to Depo Pack at the conclusion of the study along with the Drug Return/Destruction form accounting for the disposition of all clinical supplies shipped to the Investigator.

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

A combined flow chart of efficacy and safety procedures and assessments is presented in Table A

	Screening Visit (V1)	Randomization Visit (V2)	2 Week Visit (V3)	4 Week Visit (V4)	6 Week Visit (V5)	8 Week Visit (V6)	12 Week Final Visit (V7)
Informed Consent Form Signature	✓						
Inclusion/Exclusion Criteria verification	✓	✓					
Demographic Data	✓						
Medical History	✓						
Pregnancy Test	✓						
Physical examination	✓	✓					✓
Vital Signs	✓	✓	✓	✓	✓	✓	✓
Blood tests	✓						✓
Concomitant Therapies	✓	✓	✓	✓	✓	✓	✓
Adverse events reporting	✓	✓	✓	✓	✓	✓	✓
Tonometry (single assessment)	✓	✓	✓	✓	✓	✓	✓
Tonometry (24-hour assessment)		✓					✓
Slit lamp examination		✓					✓
Gonioscopy		✓					✓
Grade lens changes assessment (LOCS III grade) and retinal and optic disk examination		✓					✓
Best-corrected visual acuity testing		✓					✓
Automated visual field		✓					✓
Photographs of the eyes		✓					✓
Treatment assignment		✓		✓		✓	

The procedures listed above were performed at each visit as described below.

Screening visit (V1)

After obtaining the written informed consent from the subject, age, sex, date of birth, height, and weight were recorded in CRF and inclusion/exclusion criteria were checked. The doctor collected medical history and blood pressure and heart rate were measured with subject sitting, after 5 minutes rest with the same equipment.
The subject, then, underwent a physical examination and concomitant medications were recorded. Blood samples were taken in order to assess: glucose, creatinine, BUN, AST, ALT, Na+, K+ and uric acid. Pregnancy test was also performed on urine of women of childbearing potential.
IOP was measured and the three requested values were recorded (along with the time of registration).
The subject was requested to not apply any eye drop until the next visit scheduled between 7 and 30 days after.

Randomization visit (V2)

After 30 days or when IOP reached the requested value for entering into the study (> 21 mm Hg), at least 7 days after Visit 1 (for not naive patients), the subject came back to the hospital in the morning (before 9.00 a.m.).
The investigator asked the subject about adverse events, changes in concomitant medications and his/her interest to continue the study. A physical examination was performed. Blood pressure and heart rate were assessed. Tonometry (24-hour assessment) was performed around 9.00 a.m (at the same time as at V1), at 1.00 p.m., and at 5.00 p.m. For each assessment, three measurements were taken in order to increase method accuracy and the mean value was used for statistical analyses.
Slit lamp examinations was performed to examine conjunctiva, palpebra, bulbi, cornea, iris, lens for opacities or other changes, anterior vitreous/vitreous membrane and anterior chamber with special emphasis on cells and flare. Gonioscopy was also performed. Lens Opacities Classification System III (LOCS III) was used to grade lens changes in the lens and detailed retinal and optic disc examination was performed. The skin and margins of upper and lower lids were examined and best-corrected visual acuity tested. Automated visual field testing was also performed. Gonioscopy and automated visual field testing were not required, if they had been performed within past 12 and 3 months respectively. Photographs of the eye(s) were taken prior tonometry and prior to any drops being dispensed in the eye. The standard photographs depicted conjunctival hyperemia (grades 0, 1, 2 or 3, where 0 signifies none or trace, 1 mild, 2 moderate, and 3 severe).
The subject was then randomized into the study and given the box labelled “Treatment 1”. He/she was instructed to instil one drop of study medication in the affected eye(s) every evening at approximately 8 p.m. and to use the dropper bottles within 4 weeks of opening.
The subject was requested to come back to the centre after 14 days without carrying back the treatment box.

Visit 3 (after 2-week treatment), Visit 4 (after 4-week treatment), Visit 5 (after 6-week treatment) and Visit 6 (after 8-week treatment)

Every 14 days the subject came back to the hospital in the morning (at around 9.00 a.m.). The investigator asked the subject about adverse events, changes in concomitant medications and his/her interest to continue the study.
Blood pressure and heart rate were assessed. Tonometry was performed and the three assessments were made at the same time as at the previous visits. All the values were recorded in CRF.
At visits V3 and V5 the subject was requested to bring the medication box back at the following visit. At visits V4 and V5 he/she was supplied, by the DDP, with a new box, labelled, respectively "Treatment 2" and "Treatment 3".

End of study (V7 after 12-week treatment)

After further 28 days the subject came back to the hospital for the end of study visit in the morning (at around 9.00 a.m.). The investigator asked the subject about adverse events and changes in concomitant medications.
A physical examination was repeated. Blood pressure and heart rate were assessed and blood sample taken in order to assess: glucose, creatinine, BUN, AST, ALT, Na+, K+ and uric acid.
Tonometry (24-hour assessment) was performed around 9.00 a.m (at the same time as at V1), at 1.00 p.m., and at 5.00 p.m. For each assessment, three measurements were taken in order to increase method accuracy and the mean value was used for statistical analyses.
Slit lamp examinations was performed to examine conjunctiva, eyelid, bulbi, cornea, iris (abnormal was reported in case of iris colour change), lens for opacities or other changes, anterior vitreous/vitreous membrane and anterior chamber with special emphasis on cells and flare. Gonioscopy was also performed. Post-dilatation lens opacificities classification system was be used to grade lens changes in the lens and detailed retinal and optic disc examination was performed. The skin and margins of upper (including eyelash length) and lower lids were examined and best-corrected visual acuity tested. Automated visual field testing was also performed. Photographs of the eye(s) were taken prior tonometry and prior to any drops being dispensed in the eye. The standard photographs depicted conjunctival hyperemia (grades 0, 1, 2 or 3, where 0 signifies none or trace, 1 mild, 2 moderate, and 3 severe).
The subject was then discharged from the study and the Investigator filled in the last page of the CRF "End of study".

All the ophtalmogical procedures have been performed according to European Vision Institute SOPs. The center of Rome is a Site of Excellence of the European Vision Institute. Furthermore the center of Rome (for management of scientific research in Ophtalmology), as well as Milano Policlinic are certified ISO 9001-2008. Copy of the documents are included in this report (Appendix VIII).

All patients were monitored for any untoward medical events from the time he/she gave written informed consent to participate in the study and continued up to 30 days post study drug administration. The Investigator elicited information about the occurrence of adverse events through non-leading questioning and examination of the patient.

An **adverse event** was defined as any untoward medical event in a patient administered any dose of a pharmaceutical product and which does not necessarily have to have a causal relationship with the use of the product. Any untoward medical event which occurred outside the period of patient follow-up defined in the protocol was not considered an adverse event.

Symptoms or medically significant laboratory or instrumental (e.g., electrocardiographic) abnormalities of a pre-existing disease, such as cancer or other disease, were not considered

adverse events. However, occurrences of new symptoms or laboratory or instrumental abnormalities, as well as worsening of pre-existing ones, were considered adverse events.

Adverse events were recorded on the CRF and classified by the Investigator as serious or non-serious. A **serious adverse event** was an adverse event which satisfied the conditions for one or more of the following:

- resulted in death;
- was life-threatening, i.e., an event which, in the view of the Investigator, placed the patient at immediate risk of death from the event as it occurred, but not an event that hypothetically might have caused death if it were more severe;
- required in-patient hospitalization or prolongation of existing hospitalization;
- resulted in persistent or significant disability/incapacity, where disability was defined as a substantial disruption of a person's ability to conduct normal life functions, either reported or defined as per clinical judgment;
- was a congenital anomaly/birth defect (if exposure to product just before conception or during pregnancy resulted in an adverse outcome in the child).

The Investigator was requested to report all serious adverse events, within 24 hours, by phone or by fax, to both Sponsor and to Cronos. The Investigator had the responsibility of promptly providing the information necessary to complete the Serious Adverse Event Report Form. In this Report Form the Investigator recorded the study and site number, subject's number, sex, date of birth, treatment assigned, onset date, event description, name, address and telephone number of the Investigator.
The Investigator and Sponsor were responsible for reporting the Serious Adverse Events to the Ethics Committee and to Health Authorities according to local requirements.

In case of death, if an autopsy was performed, a copy of the autopsy report had to be sent to Sponsor and to the Cronos CRA and a copy was also attached to the Case Report Form
A **non-serious adverse event** was any adverse event that did not meet the criteria listed above for a serious adverse event.

For all adverse events, the Investigator was to record the severity of the event on the CRF according to the following criteria:

- **Mild** - Awareness of a sign or symptom which is easily tolerated;
- **Moderate** - Discomfort enough to cause interference with usual activity;
- **Severe** - Incapacitating with inability to do work or usual activity

The Investigator was to record the relationship of each adverse event to administration of the study drug as follows:

- **Probable** - the event followed a reasonable temporal sequence from administration of the study drug; the event followed a known response pattern to the study drug; the event could not be reasonably explained by the known characteristics of the patient's clinical state or by other therapy administered; and there was evidence of partial or complete disappearance of the event after withdrawal of the product (positive de-challenge).

- **Possible** - the event followed a reasonable temporal sequence from administration of the study drug; the event followed a known response pattern to the study drug but could have been produced by the patient's clinical state or by other therapy administered.
- **Not Related** - the event was either a pre-dose event or was definitely due to causes separate from the administration of the study drug, i.e., documented pre-existing condition, concomitant medication, patient's clinical state, or reported as not related and did not meet the above criteria.
- **Unknown** - the event did not meet any of the above-listed criteria because of conflicting data, dubious or insufficient/poor evidence, or the event was not judged as related or not related.

The Investigator was also asked to record the **action taken** due to the event occurrence as follows:

- **None**
- **Change in the study drug administration** (including early termination of administration, i.e. dose reduction)
- **Drug treatment required** (a medication was prescribed or changed; record on the Concomitant Medication section of the Case Report Form)
- **Non-drug treatment required** (a non-drug treatment was prescribed or changed, record in the "Comments" section of the AE form)
- **Hospitalisation or prolonged hospitalisation**
- **Diagnostic or clinical test**(s) conducted (attach a copy of the results to the Case Report Form)
- **Subject/subject discontinued from the study**.

The Investigator made every attempt to follow the patient until the adverse event had resolved or until the Investigator determined that the patient had returned to an acceptable state of health.

9.5.2 Primary Efficacy Variable

Primary outcome was the change (measured in mm Hg) in IOP from baseline in 2 study groups at 12 weeks. It was assumed that the two treatments could be declared equivalent if the two-sided 95% CI for the difference between adjusted treatment means lied entirely within the interval –1.5 to 1.5 mmHg.

9.5.3 Secondary Efficacy Variables

Secondary outcomes were the change and the percentage change in IOP from start to end of 12-week treatment induced by both formulations.

9.5.4 Safety Variables

Systemic tolerability of the two formulations was assessed in terms of changes in vital parameters (arterial blood pressure and heart rate registered at each visit), onset of systemic adverse events (registered at each visit) and changes in laboratory parameters (assessed at the entry and at the end of the 12-week treatment).
Local tolerability of the two formulations was assessed in terms of local adverse events as recorded in lid examination, slit lamp and pictures.

