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)**
Name of Finished Product: Travoprost PR	**Item #:**	
Name of Active Ingredient: Travoprost	**Item #:**	

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: 115
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

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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 115 patients of whom 54 (47.0 %) were males. Diagnoses included primary open-angle glaucoma in 87/115 (75.7 %) patients and ocular hypertension in 28/115 (24.3 %) patients. Study participants had a mean age of 63.2 years in the Travoprost PR group and 66.2 years in the Travatan® group. Mean weight and height were also well balanced between the two groups as follows: weight 74.1 kg in the Travoprost PR group and 70.5 kg in the Travatan® group; height: 166.9 cm in the Travoprost PR group and 165.4 cm in the Travatan® group. 99/115 patients (86.1 %) 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 22.55 mm Hg in the Travoprost PR group and 22.94 mm Hg in the Travatan® group. By week 12 a reduction was observed in both treatment groups (- 7.81 mm Hg in the Travoprost PR group and - 8.88 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 -7.79 - +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 115 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).

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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 115 patients were included in the intent-to-treat population (ITT), 55 in the Travoprost PR group and 60 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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