Twenty-four hour IOP variation when treated in daily-life

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Journal : American Journal of Ophthalmology

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ABSTRACT

Purpose: To verify reports that after administration travoprost controls evening and 24h intra-ocular pressure (IOP) better than latanoprost, as determined by a nationwide investigation of everyday opthalmological practice. **Design:** This cross-sectional observational study included patients with primary open-angle glaucoma or ocular hypertension treated with travoprost or latanoprost monotherapy. **Methods:** Private ophthalmologists were selected who would recruit 10 patients receiving the designated monotherapies within 4 weeks and provide quality data. A total of 2,052 patients with primary open-angle glaucoma or ocular hypertension treated with travoprost (n=1,704) or latanoprost (n=348) participated in the study. Measurements comprised IOP values, patients (%) attaining IOP targets, thresholds attained, and current treatment duration. The primary outcome variable was the proportion of patients not exceeding IOP thresholds set by ophthalmologists. Analyses comprised Chi-square and Wilcoxon tests, analysis of variance, logistic regressions, and adjustment by propensity score. **RESULTS:** With an interval between the last treatment instillation and IOP measurement (treatment/IOP interval) <24h, 85% of travoprost patients attained their IOP target at consultations times after 16.00h *versus* 61% with latanoprost (p=0.0002). Mean IOP values after 16.00h were travoprost 16.5 mmHg *versus* latanoprost 17.7 mmHg (p=0.0025). With treatment/IOP intervals >24h (n=461) travoprost was superior to latanoprost, i.e. more patients attaining their IOP target (p=0.0344), lower IOP values (p=0.0016), more patients attaining 20 mmHg IOP (p<0.0001), and duration of current treatment (p<0.0001). Adjustment by propensity score produced similar results. **Conclusions:** Travoprost was superior to latanoprost by evening and 24h after treatment administration when later taken as prescribed.

INTRODUCTION

Prostaglandin analogues are now used increasingly as monotherapy for the first-line treatment of open-angle glaucoma or ocular hypertension.[1] Results reported by Nordmann *et al.* endorse this practice by demonstrating how it may be possible to preserve vision throughout life if the most effective glaucoma treatments are used first-line.[2] Numerous drug trials confirm the greater efficacy of prostaglandins for controlling intracocular pressure (IOP), as compared to timolol.[3-6] This was confirmed by a recent meta-analysis.[7]

The two most recent prostaglandins, travoprost and bimatoprost, control IOP better throughout the day and into the evening than latanoprost.[3,8-13] This is beneficial in reducing both disease progression (less visual field deterioration)[14,15] and costs to the healthcare system (fewer ophthalmic consultations and complementary tests).[16,17]

Resource allocation for patient care is optimized by the cost/effectiveness ratio and many health economic studies of glaucoma have been conducted on this basis.[17-21] Recommendations on health economics in many countries agree that evaluation of clinical efficacy should be based, ideally, on prescribing practice and not on comparisons of clinical trial data.[22] One approach is to relate medicine reimbursement to the mean duration of unchanged treatment.[23-25] Another approach is to perform specific, prospective studies of clinical data obtained in everyday practice. To our knowledge, few studies of this kind have been performed in France.[26-28] More to the point, no study has evaluated the long-term advantages of controlling IOP with the latest prostaglandins.

The objectives of the present enquiry were first to determine the different IOP thresholds used by French ophthalmologists in deciding on a change of treatment; second, to evaluate whether or not the interval elapsing between the last dose of treatment and time of IOP measurement

influences attainment of the target IOP, and consequent therapeutic decisions in everyday practice; and, third to establish whether or not findings of Netland *et al*. and Dubiner *et al*. are supported in everyday practice.[3,8]

METHODS

This field investigation was conducted according to French law (CNIL Declaration, Ordre des Médecins, Ministère de la Recherche) and recommendations of the Association Des Epidémiologistes de Langue Française.[29]

Setting:

Investigators were selected who would recruit 10 patients, receiving prostaglandin monotherapy, within 4 weeks and devote the time necessary to generate quality data. Documentation included their age, sex, practice location, number of OHT and POAG patients in their care, and hours of consultation.