9.6 DATA QUALITY ASSURANCE

Initiation visits were made by the study monitors to the Investigators in order to discuss the protocol and the obligations of both the Sponsor and the Investigator. In particular a pharmacovigilance training was performed at Initiation visits and the study staff involved into patients management was trained and signed an attendance form. The study monitors were to perform periodic, interim monitoring visits. The purposes of these visits were to:

- verify that written informed consent was obtained prior to each patient's participation in the study;
- assess the progress of the study;
- review the compliance with the study protocol;
- determine whether all adverse events were appropriately reported;
- determine whether the Investigator was maintaining the essential documents;
- discuss any emergent problem;
- check the CRFs for legibility, accuracy, and completeness;
- validate the CRF entries against source records;
- assess the status of drug storage, dispensing, and retrieval.

The Investigators made available for verification the source documents. The study monitors performed the close-out visit at the conclusion of the Investigator's involvement in the study. All data required by the protocol were checked for accuracy on the CRF and consistency with the source documents.

Data management activities were performed by CROS-NT. Data from the CRFs were double-keyed by two independent operators into two separate SAS databases that were then compared (using the SAS PROC COMPARE procedure) and reconciled against the actual values in the CRFs. The second pass entry was enabled to for comparison failure alert. The audit trail allowed to document all changes applied to the database and occurred after the first data entry. Every change and its details were automatically recorded in the audit trail within Oracle Clinical (version 4.5.3). Each observation in the audit trail contained, for each subject, the original value, the new value, the reason for change (data entry error, data clarification), date/time in which the modification was made and the user identification of the person who performed it. Every variable (except for free text fields) was enabled to accept a set of allowed values (through DVG for character variables and lower/upper bound for numerical variables). Each discrepancy was automatically collected in the Discrepancy Management table in the OC System with an UNREVIEWED flag and UNIVARIATE discrepancy type.
The OC System allowed to verify the data recorded in the DB through a set of controls (computerized) created for the study, in order to catch all the possible discrepancies between the data. Every discrepancy was automatically collected in the Discrepancy Management table in OC System with UNREVIEWED flag and MULTIVARIATE discrepancy type. The OC System allowed exporting, with the appropriate function, of the database in SAS System in order to program listings to perform manual check planned for the study.
During the data entry activity DEC must record unsolved questions emerged during entry, in appropriate table (operator comment). These comments were automatically collected in the table "Discrepancy Management" where they were identified as MANUAL by category DATA ENTRY COMMENT. Illegible and inconsistent values were submitted to the Investigator for clarification using Data Query Forms. All CRF data discrepancies were resolved by the investigational site and corrections were made to the database. The state of operator comment

appeared as UNREVIEWED until the review by the DM, who clarified the data with DCF or closes the operator comment by changing the state into NO DISC.

Every CRF field was then evaluated for consistency by a Senior Data Manager using specific ranges and comparison with other data reported in the CRF. The database was subsequently locked so that no further modifications were allowed to the cleaned trial data.
All data table and patient data listings were reviewed by Cronos and CROS-NT to ensure their accuracy.

All statistical analyses and data processing were performed using SAS® Software (release 9.2) on a Windows XP Pro operating system.

9.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

9.7.1 Statistical and Analytical Plans

A Statistical Analysis Plan was written by CROS-NT and approved by Cronos on 02 April 2013 (before data un-blinding). A Blind Review meeting took place on 29 March 2013 (PH&T, CROS NT, and Cronos attended it) and the Data Review Document was discussed. The final version of the Data Review Document was issued on 11 April 2013 before the study was un-blinded. A second Data Review Document was issued on 11 June 2013 following the decision to further investigate the peculiar trend of IOP behavior seen in one investigational center.

All changes from the statistical plan are presented in Section 9.8 of this report.

It is presumed that the randomization plan used in the study smoothed out differences between treatment groups with respect to demographic and other baseline characteristics. Baseline comparability of treatment groups was assessed using descriptive statistics. No hypothesis testing was planned for these comparisons. Furthermore, for each patient, the randomization list also indicated the eye (left or right) to be treated and analyzed. In case of bilateral disease, both the eyes were treated but only the eye specified in the list was considered in the analysis. Therefore the choice of the eye to be investigated was decided “a priori” and it was not decided at the Investigational site. In case of mono-lateral disease, only the diseased eye was treated and analyzed, ignoring the indication reported in the randomization list.

All randomized patients who took at least one dose of study medication and with at least one available post-baseline efficacy evaluation were included in the intent-to-treat population.

All patients from ITT population who completed the study, meeting all inclusion/exclusion criteria and without any major protocol violations were included in the per protocol population.

All randomized patients who took at least one dose of study medication were included in the Safety population.

In order to increase precision and to compensate for any possible imbalance between groups due to the potential relationship between values measured after treatment and basal values, the ANCOVA models used in the analysis included IOP baseline measurement as covariate.

Descriptive statistics were provided for all variables in the summary tables by treatment group. Quantitative criteria were summarised by using n (sample size), mean, standard deviation, median, minimum and maximum. Qualitative criteria were summarized using frequency distributions and percentages.

For the analysis within groups, 95% confidence intervals for the mean changes from baseline were calculated.

Unless otherwise stated, hypothesis testing was carried out at the alpha = 0.05 level (two-sided) when comparing treatments.
All p-values were rounded to three decimal places. Statistical significance was declared if the rounded p-value was less than or equal to 0.050.

All data collected were presented in the listings.

In case an error occurred in treatment allocation, the following rule was followed: if a patient was randomised but received the incorrect treatment, he/she was reported under his/her randomised treatment group for all efficacy analyses, but he/she was reported under the treatment actually received for all safety analyses.

Demographic and baseline characteristics
Descriptive statistics (n, mean, standard deviation, minimum and maximum or frequency distributions, as appropriate) was used, summarized for each treatment group, to describe demographics and the following baseline characteristics:

- age (year)
- sex (male/female)
- race (white, black, Asian, other)
- height (cm)
- weight (kg)
- BMI (kg/m^2)
- study disease assessment (POAG/OH and mono-lateral/bilateral).

Medications were coded using World Health Organization Drug Dictionary (WHO-DD), 2011Q1 (1st Quarter of 2011). Prior and concomitant medications were summarised in the ITT population through frequency distributions and percentages by Anatomical Main Group (1st level of the Anatomical Therapeutic Chemical (ATC) classification), Chemical Subgroup (4th level of the ATC classification) and Preferred Name.

Medical history and physical examination at baseline was summarized by treatment group for the ITT population.

No formal comparison between treatment groups on demographic and screening/baseline characteristics was done.

Primary efficacy variables
IOP measurements at 9.00, 13.00 and 17.00, and the mean of the three measurements at baseline (Visit 2) and at the end of treatment (Visit 7, Week 12) were summarized by treatment using descriptive statistics for the ITT and PP populations.

Assessment of equivalence

At each Intra-Ocular Pressure assessment, three measurements (1st, 2nd and 3rd IOP value) were performed for each eye. The mean of the available measurements was used in the statistical analyses.
At Visit 2 (Randomization/Baseline) and at the end of treatment (Week 12 or End of Study), IOP was measured at 9.00, 13.00 and 17.00: the IOP at these visits was calculated as the mean of the non-missing measurements for the analyses based on ANCOVA models.
The equivalence of Travoprost PR and Travatan® in terms of change in IOP from baseline to end of treatment was analyzed by means of an ANCOVA model including treatment as fixed effect and baseline IOP value as covariate.
The assessment of equivalence was evaluated, on PP and ITT population, by calculating the two-sided 95% confidence intervals for the difference between Least Squares (LS) means, from ANCOVA model, for the two treatment groups.
Travoprost PR was declared equivalent to Travatan® if the two-sided 95% CI for the difference between LS means of the change in IOP from baseline to end of treatment will lie entirely within the interval -1.5 to 1.5 mmHg.

Secondary efficacy variables
IOP measurements taken at 9.00 at each visit were summarized by means of descriptive statistics. Mean changes and mean per cent changes from baseline were calculated with the relative 95% CIs.
Travoprost PR and Travatan® were compared in terms of percent change from baseline to end of treatment by means of an ANCOVA model including treatment as fixed effect and baseline IOP value as covariate. The adjusted means for treatment effect and their 95% confidence intervals were presented, and the two-sided 95% CI for the difference between LS means were calculated. The p-value for the null hypothesis of no difference between treatments was presented.

Safety analysis
Extent of exposure, summarized for each treatment group by means of descriptive statistics was calculated using the following formula:

- if the patient completed the study:

Exposure = Date of Visit 7 - Date of Visit 2 +1;

- if the subject discontinued the study:

Exposure = Date of discontinuation (from the Study Completion form or derived from other data recorded in the CRF) - Date of Visit 2 +1.

Adverse events (AEs) Pre-treatment AEs and TEAEs presented separately. The number of pre-treatment AEs, TEAEs, SAEs, ADRs, serious ADRs and AEs leading to discontinuation, and the number and the percentage of patients experiencing TEAEs, SAEs, ADRs, serious ADRs and AEs leading to discontinuation were summarised by treatment group. AEs were coded using the MedDRA dictionary (version 14.0). The SOCs and PTs were used for tabulation. The number of AEs and the number and the percentage of patients with at least one AE were presented by SOC and PT by treatment group for pre-treatment AEs, TEAEs, SAEs, ADRs, serious ADRs, AEs leading to discontinuation.
Differences between groups were evaluated using chi-square test or, if more than 20% of the cells in a contingency table have expected counts less than 5, Fisher's exact test.

Shift table of physical examination findings from baseline to end of treatment was provided for each treatment group.

Vital signs (systolic and diastolic blood pressure, heart rate) were analysed within each group by means of descriptive statistics. Moreover mean change and 95% confidence interval on mean change from baseline was be calculated at any time point.

Shift table of laboratory values from baseline to end of treatment with regards to normal range, was provided for each treatment group and laboratory test.

Local tolerability
Visual acuity at baseline and at the end of treatment were summarized by means of descriptive statistics for each treatment group. Mean change from baseline and its 95% CI were calculated.

Shift table from baseline to end of treatment was provided for each treatment for the following variables:

- conjunctival hyperemia;
- skin and margins of upper and lower lids abnormalities;
- slit lamp examination abnormalities;
- anterior chamber angle;
- visual field;
- lens opacities;
- retinal abnormalities;
- optic disc abnormalities.

Medications stopped before Visit 2 were distinguished from concomitant medications according to therapy end date. Any drug taken during the study (from Visit 2 up to and including Visit 7), irrespective to the start date, was considered as concomitant medication and coded using WHO Drug Dictionary – 2011Q1 and were presented in data listings and summarized with frequencies by therapeutic subgroup and chemical substance.

9.7.2 Determination of Sample Size

The sample size calculation has been based on the criteria of equivalence of Travoprost PR and Travatan® (in terms of change in IOP value from baseline to end of treatment). The calculation reported in study protocol was modified by protocol amendment n. 1. The most updated version (approved by the IECs of all the eight investigative centers) is reported below:

With 106 subject the study would have had more than 80% power to show the equivalence at a 5% significance level of Travoprost PR versus Travatan® on change in IOP after 12 weeks of treatment, assuming a standard deviation of 2.7 mm Hg and equivalence limits -1.5 and 1.5 mm Hg. Adjusting for dropout rate, it would have been necessary to randomize a total of 120 subjects.

9.7.3 Statistical/Analytical Issues

9.7.3.1 Adjustments for Covariate

In order to increase precision and to compensate for any possible imbalance between groups due to the potential relationship between values measured after treatment and basal values, the ANCOVA models used in the analysis included IOP baseline measurement as covariate.

9.7.3.2 Handling of Dropouts or Missing Data.

No imputation methods were used for patients who discontinued the study or with missing data.

9.7.3.3 Multicentre Study

The center effect was not considered in the statistical analyses.