Patients:

Patients of either sex with primary open-angle glaucoma (POAG) or ocular hypertension (OHT) were informed about the study objectives and enrolled, after giving their verbal consent, if they conformed to the following criteria: age more than 18 years, prostaglandin monotherapy used for at least 6 weeks, no surgical intervention or laser therapy since the start of prostaglandin treatment, and no participation in another clinical study. It was also required that relevant information in the patient's medical file would be accessible, or that direct questioning would be allowed. Patients who received additional therapy for POAG or OHT were excluded, as were patients with secondary glaucoma (congenital, inflammatory, neovascular, partial or complete angle closure, induced by a cataract operation....). Patients

were always free to withdraw from the study for any reason.

Patients were described by socio-demographic criteria (age, sex, profession), type of glaucoma, i.e. POAG or normotensive POAG (NPOAG), concomitant risk factors for glaucoma (diabetes mellitus (insulin-dependent or non-dependent), dyslipidemia, arterial hypertension or hypotension, vasomotor instability, cardiovascular disease, migraine, tobacco smoking, family history of glaucoma), presence of associated ocular pathology (strong myopia, cataract, age-related macular degeneration, dry-eye syndrome), glaucoma chronicity, manner of diagnostic presentation (routine examination, spontaneous visit for vision problems, eye symptoms, other reasons), and previous surgical or laser treatment.

Observation procedures:

Intraocular pressure values at diagnosis and prior to initiation of prostaglandin treatment were documented. The prostaglandin name, date and time of last dose were recorded. At the consultation, the ophthalmologist entered the applicable IOP threshold into the patient's record before measuring visual acuity and IOP in each eye. The findings and time of examination were noted. Responses to treatment were reported as 'yes/no' answers to the question "Was the threshold of IOP reached?", and complementary examinations requested, referrals for surgery or laser therapy, and date of next visit, were all recorded.

Main outcome measure:

The main evaluation criterion was defined as the proportion of patients who did not exceed IOP thresholds set by ophthalmologists.

Secondary measures:

Other evaluations included IOP measured at the consultation, number of patients with IOP

values <20 mmHg, number of patients with IOP values <17.5 to 15 mm Hg, number of complementary examinations requested, and surgery or laser treatment referrals.

Statistical analysis

The statistical analysis was performed with SAS® (SAS Institute ; North Carolina, USA). Evaluations were analyzed in relation to the time elapsing from last treatment to IOP measurement in one of the following consultation periods: 0-12.00h, 12.00-16.00h, and 16.00-24.00h. Subsequently, on examining the data, two patient populations were defined by treatment/IOP intervals <24h or >24h. Efficacy comparisons were performed on each population.

Subgroup comparisons were performed by Chi-square or Fisher's exact tests for qualititative variables, and by analysis of variance for quantitative variables, after verifying the normality of residuals and homosedasticity. When the latter assumptions did not apply, Wilcoxon's test or the Kruskal-Wallis test was substituted. The analysis of variance estimated effects of disease duration and treatment duration on IOP values after the two treatment/IOP intervals (<24 h and >24h).

The recent propensity score method produces better adjustment than linear methods and is recommended for observational data.[30] It takes account of possible imbalances between treatment groups which can bias relationships of interest. Variables included here in the propensity score were selected by step-wise logistic regression. The threshold value for inclusion was 10%. Seven variables in Tables 1 and 2, with treatment differences significant at $p<0.10$, were entered into the regression, i.e. duration of illness, vasomotor instability, cataract, bilateral visual acuity, treatment duration, time of last dose, and IOP threshold.

Statistical tests were interpreted two-tail, with alpha=0.5%.

RESULTS

Demography and other patient characteristics

The study involved 280 ophthalmologists who enrolled 2,594 patients with primary open-angle glaucoma (POAG), normal pressure primary open-angle glaucoma (NPOAG) or ocular hypertension, all treated with the designated prostaglandins. Data were incomplete for 542 patients, including 350 patients without information on the treatment/IOP interval. The data analysis, therefore, was performed on 2,052 patients treated with either travoprost (n=1,704) or latanoprost (n=348). The treatment/IOP interval was <24 h for 1,241 patients and >24 h for 461 patients.

Table 1 indicates no significant demographic difference between the two treatment groups for either of the two treatment/IOP intervals except for the <24 h interval after latanoprost, where cataracts were more frequent (p=0.0225) and current treatment was 6 months longer (p=0.0015). Demographic variables for the entire population may be summarized, as follows: males 47%, average age 64.6 years, duration of disease 44.9 months, diabetes mellitus 15.5%, dyslipidemia 24.7%, arterial hypertension 40.8%, arterial hypotension 1.7%, vasomotor instability 4.9%, cardiovascular disease 16.3%, migraine 9.0%, smokers 14.0%, family history of glaucoma 26.3%, other risk factors 7.4%, cataract 33.5%, myopia 6.7%, macular degeneration 5.9%, dry-eye syndrome 9.4%, and other pathology 11.4%.

INSERT TABLE 1 ABOUT HERE

Observations reported by ophthalmologists are presented in Table 2 which indicates no significant treatment differences of visual acuity, IOP values, time of measurement, or treatment/IOP intervals <24 h or >24h. Population means were visual acuity right eye 8.19, left eye 8.15, bilateral 9.0, and IOP 16.86 mmHg.

However, for patients in the treatment/IOP interval <24 h, a significant difference occurred when the time of last medication was divided into 5 periods (p=0.018). Data in Table 2 show that travoprost was more frequently administered early in the day and, complementarily, latanoprost more frequently in the evening. The difference was not apparent with patients in the treatment/IOP interval >24 h.

For patients in both treatment/IOP intervals (Table 2) treatment duration was longer with latanoprost (p<0.0001). The table also shows that when the treatment/IOP interval was <24 h, the average IOP target level was set significantly (p=0.0264) higher for travoprost (17.64 mmHg) than for latanoprost (17.55 mmHg), whereas the converse was true (17.89 mm Hg *versus* 17.41 mm Hg, respectively) when the treatment/IOP interval was >24 h.

Patients whose treatment/IOP interval was not documented were similar to other patients.

INSERT TABLE 2 ABOUT HERE

Treatment responses

Raw data (prior to adjustment by propensity score) are presented in Table 3. Patients treated with travoprost experienced, in general, better IOP control than those treated with latanoprost, irrespective of the treatment/IOP interval. This was true for overall IOP values and the attainment of IOP thresholds set by ophthalmologists. Differences were all statistically significant at the 5% level except for the 15 mmHg threshold.

When the treatment/IOP interval was <24 h, overall IOP values were significantly lower (-0.66 mmHg) after travoprost than latanoprost (p=0.0007). Mean IOP values of patients treated with latanoprost increased by the end of the day, whereas travoprost values diminished (Table 3). Differences were significant between 12.00 h and 16.00 h (p=0.0503) and after

16.00 h (p=0.0025).

More patients achieved the 20 mmHg threshold (p=0.0018) after travoprost, and the difference was significant after 16.00 h (p=0.0209). The proportion of responding patients remained static after latanoprost, but increased across the day from 86.85% to 92.83% after travoprost, indicating sustained hypotensive action (Table 3).

With the 17.5 mmHg threshold, the attainment rate was significantly (p=0.0062) more frequent after travoprost (65%) than latanoprost (55%), especially beyond 16.00 h (66% *versus* 46%, respectively: p=0.0082). Patients treated with travoprost maintained a constant rate of attainment throughout the day, whereas patients (13%) treated with latanoprost experienced a loss of efficacy by late afternoon (Table 3). With the 15 mmHg threshold, the attainment rate after 16.00 h was significantly (p=0.0231) more frequent after travoprost (18%) than latanoprost (4%).

When all ophthalmologists' thresholds were pooled for the treatment/IOP interval <24 h, target rate attainment was significantly (p<0.0001) greater after travoprost (81.85%) than latanoprost (67.27%), and this was maintained in all consultation periods (Table 3). The proportion of patients who benefited from travoprost (80%) was always greater than the proportion after latanoprost (<70%).