9.7.3.4 Use of an "Efficacy Subset" of Patients

The PP population has been considered for the primary efficacy variable according to ICH Topic E 9 Statistical Principles for Clinical Trials - CPMP/ICH/363/96 - in order to minimize the incidence of violations of the entry criteria, non-compliance, withdrawals, losses to follow-up, missing data and other deviations from the protocol, and also to minimize their impact on the subsequent analyses.

9.7.3.5 Examinations of Subgroups.

No subgroups were examined.

9.8 CHANGES IN THE CONDUCT OF THE STUDY PLANNED ANALYSES

A Statistical Analysis Plan was issued on 02nd April 2013, before the study was un-blinded. The final analyses performed differed from the Statistical Analysis Plan only for the following:

- In the event of an early termination, the results of all the assessments performed at the discontinuation were taken as end of treatment values (i.e. values recorded at the End of Study were taken as values recorded at Visit 7, Week 12).

Following the first database closure and the draft statistical analysis, an unjustifiable trend of the primary efficacy end-point was observed. A centre effect analysis was performed and one centre (03) was found to have a different, from the others, behavior. The centre was asked to review all the source data and to provide the correct values by answering to the queries: IOP values have been updated for 4 out of 17 patients.
Furthermore, after the first database closure, it was decided to exclude the patient 08010 treated with Travoprost PR from PP population because V7 was performed after 8 and not 12 weeks of treatment and therefore the patient had to be considered as a protocol violator.

10 STUDY PATIENTS

10.1 DISPOSITION OF PATIENTS

A total of 131 patients were enrolled in the trial. Twelve patients were excluded from the study due to screening failures and 120 patients were randomized (Safety Population), 58 patients to the Travoprost PR group and 62 patients to the Travatan® group. Except for three patients in Travoprost PR group and two patients in Travatan® group who had no post-baseline IOP value, all the randomized patients were assessed at Visit 7 or, in the event of an early termination, underwent all assessments planned for Visit 7 at the study discontinuation. Fifteen patients withdrew from the study after randomization.

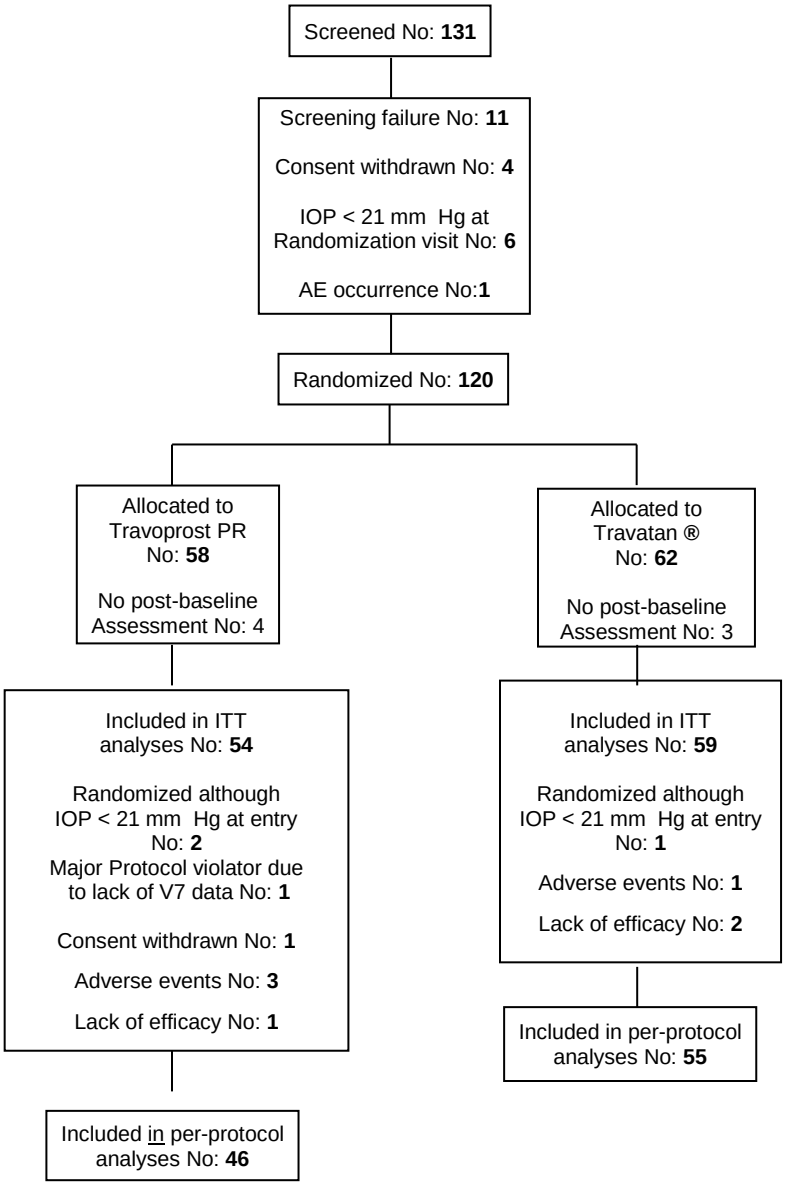

Fig. 2

Figure 2 shows the number of enrolled patients and the number of patients included in the evaluation of safety and efficacy.
The listings of all patients discontinued from the study after enrolment are reported, in Listing 16.2.1-2.2 broken down by center and treatment group, giving a patient identifier, and the specific reason for discontinuation. The data are summarized in Table T14.1-2. The blind for those patients was never broken at the time of discontinuation.

10.2 PROTOCOL DEVIATIONS

Protocol deviations and violations could affect effectiveness or safety of the study. Therefore, each possible protocol deviation or violation was examined by the Sponsor's project manager and by the CROS-NT project manager before beginning the statistical analysis during the Blind Review meeting.

Subjects 06012 and 08007 who did not meet exclusion criterion 6 for one eye, because best corrected visual acuity < 20/200 at the entry have not been considered as protocol violators because the other eye has been analyzed.

As reported in End-of-Text Table T14.1-3.1 and Listing 16.2.2-1.1, 2 patients (Patient Nos. 04007 and 04008) in the Travoprost PR group and 1 patient (Patient No. 04009) in the Travatan® group were major protocol violator because randomized although IOP at randomization visit was < 21 mm Hg. Therefore they have been included in the ITT population but excluded from the PP population. Although, Patient No. 06010 (Travoprost PR group) was a major protocol violator because of IOP at randomizations visit below 21 mm Hg he was not included in ITT because he had no post baseline assessment. Patient No 08010 (Travoprost PR group) was considered as major protocol violator because time windows between visits not respected: he was included in ITT population but excluded from PP population.

As reported in End-of-Text Table T14.1-3.2 and Listing 16.2.2-1.2, Subjects 05020 and 05011 had baseline lab tests performed earlier or later than the Randomization visit, while subjects 03009 and 03015 had end-of-study lab tests performed later than Visit 7. They have been considered as minor protocol violators.

As reported in End-of-Text Table T14.1-3.2 and Listing 16.2.2-1.2, 7 patients in the Travoprost PR group and 3 patients in the Travatan® group were considered as minor protocol violators because they had at least one post-baseline visit (from Visit 3 to Visit 7) postponed or anticipated more than 5 days compared with the date of Visit 2 and/or with date of Visit 2 outside the interval 7-30 days from Screening.

11 EFFICACY EVALUATION

11.1 DATA SETS ANALYSED

The summary of populations for analysis is presented in End-of-Text Table T14.1-4.
A total of 120 patients were included in the Safety population, 58 in the Travoprost PR group and 62 in the Travatan® group.
A total of 113 patients were included in the intent-to-treat population (ITT), 54 in the Travoprost PR group and 59 in the Travatan® group.
A total of 101 patients were included in per protocol population (PP), 46 in the Travoprost PR group and 55 in the Travatan® group.

The number of recruited patients is presented by center in End-of-Text Table T14.1-5.

Population for analysis is also described, patient by patient, in Listing 16.2.3.

11.2 DEMOGRAPHY AND OTHER BASELINE CHARACTERISTICS

Demographic characteristics for the efficacy population (ITT population) are summarized in End-of-Text Table T14.1-6. A listing of demographic and baseline data for individual patients is presented in Listing 16.2.4-1.

A summary of patient demographics is presented in Table B.

TABLE B
DEMOGRAPHIC CHARACTERISTICS

Parameter	Travoprost PR N= 54	Travatan® N=59
Sex, n (%)		
Male	30 (55.6 %)	23 (39.0 %)
Female	24 (44.4 %)	36 (61.0 %)
Age (yrs)		
Mean (SD)	63.2 (11.9)	66.3 (9.3)
Range	32 - 88	44 - 80
Race, n (%)		
White	53 (98.1 %)	58 (98.3 %)
Asian	0	0
Other	1 (1.9 %)	1 (1.7 %)
Weight (kg)		
Mean (SD)	74.2 (15.7)	70.7 (14.3)
Range	47 - 120	48 - 140
Height (cm)		
Mean (SD)	166.9 (9.6)	165.5 (8.1)
Range	146 - 190	150 – 181
BMI (kg/ m^2)		
Mean (SD)	26.5 (4.4)	25.7 (4.4)
Range	19 – 44	19 – 47
Study disease		
Primary open-angle-glaucoma, n (%)	40 (74.1)	46 (78.0)
Ocular hypertension, n (%)	14 (25.9)	13 (22.0)
Study disease		
Mono-lateral, n (%)	7 (13.0)	8 (13.6 %)
Bilateral, n (%)	47 (87.0 %)	51 (86.4 %)

The ITT population includes 24 females (44.4 %) and 30 males (55.6 %) in the Travoprost PR group, and 36 females (61.0 %) and 23 males (39.0 %) in the Travatan® group.

Mean age was balanced between the two treatment groups as follows: 63.2 years in the Travoprost PR group and 66.3 years in the Travatan® group.

Mean weight and height were also balanced between the two groups as follows: weight: 74.2 kg in the Travoprost PR group and 70.7 kg in the Travatan® group; height: 166.9 cm in the

Travoprost PR group and 165.5 cm in the Travatan® group. The high mean values in the Travoprost PR group are well explained by the higher number of male patients in this group.

As reported in End-of-Text Table T14.1-7 and Listings 16.2.4-2, 40 patients (74.1 %) in the Travoprost PR group were affected by primary open-angle-glaucoma and 14 (25.9 %) by ocular hypertension. A similar distribution was observed in the Travatan® group, where 46 patients (78.0 %) were affected by primary open-angel-glaucoma and 13 (22.0 %) by ocular hypertension. As foreseen most of the patients had a bilateral disease (47 in Travoprost PR and 51 in Travatan® group).

The results of medical history in the ITT population are presented in End-of-Text Table T14.1-8.1 and Listing 16.2.4-5.1.
The number of patients with at least one abnormal previous medical condition was 25 (46.3%) in the Travoprost PR group and 30 (50.8%) in the Travatan® group. The most commonly involved systems were: gastro-intestinal system, with 9 abnormal patients (16.7%) in the Travoprost PR group and 11 (18.6%) in the Travatan® group; eyes, ears, nose, throat, with 10 abnormal patients (18.5%) in the Travoprost PR group and 10 (16.9%) in the Travatan® group; genito-urinary with 6 abnormal patients (11.1%) in the Travoprost PR group and 9 (15.3%) in the Travatan® group; neurological with 3 abnormal patients (5.6%) in the Travoprost PR group and 7 (11.9%) in the Travatan® group.