Prescriptions of additional medication and referrals for rescue laser therapy or surgery were similar between treatments.

INSERT TABLE 3 ABOUT HERE

Table 3 does not detail the consultation times for patients in the treatment/IOP interval <24 h because those treated with travoprost (n=358) or latanoprost (n=103) were too few for a

reliable analysis. Average IOP values with travoprost, however, were not affected by the treatment/IOP interval difference (16.72 mmHg *versus* 16.76 mmHg). By contrast, IOP values increased markedly with latanoprost when treatment/IOP interval lengthened (from 17.38 mmHg to 17.80 mmHg). Consequently, the difference of hypotensive efficacy between travoprost and latanoprost increased by 58%, from -0.66 mmHg (p=0.0007) to -1.04 mmHg (p=0.0016).

With the 20 mmHg threshold, the attainment rate was significantly (p<0.0001) more frequent after travoprost (88.00%) than latanoprost (69.61%). With the 17.5 mmHg threshold, attainment rates again differed significantly (p=0.0448), i.e. travoprost (64.86%) compared to latanoprost (53.92%). Treatment differences were not significant when the IOP threshold was set at 15 mmHg.

When all ophthalmologists' thresholds were pooled for the treatment/IOP interval >24 h, the rate of target attainment was significantly (p=0.0344) greater after travoprost (78.53%) than latanoprost (68.3%), and this was maintained across all consultation times (Table 3).

Additional medication and referrals for rescue laser therapy, or surgery did not differ significantly between treatment groups.

Analysis of variance estimates of disease duration and treatment duration effects on treatment efficacy (IOP values) showed that both variables accounted for very little of the variance. The treatment difference met the p=0.0001 threshold. By contrast, when the treatment/IOP interval was <24 h, the treatment duration effect was weak (p=0.014) and disease duration was without significant effect (p<0.20). The corresponding effects were similar for the treatment/IOP interval >24 h, i.e. treatment duration (p<0.03) and disease duration (p<0.11).

Adjustment by propensity score (Table 4) yielded yet stronger results in favour of travoprost when the treatment/IOP interval was <24 h, than those seen in Table 3. Differences between the proportion of patients attaining the various IOP thresholds were significant at all consultation times, especially after 16.00 h (Table 4). Attainment of the IOP thresholds 20

mmHg (p=0.0128), 17.5 mmHg (p=0.0038) and 15 mmHg (p=0.0225) were more frequent with travoprost after 16.00 h.

When the treatment/IOP interval was >24 h, mean IOP was 0.83 mmHg less in the travoprost group than the latanoprost group (p=0.0289). Also, the proportion of patients attaining the 20 mmHg IOP threshold was higher (p=0.0101) after travoprost (88.19%) than latanoprost (74.70%).

INSERT TABLE 4 ABOUT HERE

DISCUSSION

This field study confirms the randomized clinical trials reported by Netland *et al.* and Dubiner *et al.*.[3,8] The present findings show that daily instillation of travoprost controlled IOP significantly better than latanoprost, during the 24 h after administration, with better average IOP control throughout the day and into the evening. Target IOP thresholds set by ophthalmologists were achieved more frequently with travoprost (always >80%) than latanoprost (always <70%) when treatments were instilled 24 h before IOP measurement, whatever the time of measurement.

The results were robust since they were not diminished after adjustment by the score propensity method. Another effect of adjustment was to augment difference magnitudes between the treatment groups (*c.f.* Table 3 and Table 4). Linear and logistic regression methods, not presented in this paper, produced similar results.

The general effect indicates that switches of therapy should be more frequent when patients are treated with latanoprost, as compared to travoprost, as predicted by Dubiner *et al.*. The pharmaco-economic consequences are higher costs of treatment and more visual field deterioration, which also incur costs.[16,17,26] Long-term longitudinal studies are needed to confirm the hypothesis.

Our results support, too, another conclusion of Dubiner *et al*., that the extended activity of travoprost should provide better IOP control, than latanoprost, for treatment compliant patients and a degree of coverage for patients who occasionally forget a dose.[8] In the present study, values of IOP at the start of treatment were similar to those reported by Netland *et al*. and Dubiner *et al*., i.e. approximately 25 mmHg without treatment.[3,8] The average IOP threshold targeted by practicing ophthalmologists was 17.5 mmHg, a value close to AGIS recommendations.[31] Therefore, it would seem that criteria used in therapeutic clinical trials do not differ much from current everyday practice, meaning that in this case one can extrapolate safely from clinical trials.

Mean IOP measured in our study was 1.0 mmHg less than the average IOP value reported by Netland *et al*.[3] In drug trials, patients with inadequately controlled IOP continue to be treated if their vision is not at risk. Accordingly, patients who do not respond to a treatment, augment the difference between trial products. In daily practice, a patient who does not attain the IOP target would be treated with another drug, or by combination therapy. Hence, in field studies fewer patients stop responding to continued treatment and treatment failure contributes less to treatment differences. This might explain why we found a weak association between IOP values and treatment duration, or disease duration. All patients in our study were monitored according to AGIS criteria, therefore evaluation of tachyphylaxis to the products was evaluable within only a narrow range of IOP values. Consequently, a proper pharmacological evaluation of tachyphylaxis can only be performed in an experimental context. This explains the small changes resulting from adjustment by the propensity score method. Conversely, this study confirms that IOP is better controlled when travoprost is used according to prescription. More effective 24 h IOP control with travoprost was also demonstrated when the norms set by AGIS were observed.

Control of IOP to below 15 mmHg is difficult with protoglandins as monotherapy. Our results suggest that combination therapy should be used from the outset coupled with measures to ensure compliance.

Treatment group comparability is always in question when studies are conducted by field observation. It is the accepted theory that treatment randomization is the only guarantee of group comparability. This tenet, however, is incompatible with daily practice. Seven variables associated with significant ($p<0.01$) treatment differences were identified. All were known confounding factors for glaucoma. The small number observed should be set against the 54 statistical tests demonstrating group comparability. We used the generally recommended method of propensity score, which enables a comparison of two treatment groups with adjustment on one variable, to summarize the information collected.[30] The seven confounding variables were selected from the ensemble of glaucoma factors on the basis of group differences within the 10% limit. Accordingly, the propensity score used as adjustment factors were based on logistic regressions. Other methods were possible. However, we believe that the convergence of results from our two different methods (propensity score and linear model) consolidated the validity for our results.

Our study has several limitations. First, an important imbalance remained between the two treatment group sample sizes which allowed us, in fact, to observe 24 h IOP variations with travoprost. Second, we were unable to demonstrate the impact of better IOP control on referrals for laser therapy or surgery. Such interventions are necessary only when drug treatment fails and so are rarely needed with prostaglandin monotherapy. Complementary treatments were seldom required and would need a prospective study to detect a difference. Indeed, long-term longitudinal studies are needed to fully describe the consequences of better IOP control. Third, the IOP thresholds set as targets are a possible source of bias.

Collaboration in a clinical study may encourage ophthalmologists to follow good clinical practice more assiduously. A retrospective search into medical files would probably disclose how the present IOP targets were set. Fourth, a cross-sectional study design limits comparisons over time because effects are not observed 'within' individuals. This problem is usually attenuated by recruiting far more patients than required for clinical trials. It is the price to pay for working with observational data. In any case, our design assumed that ophthalmologists' consultation times were independent of the IOP values measured. Accordingly, variation results from the pharmacological profiles of the products studied.

In conclusion, the results of our study show that in everyday practice travoprost produces effects similar to those published by Netland *et al.* and Dubiner *et al*., i.e. better IOP control than latanoprost averaged over the day and in the evening, and travoprost produces a greater residual effect.[3,8] Thus, IOP targets set by ophthalmologists are more frequently achieved with travoprost.

Acknowledgement

This survey was supported by an unrestricted grant from Alcon France SA, Rueil-Malmaison, France, and was conducted according to local laws. It was contracted to REES France, Paris, France. Gilles Berdeaux is employed by Alcon France.