The results of concomitant diseases in the ITT population are presented in End-of-Text Table T14.1-8.2 and Listing 16.2.4-5.2.
The number of patients with at least one abnormal medical condition was 46 (85.2%) in the Travoprost PR group and 51 (86.4%) in the Travatan® group. The most commonly involved systems were: eyes, ears, nose, throat with 24 abnormal patients (44.4%) in the Travoprost PR group and 23 (39.0%) in the Travatan® group; cardiovascular with 27 abnormal patients (50.0%) in the Travoprost PR group and 34 (57.6%) in the Travatan® group; endocrine and metabolic with 19 abnormal patients (35.2%) in the Travoprost PR group and 29 (49.2%) in the Travatan® group; muscoloskeletal with 11 abnormal patients (20.4%) in the Travoprost PR group and 10 (16.9%) in the Travatan® group; gastro-intestinal with 5 abnormal patients (9.3%) in the Travoprost PR group and 13 (22.0%) in the Travatan® group

The number of patients with medications stopped before Visit 2 in the ITT population is presented in End-of-Text Table T14.1-9.1 and Listing 16.2.5. The number of patients with at least one medication stopped before Visit 2 was 16 (29.6%) in the Travoprost PR group and 12 (20.3%) in the Travatan® group. The most common medications were sensory organs drugs (ophtalmologicals), with 16 patients (29.6%) in the Travoprost PR group and 10 (16.9%) in the Travatan® group.

The number of patients with concomitant medications in the ITT population is presented in End-of-Text Table T14.1-9.2 and Listing 16.2.5. The number of patients with at least one concomitant medication was 45 (83.3%) in the Travoprost PR group and 50 (84.7%) in the Travatan® group. The most common medications (i.e. recorded for at least 10% of patients in one of the two groups) were: agents acting on alimentary tract and metabolism, with 17 patients (31.5%) in the Travoprost PR group and 18 (30.5%) in the Travatan® group; anti-infectives for systemic use agents, with 2 patients (3.7%) in the Travoprost PR group and 7 (11.9%) in the Travatan® group; agents acting on blood and blood forming organs, with 12 patients (22.2%) in the Travoprost PR group and 13 (22.0%) in the Travatan® group; agents acting on cardiovascular system, with 34 patients (63.0%) in the Travoprost PR group and 39 (66.1%) in the Travatan® group; agents

acting on the musculoskeletal system, with 5 patients (9.3%) in the Travoprost PR group and 11 (18.6%) in the Travatan® group; agents acting on nervous system, with 10 patients (18.5%) in the Travoprost PR group and 11 (18.6%) in the Travatan® group; agents acting on respiratory system, with 0 patients in the Travoprost PR group and 6 (10.2%) in the Travatan® group; systemic hormonal preparations (excluding sex hormones) with 6 patients (11.1%) in the Travoprost PR group and 10 (16.9%) in the Travatan® group.
None of these drugs are considered likely to interfere with the study drugs.

The results of physical examination at baseline in the Safety population are presented in End-of-Text Shift Table T14.3.4-1 and Listing 16.2.4-4. The number of patients with at least one abnormal condition was 11 (20.0%) in the Travoprost PR group and 12 (20.0%) in the Travatan® group. The most common abnormalities were observed in: eyes, ears, nose, with 7 abnormal patients (12.0%) in the Travoprost PR group and 5 (8.1%) in the Travatan® group; abdomen, with 2 abnormal patients (4.4%) in the Travoprost PR group and 3 (4.8%) in the Travatan® group; heart, with 1 abnormal patient (1.7%) in the Travoprost PR group and 2 (3.2%) in the Travatan® group; skin, with 1 abnormal patient (1.7%) in the Travoprost PR group and 2 (3.2%) in the Travatan® group; chest, with 1 abnormal patient (1.7%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group.

Vital signs at baseline in the Safety population are presented in End-of-Text Table T14.3.4-2.1 and Listing 16.2.7-5.
The mean (± SD) systolic blood pressure of the patients was 132.1 ± 11.6 mmHg (range 110 – 170) in the Travoprost PR group, and 129.9 ± 12.7 mmHg (range 105 – 180) in the Travatan® group. The mean (± SD) diastolic blood pressure of the patients was 79.1 ± 9.4 mmHg (range 60 – 100) in the Travoprost PR group, and 79.4 ± 9.1 mmHg (range 60 – 100) in the Travatan® group. The mean (± SD) heart rate of the patients was 71.0 ± 8.5 bpm (range 56 – 90) in the Travoprost PR group, and 70.5 ± 0.3 bpm (range 48 – 104) in the Travatan® group.

Abnormalities in laboratory tests at screening in the Safety population are summarised in End-of-Text Shift Tables from T14.3.4-3.1 to T14.14.3.4-3.8 and Listing 16.2.7-6. The number of patients with at least one clinically significant abnormality was 6 (10.2%) in the Travoprost PR group and 4 (6.4%) in the Travatan® group.
High, clinically significant values were recorded for the following tests: glucose, with 2 abnormal patients in either groups (3.4% in the Travoprost PR group and 3.2% in Travatan® group); creatinine, with 1 abnormal patient in either groups (1.7 % in Travoprost PR group and 1.6% in Travatan® group; BUN, with 1 abnormal patient (1.6%) in the Travatan® group; uric acid, with 2 abnormal patients (1.1%) in the Travatan® group; ALT, with 1 abnormal patient (1.7%) in Travoprost PR group.

The results of conjunctival hyperemia and lids examination at baseline in the Safety population are presented in End-of-Text Tables T14.3.4-4 and T14.3.4-5 and Listing 16.2.7-1.
The number of patients with mild conjunctival hyperemia was slightly lower in the Travoprost PR group (14 patients, 24.2%) than in the Travatan® group (22 patients, 35.5%). Six patients (10.3%) in the Travoprost PR group and five patients (8.0%) in the Travatan® group had moderate conjunctival hyperemia.
With regards to lids examination, the number of patients with abnormal skin, margin of upper lids and margin of lower lids was 1 (1.7%), 3 (5.2%) and 3 (3.4%), respectively, in the Travoprost PR group, and 3 (4.8%), 4 (6.4%) and 4 (6.4%), respectively, in the Travatan® group.

The results of Visual acuity are presented in Listing 16.2.7-1. Thirty-four patients (61.8 %) in the Travoprost PR group and 33 (55%) in the Travatan® group had visual acuity of 10/10 (or 20/20). All the remaining patients had an adequate visual acuity to be entered into the study (>20/200).

The results of slit lamp examination at baseline in the Safety population are presented in End-of-Text Table T14.3.4-6 and Listing 16.2.7-2. The number of patients with at least one abnormality was 32 (54.4%) in the Travoprost PR group and 39 (62.4%) in the Travatan® group.
Abnormalities were recorded for the following parts of the eye: len, with 17 abnormal patients (29.3%) in the Travoprost PR group and 28 (45.1% a higher frequency) in the Travatan® group; conjunctiva, with 15 abnormal patients (25.8%) in the Travoprost PR group and 20 (31.2%, a slightly higher frequency) in the Travatan® group; cornea, with 3 abnormal patients (5.2%) in the Travoprost PR group and 6 (9.7 %) in the Travatan® group; palpebra, with 2 abnormal patients (3.4%) in the Travoprost PR group and 5 (8.1%) in the Travatan® group; margin upper lids, with 3 abnormal patients (5.2%) in the Travoprost PR group and 4 (6.4%) in the Travatan® group; margin lower lids, with 3 abnormal patients (5.2%) in the Travoprost PR group and 4 (6.4%) in the Travatan® group; iris, with 2 abnormal patients (3.4%) in the Travoprost PR group and 2 (3.2%) in the Travatan® group; vitreous, with 1 abnormal patient (1.7%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group; bulbus, with 1 abnormal patient (1.6%) in the Travatan® group.

The results of anterior chamber angle and visual field at baseline in the Safety population are presented in End-of-Text Tables T14.3.4-7 and T14.3.4-8 and Listing 16.2.7-3. With regards to anterior chamber angle, the value 35-20 was observed in 24 patients (41.4%) in the Travoprost PR group and in 21 (33.9%) in the Travatan® group, while the value 45-35 was observed in the remaining patients in either groups except for 1 patient (1.7%) in the Travatan P group who showed a value of 20. The number of patients with abnormal visual field was 18 (31.0%) in the Travoprost PR group and 26 (42.0 a higher frequency%) in the Travatan® group.

The results of lens opacities, retina and optic disc examination at baseline in the Safety population are presented in End-of-Text Tables T14.3.4-9.1 to T14.3.4-9.4 and Listing 16.2.7-4. With regards to lens opacities, the following distribution was observed for cortical cataract (value, number of patients (%) in the Travoprost PR group, number of patients (%) in the Travatan® group): Ctr, 0 (0%), 0 (0); C1, 26 (44.8%), 28 (45.1%); C2, 12 (20.7%), 13 (20.9%); C3, 1 (1.7%), 3 (4.8%); C4, 1 (1.7%), 0 (0%). The following distribution was observed for nuclear color: NC1, 15 (25.9%), 14 (22.5%); NC2, 12 (120.6%), 18 (29.0%); NC3, 5 (8.6%), 6 (9.7%); NC4, 2 (3.4%), 1 (1.6%). The following distribution was observed for nuclear opalescence: NO1, 14 (24.1%), 16 (25.8%); NO2, 13 (22.4%), 13 (20.9%); NO3, 4 (6.9%), 7 (11.3%); NO4, 2 (3.4%), 2 (3.2%), NO5 0 (o%), 1 (1.6%). The following distribution was observed for posterior subcapsular cataract: PI, 27 (46.6%), 31 (50.0%); P2, 4 (6.9%), 6 (9.7%); P3, 1 (1.7%), 2 (3.2%).

The number of patients with abnormal retina was 9 (15.5%) in the Travoprost PR group and 17 (27.4% a higher frequency) in the Travatan® group, while the number of patients with abnormal optic disc was 25 (43.1%) in the Travoprost PR group and 27 (43.6%) in the Travatan® group.

11.3 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENT DATA

11.3.1 Analysis of Efficacy

The number of patients that were randomized, dosed, and completed the study are displayed in Table C.

TABLE C
EVALUABILITY OF PATIENTS

	Travoprost PR	Travatan®	All Doses
Number of Patients Randomized	58	62	120
Safety Population (Patients Dosed and Evaluable for Safety)	58	62	120
ITT Population (Patients Dosed and with at least one available post-baseline efficacy evaluation)	54	59	113
PP Population (Patients included in the ITT population who completed the study, meeting all exclusion/inclusion criteria and without any major protocol violation and evaluable for Efficacy)	46	55	101

Table data derived from *End-of-Text Tables T14.1-4*

Primary Efficacy Results

Per protocol population (PP)

The results of IOP at baseline and at the end of treatment (Week 12 or End of Study) in the PP population are presented in End-of-Text Table T14.2-2.1.
With regards to the mean of IOP measured at 9.00, 13.00 and 17.00, the mean (± SD) of the patients at baseline was 22.59 ± 1.91 mmHg (range 18.7 – 30.3) in the Travoprost PR group, and 23.02 ± 2.55 mmHg (range 19.7 – 34.0) in the Travatan® group, while the mean (± SD) of the patients at the end of treatment was 14.35 ± 2.08 mmHg (range 10.0 – 20.2) in the Travoprost PR group, and 14.07 ± 2.76 mmHg (range 8.9 – 20.4) in the Travatan® group.
The mean values (± SD) recorded at each single time point at the end of the study reflect the above results: 14.45 ± 2.28 mmHg (range 10.0 – 20.0) in the Travoprost PR group and 14.26 ± 2.99 mmHg (range 8.7 – 22.0) in the Travatan® group at 9.00; 14.20 ± 2.25 mmHg (range 10.0 – 20.0) in the Travoprost PR group and 14.04 ± 3.12 mmHg (range 8.7 – 23.0) in the Travatan® group at 13.00 and 14.40 ± 2.56 mmHg (range 10.0 – 20.7) in the Travoprost PR group and 13.96 ± 2.88 mmHg (range 8.2 – 20.7) in the Travatan® group at 17.00,

The results of primary efficacy analysis on change in IOP from baseline to end of treatment (Week 12 or End of Study) in the PP population are presented in End-of-Text Table T14.2-2.2.
The estimation of the ANCOVA model was based on all 101 patients included in the PP population. A significant effect of the baseline IOP was observed (p-value < 0.001). The LS means of change in IOP from baseline to end of treatment were -8.400 mmHg (95% CI: -9.094 - 7.706) in the Travoprost PR group and -8.823 mmHg (-9.457, -8.189) in the Travatan® group.
The estimate of the difference between treatments (Travoprost PR - Travatan®) was 0.423 mmHg (95% CI: -0.519, 1.365). Since the 95% CI of this difference lays within the margins of equivalence -1.5 to 1.5 mmHg, the equivalence of Travoprost PR and Travatan® was demonstrated.

Intent-to-treat population (ITT)

The results of IOP at baseline and at the end of treatment (Week 12 or End of Study) in the ITT population are presented in End-of-Text Table T14.2-1.1 and Listing 16.2.6.

With regards to the mean of IOP measured at 9.00, 13.00 and 17.00, the mean (± SD) of the patients at baseline was 22.61 ± 1.87 mmHg (range 18.7 – 30.3) in the Travoprost PR group, and 23.04 ± 2.92 mmHg (range 16.1 – 34.0) in the Travatan® group, while the mean (± SD) of the patients at the end of treatment was 14.74 ± 3.35 mmHg (range 10.0 – 33.7) in the Travoprost PR group, and 14.06 ± 2.73 mmHg (range 8.9 – 20.4) in the Travatan® group.

The results of primary efficacy analysis on change in IOP from baseline to end of treatment (Week 12 or End of Study) in the ITT population are presented in End-of-Text Table T14.2-1.2.
The estimation of the ANCOVA model was based on 108 out of the 113 patients included in the ITT population. A significant effect of the baseline IOP was observed (p-value < 0.001). The LS means of change in IOP from baseline to end of treatment were -7.911 mmHg (95% CI: -8.722, -7.099) in the Travoprost PR group and -8.725 mmHg (-9.507, -7.943) in the Travatan® group.
The estimate of the difference between treatments (Travoprost PR - Travatan®) was 0.814 mmHg (95% CI: -0.315, 1.943). Since the 95% CI of this difference does not lay within the margins of equivalence -1.5 to 1.5 mmHg, the equivalence of Travoprost PR and Travatan® was not demonstrated.

Secondary Efficacy Results

- Change and percent change in IOP

The IOP measured at 9.00 during the study and change and percent change from baseline in the ITT population are summarized in End-of-Text Tables T14.2-1.1 and T14.2-1.3.
The mean change from baseline in IOP measured at 9.00 was significant from Visit 3 on in both groups, with a relevant reduction from Visit 2 to Visit 3, followed by a slow decrease until Visit 7 (or End of Study). The mean change from baseline in IOP measured at 9.00 was significant from Visit 3 on in both groups, with a relevant reduction from Visit 2 to Visit 3, followed by a slow decrease until Visit 7 (or End of Study). At Visits 3, 5 and 7 (or End of Study) the mean change from baseline was -7.79 mmHg (range -15.0 - +4.0), -8.28 mmHg (range -13.0 - +5.0) and -7.83 mmHg (range -20.0 - +11.7), respectively, in the Travoprost PR group, and -8.33 mmHg (range -22.0 - -2.0), -8.60 mmHg (range -16.0 – 0.0) and -8.93 mmHg (range -19.0 - +3.0), respectively, in the Travatan® group. A similar trend was observed for mean percent change from baseline in IOP measured at 9.00. At Visits 3, 5 and 7 (or End of Study) the mean percent change from baseline was -33.92% (range -54.5 - +18.5), -36.06% (range -56.5 - +23.1) and -33.76 (range -66.7 - +53.8), respectively, in the Travoprost PR group, and -35.33% (range -64.7 - -7.7), -36.57% (range -62.0 – 0.0) and -37.7% (range -60.6 - +22.0), respectively, in the Travatan® group.

The estimation of the ANCOVA model was based on 108 out of 113 patients included in the ITT population. The LS means of percent change in IOP from baseline to end of treatment were -34.611% (95% CI: -38.139, -31.084) in the Travoprost PR group and -38.061% (-41.460, -34.663) in the Travatan® group.
The estimate of the difference between treatments (Travoprost PR - Travatan®) was 3.450 (95% CI: -1.456, 8.356, p-value = 0.166).

11.4 EFFICACY CONCLUSIONS

The estimate of the difference between treatments (Travoprost PR - Travatan®) in change in IOP from baseline to end of treatment (Week 12 or End of Study) was 0.814 mmHg (95% CI: -0.315, 1.943) in the ITT population and 0.423 mmHg (95% CI: -0.519, 1.362) in the PP population.

Since the confidence intervals in the PP population lay within the margins of equivalence -1.5 to 1.5 mmHg, equivalence of Travoprost PR and Travatan® in the treatment of subjects affected by primary angle glaucoma or ocular hypertension in terms of intra-ocular pressure (change from baseline to end of treatment) was demonstrated. In the ITT population the incidence of violations of the entry criteria, withdrawals, and lack of efficacy could have had an impact on the subsequent analyses.
The estimate of the difference between treatments (Travoprost PR - Travatan®), in the ITT population, in per cent change in IOP from baseline to end of treatment (Week 12 or End of Study) was 3.450% (95% CI: -1.456, 8.356) with a p value of 0.166.

12 SAFETY EVALUATION

12.1 EXTENT TO EXPOSURE

The duration of exposure in the Safety population is presented in End-of-Text Table T14.3-1.
The median duration of exposure was 83 days (range 7 – 96) in the Travoprost PR group and 84 days (range 5 – 100) in the Travatan® group.

12.2 ADVERSE EVENTS (AEs)

The summary of adverse events during the run-in period in the Safety population is presented in End-of-Text Table T14.3.1-1.1 and single data are presented in Listing 16.2.7-7.
The total number of adverse events was 1 in each treatment group (1.7% in the Travoprost PR group and 1.6% in Travatan® group).

The summary of adverse events during the treatment period in the Safety population is presented in End-of-Text Table T14.3.1-1.2 and single data are presented in Listing 16.2.7-7..
The total number of adverse events during the treatment period was not substantially different and the number of patients with at least one AE was not statistically different between Travoprost PR group and the Travatan® group, with 57 AEs in the Travoprost PR group and 73 in the Travatan® group.

The number of patients with at least one AE was 22 (37.9%) in the Travoprost PR group and 27 (43.5%) in the Travatan® group. The difference between groups was not significant (chi-square test p-value = 0.532).

The total number of drug-related adverse events was 38 in the Travoprost PR group and 43 in the Travatan® group.
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The number of patients with at least one drug-related AE was 19 (32.8%) in the Travoprost PR group and 22 (35.5%) in the Travatan® group. The difference between groups was not significant (chi-square test p-value = 0.753).
The number of patients reporting adverse events during the treatment period by System Organ Class and Preferred Term in the Safety population is presented in End-of-Text Table T14.3.1-2.
The most commonly involved SOCs were: eye disorders, with 16 patients (27.6%) in the Travoprost PR group and 17 (27.4%) in the Travatan® group; infections and infestations, with 2 patients (3.4%) in the Travoprost PR group and 9 (14.5%) in the Travatan® group; musculoskeletal and connective tissue disorders, with 2 patients (3.4%) in the Travoprost PR group and 5 (8.1%) in the Travatan® group; skin and subcutaneous tissue disorders, with 4

patients (6.9%) in the Travoprost PR group and 3 (4.8%) in the Travatan® group; vascular disorders, with 4 patients (6.9%) in the Travoprost PR group and 3 (4.8%) in the Travatan® group; respiratory, thoracic and mediastinal disorders, with 2 patients (3.4%) in the Travoprost PR group and 4 (6.5%) in the Travatan® group; gastrointestinal disorders, with 1 patient (1.7%) in the Travoprost PR group and 4 (6.5%) in the Travatan® group; nervous system disorders, with 2 patients (3.4%) in the Travoprost PR group and 3 (4.8%) in the Travatan® group.
The most commonly reported AEs by PT (i.e. those reported by at least 3% of patients in either group) were: conjuctival hyperaemia, with 6 patients (10.3%) in the Travoprost PR group and 5 (8.1%) in the Travatan® group; eye irritation, with 4 patients (6.9%) in the Travoprost PR group and 7 (11.3%) in the Travatan® group; eyelid oedema, with 2 patients (3.4%) in the Travoprost PR group and 0 (0%) in the Travatan® group; ocular hyperaemia, with 3 patients (5.2%) in the Travoprost PR group and 2 (3.2%) in the Travatan® group; vision blurred, with 2 patients (3.4%) in the Travoprost PR group and 0 (0%) in the Travatan® group; fatigue, with 0 patients (0%) in the Travoprost PR group and 2 (3.2%) in the Travatan® group; ear infections, with 0 patients (0%) in the Travoprost PR group and 3 (4.8%) in the Travatan® group; nasopharyngitis, with 2 patients (3.4%) in the Travoprost PR group and 3 (4.8%) in the Travatan® group; arthralgia, with 1 patient (1.7%) in the Travoprost PR group and 2 (3.2%) in the Travatan® group; neck pain, with 1 patient (1.7%) in the Travoprost PR group and 2 (3.2%) in the Travatan® group; headache, with 2 patients (3.4%) in the Travoprost PR group and 2 (3.2%) in the Travatan® group; dyspnoea, with 2 patients (3.4%) in the Travoprost PR group and 0 (0%) in the Travatan® group; oropharingeal pain, with 0 patients (0%) in the Travoprost PR group and 3 (4.8%) in the Travatan® group; pruritus, with 2 patients (3.4%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group; hyperaemia, with 2 patients (3.4%) in the Travoprost PR group and 3 (4.8%) in the Travatan® group.

The number of patients reporting drug-related adverse events during the treatment period by System Organ Class and Preferred Term in the Safety population is presented in End-of-Text Table T14.3.1-4.
The involved SOCs were: ear and labyrinth disorders, with 1 patient (1.7%) in the Travoprost PR group and 0 (0%) in the Travatan® group; eye disorders, with 14 patients (24.1%) in the Travoprost PR group and 16 (25.8%) in the Travatan® group; gastrointestinal disorders, with 0 patients (0%) in the Travoprost PR group and 2 (3.2%) in the Travatan® group; general disorders and administration site conditions, with 1 patient (1.7%) in the Travoprost PR group and 2 (3.2%) in the Travatan® group; infections and infestations, with 0 patients (0%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group; investigations, with 1 patient (1.7%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group; musculoskeletal and connective tissue disorders, with 0 patient (0%) in the Travoprost PR group and 2 (3.2%) in the Travatan® group; nervous system disorders, with 2 patients (3.4%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group; psychiatric disorders, with 0 patient (0%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group; respiratory, thoracic and mediastinal disorders with 2 patients (3.4%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group; skin and subcutaneous tissue disorders, with 4 patients (6.9%) in the Travoprost PR group and 3 (4.8%) in the Travatan® group.

The most commonly reported drug-related AEs by PT (i.e. those reported by at least 3% of patients in either group) were: conjuctival hyperaemia, with 6 patients (10.3%) in the Travoprost PR group and 5 (8.1%) in the Travatan® group; dry eye, with 1 patient (1.7%) in the Travoprost PR group and 2 (3.2%) in the Travatan® group; eye irritation, with 3 patients (5.2%) in the Travoprost PR group and 7 (11.3%) in the Travatan® group; eye pruritus, with 1 patient (1.7%) in the Travoprost PR group and 3 (4.8%) in the Travatan® group; eyelid oedema, with 2 patients (3.4%) in the Travoprost PR group and 0 (0%) in the Travatan® group; ocular hyperaemia, with 3

patients (5.2%) in the Travoprost PR group and 2 (3.2%) in the Travatan® group; headache, with 2 patients (3.4%) in the Travoprost PR group and 0 (0%) in the Travatan® group; dyspnoea, with 2 patients (3.4%) in the Travoprost PR group and 0 (0%) in the Travatan® group; pruritus, with 2 patients (3.4%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group; hyperaemia, with 2 patients (3.4%) in the Travoprost PR group and 3 (4.8%) in the Travatan® group; hypertension, with 2 patients (3.4%) in the Travoprost PR group and 0 (0%) in the Travatan® group.

12.3 ADVERSE EVENTS LEADING TO PREMATURE DISCONTINUATION OF INVESTIGATIONAL PRODUCT AND/OR STUDY

The summary of adverse events during the run-in period in the Safety population is presented in End-of-Text Table T14.3,1-1.1.
No adverse events leading to withdrawal were reported during the run-in period.

The summary of adverse events during the treatment period in the Safety population is presented in End-of-Text Table T14.3.1-1.2.
The total number of adverse events leading to withdrawal was 14 in the Travoprost PR group and 5 in the Travatan® group.
The number of patients with at least one AE leading to withdrawal was 5 (8.6%) in the Travoprost PR group and 3 (4.81%) in the Travatan® group. The difference between groups was not significant (Fisher exact test p-value = 0.481).

The number of patients reporting adverse events leading to withdrawal during the treatment period by System Organ Class and Preferred Term in the Safety population is presented in End-of-Text Table T14.3.1-6.
The involved SOCs were the following: eye disorders, with 3 patients (5.2%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group; general disorders and administration site conditions, with 1 patient (1.7%) in the Travoprost PR group and 0 (0%) in the Travatan® group; injury, poisoning and procedural complications, with 0 patients (0%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group; investigations (heart rate increase), with 1 patient1 (1.7%) in the Travoprost PR group and 0 (0%) in the Travatan® group; musculoskeletal and connective tissue disorders, with 0 patient (0%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group; nervous system disorders, with 2 patients (3.4%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group; psychiatric disorders, with 0 patients (0%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group; respiratory, thoracic and mediastinal disorders, with 2 patients (3.4%) in the Travoprost PR group and 0 (0%) in the Travatan® group; skin and subcutaneous tissue disorders, with 1 patient (1.7%) in the Travoprost PR group and 0 (0%) in the Travatan® group; vascular disorders, with 1 patient (1.7%) in the Travoprost PR group and 0 (0%) in the Travatan® group.

12.4 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

12.4.1 Listing of Deaths, other Serious Adverse Events and Other Significant Adverse Events

The summary of adverse events during the run-in period in the Safety population is presented in End-of-Text Table T14.3.1-1.1.

No serious adverse events were reported during the run-in period.

The summary of adverse events during the treatment period in the Safety population is presented in End-of-Text Table T14.3.1-1.2 and single data are presented in Listing 16.2.7-7.

12.4.1.1 Deaths

No death occurred during this trial.

12.4.1.2 Other Serious Adverse Events

The total number of serious adverse events was 2, reported by 1 patient (1.7%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group. The difference between groups was not significant (Fisher exact test p-value = 1.000).

The number of patients reporting serious adverse events during the treatment period by System Organ Class and Preferred Term in the Safety population is presented in End-of-Text Table T14.3.1-3.
One patient (1.7%) in the Travoprost PR group reported eyelid ptosis and 1 patient (1.6%) in the Travatan® group reported femur fracture.

12.4.2 Narrative of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

Femur fracture [Femur fracture] (10016454) (v.16.0)
This case comes from the clinical study TRAVOPROST 01/11 (EUDRACT NR 2011-005419-10) . The SAE form was received on 09/01/2013 from the Investigator by fax. A female, white, 77-year old patient (01-013-013) experienced a femoral bone fracture on 14/12/2012, due to an accident. The event was considered as serious (hospitalization), not related by the investigator. She underwent a surgical operation and at the time of the reporting was still hospitalized in a private clinic so the outcome was unknown. She was affected by bilateral glaucoma and had been in treatment with Travoprost 1 drop every day in both eyes, from 19/09/2012. On 10/01/2013 follow up information has been received: the CRO confirmed that the patient suspended Travoprost and was dropped-out from the study in an unspecified date. On 13/01/2013 follow up information has been received: the updated SAE form has been received. The patient underwent a total femoral replacement (prosthesis) at the outcome of the event was recovered with sequelae. Concomitant drugs were Bifril (Zofenopril) tablets 30 mg/die p.o. for hypertension; Acetylsalicylic acid tables 100 mg/die p.o. for heart protection. Her medical history included various bone injuries in the past years, a surgery for discal hernia (L4-L5) in 1977 and 1981.
On 27/03/2013 follow up information has been received: the patient was not previously treated with any drug due to high IOP values (naïf patient). She underwent a surgery for breast cancer in 2003. She was affected by gastritis and albinism. The discharge date of the surgery (femur prosthesis) was not available. The patient did not perform V7 and she was considered as withdrawn on 18 December 2012 when the investigator became aware of the SAE.
Sender comments:

The event femoral bone fracture was considered as severe, serious (involved or prolonged hospitalisation) and not related to the study drug by both investigator and sponsor (WHO-UMC System). It was considered as unexpected according to the Investigator Brochure.
On 16/04/2013 follow up information has been received from the CRO: the patient continued the treatment with the study drug until the period scheduled, even if she was hospitalised. She didn't perform last visit (V7), as she was still hospitalised, and so was considered as dropped-out from the study.
Sender comments:
This information does not change the assessment of this case: the sponsor considered it as a serious (hospitalization) not related adverse event.

Paresis cranial nerve [Paresis cranial nerve] (10061911) (v.16.0)
This case comes from the clinical study TRAVOPROST 01/11 (EUDRACT NR 2011-005419-10) . The SAE form was received on 13/03/2013 from the CRO. A male, white, 72-year old patient (04-007-127) experienced ptosis due to III cranial nerve right paresis on 30/11/2012 due to cold. The event was considered as severe, serious (persistent and significant disability) and not related to the study treatment by the investigator.No lab tests or technical procedures were performed due to the event. The adverse event was treated with Nicetile (L-acetylcarnitine HCl) 500 mg, one vial i.m. daily (from 03/12/2012 ongoing at the end of the study) and Deltacortene (prednisone) 25 mg tablets p.o. once a day (from 03/12/2012 ongoing at the end of the study). The event was unchanged or worsening at the time of the reporting: the patient was followed by his doctor and was scheduled for a neurological visit. The patient was treated with Travoprost two drops daily for primary angle glaucoma from 25/09/2012 to 17/12/2012. The patient suffered from hypertension and was in treatment with Pritorplus 40-12.5 mg tablets (Telmisartan 40 mg + Hydrochlorthiazide 12.5 mg). This treatment was ongoing at the end of the study. On 27/03/2013 follow up information has been received: the patient was also in treatment with Bifril (Zofenopril) for arterial blood pressure since unknown date. No action was taken with the study drug and the patient completed the study on 04/12/12.
Sender comments:
The event paresis cranial nerve was considered as serious (persistent and significant disability) and not related to the study drug by both investigator and sponsor (WHO-UMC System).
It was considered as unexpected according to the Investigator Brochure.

One patient experienced a serious event during the run-in phase and ended the study as Screening Failure, therefore he was not considered within the Safety population analysis but a CIOMS was issued by the Sponsor. The narrative is reported below.

Asthenia [Asthenia] (10003549) (v.16.0)
This case comes from the clinical study TRAVOPROST 01/11 (EUDRACT NR 2011-005419-10) . It was received on 13/03/2013 from the CRO as line listing of SAEs for reconciliation purpose. Patient 06-002-NA (unknown sex, age and race) experienced asthenia on 24/07/2012 , after the first visit and before starting the treatment with the study drug (pre-treatment event). The event was considered as severe, serious (involved or prolonged hospitalisation) and not related to the study treatment by the investigator. The adverse event caused the study discontinuation and ended on 05/09/2012 (date of discharge) with sequelae. On 27/03/2013 follow up information has been received: a lung cancer with bone metastasis was diagnosed. The patient was affected by hypertension, treated with Olpress (olmesartan medoxomil) since an unknown date, type II diabetes, treated with Lantus (insulin glargine) and Insuman (human insulin) since unknown date,

diabetic nephropathy and neuropathy and anaemia. The patient was discontinued from the study on 09/09/2012 before drug assignment.
Sender comments:
The event asthenia was considered as severe and serious (involved or prolonged hospitalization). It was a pre-treatment event therefore relationship between event occurrence and study drug was assessed as not related. It was considered as unexpected according to the Investigator Brochure.

Finally, two more not serious adverse events, according the Investigators, have been assessed as serious, because medically relevant by the Sponsor and CIOMS had been issued. Here below the narratives are reported.

Uterine Polypectomy [Uterine Polypectomy] (10046813) (v.16.0)
This case comes from the clinical study TRAVOPROST 01/11 (EUDRACT NR 2011-005419-10) and was received on 28/03/2013 from the CRO as line listing of AEs for reconciliation purpose. The patient (006-009 of the study centre 06) underwent an endometrial polypectomy on 15/10/2012. The event was considered as not serious, not related to the study drug and with a moderate intensity by the investigator. The outcome was also provided: recovered without sequelae. No further information was provided.
Sender comments:
On 03/04/2013 further information has been requested to the CRO, in order to better evaluate this case. According to the information provided, this case is a serious event (medically important condition). On 03/04/2013 the CRF was received by the CRO: in screening visit (V1) uterine polypus was reported in the medical history of the patient. The event was described as endometrial polypectomy, started on 15/10/2012 and ended on 15/10/2012 without sequelae.
Patient medical history included myopia, hypertension treated with Zestoretic (Lisinopril 20mg + hydrochlorothiazide12.5mg) tablets once a day p.o. since 1983 and arthrosis. The patient was affected by bilateral glaucoma and has been in treatment with Xalacom (Latanoprost and timololo maleate) ocular drops, 1 drop, once a day, from 02/07/2008 to 24/09/2012. The patient started treatment with Vytorin (ezetimibe 10 mg + simvastatin 10 mg) tablets, once a day p.o. on 13/11/2012 for hypercholesterolemia. The patient experienced also itchy superior limbs skin spots on 05/10/2012 and vertigo on 09/10/2012. These were considered as not serious, mild events by the investigator. The patient completed the study within the Travoprost PR group.
Sender comments:
The event uterine polypectomy was upgraded as serious (medically important condition) by the sponsor. It was judged as not related to the study drug (WHO-UMC system) and unexpected according to the Investigator Brochure. Further information was requested to the investigator.
The sponsor agrees with the investigator: itchy superior limbs skin spots (p.t.: Rash pruritic) and vertigo (p.t.: Vertigo) are judged as not serious events. Also hypercholesterolemia has to be included in the not serious adverse events. On 03/04/2013 the CRO informed the sponsor that the patient was not hospitalised for polypectomy but was treated in day hospital regimen.
Sender comments:
This information does not change the assessment of this case: the sponsor considered it as a serious (medically important condition) not related adverse event. On 10/04/2013 follow up information has been received by the Investigator: the patient was already affected by uterine polyposis at the time of the screening visit (V1). The surgery performed on 15/10/2012 was scheduled before the enrolment. There wasn’t a worsening of her clinical condition and the polyp was benign in nature.
Sender comments:
This information does not change the assessment of this case: the sponsor considered it as a serious (medically important condition) not related adverse event.

Epithelioma excision [Skin neoplasm excision] (10053063) (v.16.0)
Eye redness [Ocular hyperaemia] (10015963) (v.16.0)
Ocular itching [Eye pruritus] (10030048) (v.16.0)
This case comes from the clinical study TRAVOPROST 01/11 (EUDRACT NR 2011-005419-10) and was received on 28/03/2013 from the CRO as line listing of AEs for reconciliation purpose. The patient (005-015-138 of the study centre 05) underwent an epithelioma surgery on 20/09/2012. On the same day she experienced ocular redness and ocular itching.
Epithelioma surgery was considered as not serious, not related to the study drug and with a moderate intensity by the investigator. No actions were taken for the event that recovered without sequelae. The other two events were considered not serious, probable related to the study drug and with a mild intensity by the investigator. No actions were taken for the events that were ongoing at the time of the reporting. No further information was provided.
Sender comments:
On 03/04/2013 further information has been requested to the CRO, in order to better evaluate this case. According to the few information provided, the sponsor suspected that the event epithelioma surgery should be considered as a medically important condition and therefore considered as serious. On 04/04/2013 follow up information has been received: the CRO provided the sponsor with the CRF. The medical history of the patient reported that the suspect skin epithelioma was a pre-existent condition already recorded in screening visit (V1). The epithelioma excision was performed on 20/09/2012 and ended on the same day without sequelae. It was considered as not serious, not related to the study drug and with a moderate intensity by the investigator. On the same day the patient experienced also ocular redness and ocular itching, considered as not serious. The patient was affected by bilateral primary open-angle-glaucoma. Her medical history included spastic colitis, reumathic pain, skin fungus, bilateral hallux valgus surgery. The patient experienced also knee pain on 29/09/2012, that was treated with Voltaren tablets 75 mg once a day per os (treatment dates: 29/09/2012 – 30/09/2012). The event ended on 30/09/2012 without sequelae. She experienced also right arm pain on 02/11/2012, treated with Ibuprofene tablets 600 mg once a day per os (treatment dates: 05/11/2012 –09/11/2012) and ended on 09/11/2012 without sequelae. These events were all considered as not serious, not related to the study drug with moderate intensity by the investigator. The patient took also Ibuprofene (tablets 600 mg twice a day per os) for thorax pain on 08/09/2012. The patient completed the study within Travatan® group.
Sender comments:
The event epithelioma excision was upgraded as serious (medically important condition) by the sponsor. It was judged as not related to the study drug (WHO-UMC system) and unexpected according to the Investigator Brochure. Further information were requested to the investigator.
The sponsor agreed with the investigator: eye redness and ocular itching are judged as expected (according to the Investigator Brochure) not serious events and these not serious events were probably related to the study drug. The sponsor thought that also thorax pain has to be included in the not serious adverse events. On 11/04/2013 follow up information has been received from the CRO: the investigator stated that epithelioma excision has been already scheduled in a date to be defined. In the enrolment period, changes in lesions have not been reported.
Sender comments:
This information does not change the assessment of this case: the sponsor considered it as a serious (medically important condition), not related adverse event.

12.5 CLINICAL LABORATORY EVALUATION

Single patient lab data are presented in Listing 16.2.7-6.

Shift from screening to end of treatment (Week 12 or End of Study) in glucose in the Safety population is presented in End-of-Text Table T14.3.4-3.1.
The only shift to clinically significant abnormalities was observed in one patient (1.6%) in the Travatan® group (from clinically insignificant at screening to high clinically significant at the end of treatment).

Shift from screening to end of treatment (Week 12 or End of Study) in creatinine in the Safety population is presented in End-of-Text Table T14.3.4-3.2.
No shifts to clinically significant abnormalities were observed.

Shift from screening to end of treatment (Week 12 or End of Study) in BUN in the Safety population is presented in End-of-Text Table T14.3.4-3.3.
The only shift to clinically significant abnormalities was observed in one patient (1.7%) in the Travoprost PR group (from normal at screening to high clinically significant at the end of treatment because of a too low value).

Shift from screening to end of treatment (Week 12 or End of Study) in AST in the Safety population is presented in End-of-Text Table T14.3.4-3.4.
No shifts to clinically significant abnormalities were observed.

Shift from screening to end of treatment (Week 12 or End of Study) in ALT in the Safety population is presented in End-of-Text Table T14.3.4-3.5.
No shifts to clinically significant abnormalities were observed.

Shift from screening to end of treatment (Week 12 or End of Study) in sodium in the Safety population is presented in End-of-Text Table T14.3.4-3.6.
No shifts to clinically significant abnormalities were observed.

Shift from screening to end of treatment (Week 12 or End of Study) in potassium in the Safety population is presented in End-of-Text Table T14.3.4-3.7.
No shifts to clinically significant abnormalities were observed.

Shift from screening to end of treatment (Week 12 or End of Study) in uric acid in the Safety population is presented in End-of-Text Table T14.3.4-3.8.
No shifts to clinically significant abnormalities were observed.

12.6 VITAL SIGNS, PHYSICAL FINDINGS AND OPHTALMOLOGICAL ASSESSMENTS

Vital signs
Systolic blood pressure, diastolic blood pressure and heart rate during the study and changes from baseline in the Safety population are presented in End-of-Text Tables T14.3.4-2.1, T14.3.4-2.2, and T14.3.4-2.3 respectively. The single patient data are presented in Listing 16.2.7-58.
No significant changes from baseline observed were observed.

Physical examination
Shift from baseline to end of treatment (Week 12 or End of Study) in physical examination in the Safety population is presented in End-of-Text Table T14.3.4-1. The single patient data are presented in Listing 16.2.4-4.

Shifts from normal baseline to abnormality were observed in the following systems: eyes, ears, nose, with 4 patient (6.9%) in the Travoprost PR group; mouth and throat, with 1 patient (1.7%) in the Travoprost PR; neck, with 1 patient (1.6%) in the Travatan® group; chest, with 1 patient (1.7%) in the Travoprost PR group and 1 patient (1.6%) in the Travatan® group; heart, with 1 patient (1.6%) in the Travoprost PR group and 2 patients (3.2%) in the Travatan® group; abdomen with 2 patients (3.4%) in the Travoprost PR group and 1 patient (1.6%) in the Travatan® group; neurological, with 1 patient (1.6%) in the Travatan® group; skin, with 1 patient (1.6%) in the Travatan® group; limbs, with 1 patient (1.6%) in the Travatan® group.

Local tolerability

Visual acuity at baseline and at the end of treatment (Week 12 or End of Study) in terms of frequency of the values in the Safety population is presented in End-of-Text Table T14.3.4-4.1. The single patient data are presented in Listing 16.2.7-1.
No significant changes from baseline were observed in both groups.

Shift from baseline to end of treatment (Week 12 or End of Study) of conjunctival hyperemia in the Safety population is presented in End-of-Text Table T14.3.4-4.2. The single patient data are presented in Listing 16.2.7-1.
The following shifts were observed: from none or trace at baseline to mild at the end of treatment, with 10 patients (17.2%) in the Travoprost PR group and 10 (16.1%) in the Travatan® group; from none or trace at baseline to moderate at the end of treatment, with 4 patients (6.9%) in the Travoprost PR group and 5 patients (8.1) in the Travatan® group; from none or trace at baseline to severe at the end of treatment, with 1 patient (1.7%) in the Travoprost PR group; from mild at baseline to moderate at the end of treatment, with 7 patients (12.1%) in the Travatan® group and 8 patients (12.9%) in the Travatan® group; from mild at baseline to severe at the end of treatment, with 2 patients (3.2%) in the Travatan®. Furthermore two subjects in the Travoprost PR group and two in the Travatan® group had an improvement from mild to none.

Shift from baseline to end of treatment (Week 12 or End of Study) in lids examination in the Safety population is presented in End-of-Text Table T14.3.4-5. The single patient data are presented in Listing 16.2.7-1.

Shifts from normal baseline to abnormality were observed in the following parts of the eye: skin, with 1 patient (1.7%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group; margin of lower lids, with 1 patient (1.7%) in the Travatan® group; margin of upper lids, with 2 patients (3.4%) in the Travoprost PR group and 2 (3.2%) in the Travatan® group.

Shift from baseline to end of treatment (Week 12 or End of Study) in slit lamp examination in the Safety population is presented in End-of-Text Table T14.3.4-6. The single patient data are presented in Listing 16.2.7-2 4.
Shifts from normal baseline to abnormality were observed in conjunctiva, with 10 patients (17.2%) in the Travoprost PR group and 14 (22.6%) in the Travatan® group; palpebra, with 2 patients (3.4%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group; len, with 1 patient (1.6%) in the Travatan® group; vitreous membrane, with 1 patient (1.6%) in the Travatan® group.

Shift from baseline to end of treatment (Week 12 or End of Study) of anterior chamber angle in the Safety population is presented in End-of-Text Table T14.3.4-7. The single patient data are presented in Listing 16.2.7-3.
The shifts were observed in 4 patients (6.9%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group (from 35-20 at baseline to 45-35 at the end of treatment) and in 1 patient (1.7%)

in the Travoprost PR group and 2 (3.2%) in the Travatn® group (from 45-35 at baseline to 35-20 at the end of treatment).

Shift from baseline to end of treatment (Week 12 or End of Study) in visual field in the Safety population is presented in End-of-Text Table T14.3.4-8. The single patient data are presented in Listing 16.2.7-3.
The following shifts were observed: from normal at baseline to abnormal at the end of treatment, with 4 patients (6.9%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group; from abnormal at baseline to normal at the end of treatment, with 1 patient (1.7%) in the Travoprost PR group and 5 (8.1) in the Travatan® group.

Shift from baseline to end of treatment (Week 12 or End of Study) in cortical cataract in the Safety population is presented in End-of-Text Table T14.3.4-9.1. The single patient data are presented in Listing 16.2.7-4.
The following shifts were observed: from: from C1 at baseline to C2 at the end of treatment in 1 patient (1.7 %) in the Travoprost PR and 2 (3.2%) in the Travatan® group; from C1 at baseline to C3 at the end of treatment in 1 patient (1.6%) in the Travatan® group; and from C2 to C1 in 1 patient (1.7 %) in the Travoprost PR group and 2 (3.2%) in the Travatan® group.

Shift from baseline to end of treatment (Week 12 or End of Study) in nuclear color in the Safety population is presented in End-of-Text Table T14.3.4-9.2. The single patient data are presented in Listing 16.2.7-4.
The following shifts were observed: from NC2 at baseline to NC3 at the end of treatment in 2 patients (3.4%) in the Travoprost PR group; from NC3 at baseline to NC4 at the end of treatment in 1 patient (1.7%) in the Travoprost PR group; from NC2 at baseline to NC4 at the end of treaement in 1 patient (1.6%) in the Travatan® group.

Shift from baseline to end of treatment (Week 12 or End of Study) in nuclear opalescence in the Safety population is presented in End-of-Text Table T14.3.4-9.3. The single patient data are presented in Listing 16.2.7-4.
The following shifts were observed: from NO2 at baseline to NO3 at the end of treatment, with 3 patients (5.2%) in the Travoprost PR group and 2 (3.2%) in the Travatan® group; from NO3 at baseline to NO4 at the end of treatment, with 1 patient (1.1%) in the Travatan® group; from NO3 at baseline to NO2 at the end of treatment, with 1 patient (1.1%) in the Travatan® group.

Shift from baseline to end of treatment (Week 12 or End of Study) in posterior subcapsular cataract in the Safety population is presented in End-of-Text Table T14.3.4-9.4. The single patient data are presented in Listing 16.2.7-4.
Only one shift was observed, from P3 at baseline to P2 at the end of treatment in 1 patient (1.6%) in the Travatan® group.

Shift from baseline to end of treatment (Week 12 or End of Study) in retina and optic disc examination in the Safety population are presented in End-of-Text Table T14.3.4-10. The single patient data are presented in Listing 16.2.7-4.
The only shift, from normal baseline to abnormality, in the detailed retinal examination was observed in one patient (1.7%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group.
The only shift, from abnormal baseline to normality, in the detailed optic disk examination was observed in 4 patients (6.5%) in the Travatan® group.

12.7 SAFETY CONCLUSIONS

The median duration of exposure was 83 days (range 7 – 96) in the Travoprost PR group and 84 days (range 5 – 100) in the Travatan® group.

The total number of adverse events during the treatment period was 57 in the Travoprost PR group and 73 in the Travatan® group.
The number of patients with at least one AE during the treatment period was 22 (37.9%) in the Travoprost PR group and 27 (43.5%) in the Travatan® group. The difference between groups was not significant (chi-square test p-value = 0.532).
The total number of drug-related adverse events was 38 in the Travoprost PR group and 41 in the Travatan® group.
The number of patients with at least one drug-related AE was 19 (32.8%) in the Travoprost PR group and 22 (35.5%) in the Travatan® group. The difference between groups was not significant (chi-square test p-value = 0.753).

The total number of serious adverse events during the treatment period was 2, reported by one patient (1.7%) in the Travoprost PR group and 1 patient (1.6%) in the Travatan® group, both not drug related. The difference between groups was not significant (Fisher exact test p-value = 1.000).

The total number of adverse events leading to withdrawal during the treatment period was 14 in the Travoprost PR group and 5 in the Travatan® group.
The number of patients with at least one AE leading to withdrawal during the treatment period was 5 (8.6%) in the Travoprost PR group and 3 (4.8%) in the Travatan® group. The difference between groups was not significant (Fisher exact test p-value = 0.481).

With regards to laboratory, shifts to clinically significant abnormalities were observed in the following tests: glucose, with 1 patient (1.6%) in the Travatan® group; BUN, with 1 patient (1.7%) in the Travoprost PR group (below the lower limit).

With regards to physical examination, shifts from normal baseline to abnormality were observed in the following systems: chest, with 1 patient (1.7%) in the Travoprost PR group and 1 patient (1.6%) in the Travatan® group; heart, with 1 patient (1.6%) in the Travoprost PR group and 2 patients (3.2%) in the Travatan® group; abdomen with 2 patients (3.4%) in the Travoprost PR group and 1 patient (1.6%) in the Travatan® group: Furthermore the following shifts were observed only in one treatment group: eyes, ears, nose, with 4 patient (6.9%) and mouth and throat, with 1 patient (1.7%) in the Travoprost PR group; neck, with 1 patient (1.6%), neurological, with 1 patient (1.6%), skin, with 1 patient (1.6%), and limbs, with 1 patient (1.6%) in the Travatan® group.

With regards to vital signs no significant changes were observed.

With regards to visual acuity, no significant changes from baseline were observed in both groups.

With regards to conjunctival hyperemia, worsening shifts were observed in 22 patients (37.4%) in the Travoprost PR group and in 25 patients (40.0%) in the Travatan® group. One patient in Travoprost PR group and two in Travatan® group reported a worsening (from none to mild or moderate) of conjuctival hyperemia in both eyes although affected by monolateral disease and therefore applying study drug only to one eye. Only seven out of the twenty-two patients in

Travoprost PR group with a worsening of conjuctival hyperemia reported it as an adverse event related to study drug and eight out of the twenty-five patient in the Travatan® group.

With regards to lids examination, shifts from normal baseline to abnormality were observed in the following parts of the eye: skin, with 1 patient in each treatment group; margin of upper lids, with 2 patients in each treatment group; margin of lower lids, with one patient (1.7%) in the Travoprost PR group. None of the negative changes have been reported as adverse events. Two patients in the Travatan PR group and one in Travatan® group improved (from abnormal to normal) in margin of upper lids assessment and one in each treatment group in margin of lower lids assessment.

With regards to slit lamp examination, shifts from normal baseline to abnormality were observed for conjunctiva, with 10 patients (17,2%) in the Travoprost PR group and 14 (22.6%) in the Travatan® group; for palpebral with 2 patients (3.4%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group; for len and vitreous only in Travatan® group, 2 and 1 patients respectively.

With regards to anterior chamber angle, the only worsening shift was observed in 4 patients (6.9%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group. Of note 1 patient (1.7%) in the Travoprost PR group and 2 (3.2%) in the Travatan® group improved.

With regards to visual field, worsening shifts were observed in 4 patients (6.9%) in the Travoprost PR group and in 1patient (1.6%) in the Travatan® group Of note 1 patient (1.7%) in the Travoprost PR group and 5 (8.1%) in the Travatan® group improved.

With regards to lens opacities, shifts from baseline were observed in the following characteristics: cortical cataract with 1 patient (1.7 %) in the Travoprot PR group and three patients (4.8 %) in the Travatan® group reported a worsening in score while 1 patient (1.6%) in the Travoprost PR group and 2 in the Travatan® group had an improvement), nuclear color, with 3 patients (3.4%) in the Travoprost PR group and 4 (6.9) in the Travatan® group (all patients had a worsening in score); nuclear opalescence, with 3 patient (4.8%) in the Travoprost PR group and 5 patients (8.1%) in the Travatan® group reporting a worsening in score and 2 patients (3.2%) in the Travatan® group who improved. One patient (1.6%) in the Travatan® group improved in posterior subcapsular cataract assessment.

With regards to detailed retinal examination, the only shift from normal baseline to abnormality was observed in one patient (1.7%) in the Travoprost PR group and 1 (1.6%) in the Travatan® group.

13 DISCUSSION AND OVERALL CONCLUSIONS

The primary objective of the study was to assess the therapeutic equivalence, in the PP population, of two different formulations of Travoprost (Travoprost PR versus Travatan®) in the treatment of subjects affected by primary angle glaucoma (POAG) or ocular hypertension (OH) in terms of intra-ocular pressure (change from baseline to Week 12 or End of Study Visit).
A total of 131 patients were included in the Safety population, 58 in the Travoprost PR group and 62 in the Travatan® group.
A total of 113 patients were included in the intent-to-treat population (ITT), 54 in the Travoprost PR group and 59 in the Travatan® group.

A total of 101 patients were included in per protocol population (PP), 46 in the Travoprost PR group and 55 in the Travatan® group.
With respect to the primary endpoint of the study for PP populations, equivalence of Travoprost PR and Travatan® was demonstrated: the estimate of the difference between treatments (Travoprost PR - Travatan®) in change in IOP from baseline to end of treatment (Week 12 or End of Study) was 0.423 mmHg (95% CI: -0.519, 1.365). In the ITT population the estimate of the difference was 0.814 mmHg (95% CI: -0.315, 1.943). Since the confidence intervals in the PP population lay within the margins of equivalence -1.5 to 1.5 mmHg, equivalence of Travoprost PR and Travatan® in the treatment of subjects affected by primary angle glaucoma or ocular hypertension in terms of intra-ocular pressure (change from baseline to end of treatment) was demonstrated. In the ITT population the incidence of violations of the entry criteria, withdrawals, and lack of efficacy could have had an impact on the subsequent analyses.

The mean IOP values assessed at the end of the study at each single time-point were also comparable being respectively in Travoprost PR and Travatan® groups: 14.45 and 14.26 mmHg at 09.00, 14.20 and 14.04 mmHg at 13.00 and 14.40 and 13.96 mmHg at 17.00.

The mean change from baseline in IOP measured at 9.00 showed a relevant reduction from Visit 2 to Visit 3, followed by a slow decrease until Visit 7 (or End of Study). The 9.00 AM determination was chosen prospectively as it approximates the time of maximal IOP reduction by Travoprost and the time of enhanced probability of pressure peak based on circadian IOP patterns in studies of patients with glaucoma (10, 12).
The estimate of the difference between treatments (Travoprost PR - Travatan®) in percent change in IOP from baseline to end of treatment (Week 12 or End of Study) was 3.450% (95% CI: -1.456- 8.356).

As concerns the safety, the median duration of exposure was 73.6 days (range 7 – 96) in the Travoprost PR group and 79.3 days (range 5 – 100) in the Travatan® group.

The total number of adverse events during the treatment period was 57 in the Travoprost PR group and 73 in the Travatan® group. The number of patients with at least one AE was 22 (37.9%) in the Travoprost PR group and 27 (43.5%) in the Travatan® group. The difference between groups was not significant (chi-square test p-value = 0.532). The total number of drug-related adverse events was 38 in the Travoprost PR group and 43 in the Travatan® group. The number of patients with at least one drug-related AE was 19 (32.8%) in the Travoprost PR group and 22 (35.5%) in the Travatan® group. The difference between groups was not significant (chi-square test p-value = 0.753).

The most frequent drug related adverse events were referred to eye disorder (27.6 % in the Travoprost PR group and 27.4 % in the Travatan® group). The most common drug related adverse events were conjuctival hyperemia, eye irritation, and ocular hyperemia in both groups of treatment. Patient reports of ocular adverse event were consistent with grading of ocular hyperemia by masked investigators.
Only two serious adverse events have been reported, by one patient in each treatment group during the treatment period and both have been assessed as not drug related.

One patient experienced a serious adverse event during the run-in phase and was ended the study as screening failure (not included in the Safety population).

Two further events assessed as not serious and unrelated to study drugs (one in each treatment group) by the Investigators had been upgraded by the Sponsor to serious but still considered as unrelated to study drugs.

The total number of adverse events leading to withdrawal during the treatment period was 14 in the Travoprost PR group and 5 in the Travatan® group. The number of patients with at least one AE leading to withdrawal during the treatment period was 5 (8.6%) in the Travoprost PR group and 3 (4.81%) in the Travatan® group. The difference between groups was not significant (Fisher exact test p-value = 0.481).
There were no substantial differences between groups in the results of the other safety endpoints (laboratory tests, physical examination findings, vital signs and local tolerability variables).
In conclusion this 12-week study demonstrates that Travoprost PR and Travatan® are equally potent IOP-lowering treatments and they are generally well tolerated.

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LIST OF TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

	(safety population)
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The following Tables were updated following this Revised Clinical Study Report version:

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T14.1-5	Patient recruitment by center (randomized population)
T14.1-6	Demographic characteristics (intent-to-treat population)
T14.1-7	Study disease assessment (intent-to-treat population)
T14.1-8.1	Medical history (intent-to-treat population)
T14.1-8.2	Concomitant diseases (intent-to-treat population)
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T14.2-1.1	IOP (mmHg) at each visit and change and percent change from baseline to end of treatment (intent-to-treat population)
T14.2-1.2	Primary efficacy analysis: change in IOP (mmHg) from baseline to end of treatment analysis of covariance - (intent-to-treat population)
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The following Appendix was updated following this Revised Clinical Study Report version:

XVI.	Listing 16.2.3 Populations for analysis