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Table 1: Demographic characteristic, description of glaucoma and other ocular pathologies.

Parameter	Time since last dose <24h			Time since last dose >24h		
	Travoprost (n=1.015)	**Latanoprost (n=226)**	***p*-value**	**Travoprost (n=358)**	**Latanoprost (n=103)**	***p*-value**
Age (years)	64.62 (±12.42)	65.62 (±11.67)	0.4857	64.74 (±11.58)	62.66 (±12.14)	0.1207
Gender (male%)	488 (48.51%)	104 (46.85%)	0.6571	154 (43.5%)	48 (46.6%)	0.5657
Disease duration (months)	44.89 (±54.34)	50.67 (±50.48)	0.0015	50.80 (±56.86)	46.01 (±43.24)	0.8227
Glaucoma surgery (%)	44 (4.39%)	10 (4.50%)	1	15 (4.23%)	3 (2.91%)	0.7744
Glaucoma laser treatment (%)	50 (5.02%)	13 (5.86%)	0.6152	16 (4.51%)	3 (2.91%)	0.5857
Glaucoma risk factors						
Mellitus diabetes	165 (16.52%)	36 (16.90%)	0.8909	49 (14.00%)	12 (12.00%)	0.6064
Dyslipidemia	251 (25.25%)	61 (28.50%)	0.324	88 (25.14%)	25 (25.00%)	0.9768
Arterial hypertension	421 (41.85%)	83 (38.07%)	0.3045	150 (42.49%)	40 (39.60%)	0.6038
Arterial hypotension	16 (1.62%)	7 (3.33%)	0.1026	7 (2.00%)	1 (1.00%)	0.691
Vasomotor instability	45 (4.55%)	16 (7.51%)	0.074	21 (6.00%)	5 (5.00%)	0.7054
CV diseases	174 (17.45%)	33 (15.49%)	0.4906	59 (16.81%)	19 (19.19%)	0.5802
Migraine	93 (9.41%)	25 (11.74%)	0.3013	33 (9.40%)	12 (12.24%)	0.4073
Smoker	148 (14.86%)	30 (14.08%)	0.772	47 (13.35%)	18 (17.82%)	0.2587
Familial glaucoma history	275 (27.98%)	59 (27.19%)	0.815	93 (26.65%)	27 (27.55%)	0.8585
Other risk factors	42 (6.33%)	9 (6.16%)	0.9422	22 (9.48%)	8 (11.27%)	0.6595
Eye comorbidity						
Myopia	71 (7.14%)	14 (6.48%)	0.7303	27 (7.65%)	7 (7.07%)	0.8472
Cataract	324 (32.30%)	88 (40.37%)	0.0225	109 (30.97%)	31 (30.69%)	0.9583
AMD	59 (5.98%)	16 (7.51%)	0.4016	17 (4.80%)	5 (5.00%)	1
Dry eye	104 (10.66%)	23 (10.80%)	0.9514	25 (7.10%)	9 (9.09%)	0.5079
Other	77 (10.35%)	16 (9.30%)	0.682	30 (10.75%)	10 (12.66%)	0.6351

CV: Cardiovascular. AMD: Age-related Macular Degeneration.

Table 2: Visual acuity, glaucoma treatment, IOP values

Parameter	Time since last dose <24h			Time since last dose >24h		
	Travoprost	**Latanoprost**	***p*-value**	**Travoprost**	**Latanoprost**	***p*-value**
Visual Acuity (decimal)						
Bilateral	8.92 (±2,04)	9.08 (±1,75)	0.084	9.10 (±1.78)	9.09 (±1.69)	0.7366
Time of the last medccation						
0-8h	33 (3.25%)	4 (1.77%)		16 (4.47%)	9 (8.74%)	
8-12h	141 (13.89%)	21 (9.29%)		127 (35.47%)	35 (33.98%)	
12-16h	72 (7.09%)	7 (3.10%)	0.018	70 (19.55%)	18 (17.48%)	0.559
16-20h	118 (11.63%)	26 (11.50%)		74 (20.67%)	20 (19.42%)	
20-24h	651 (64.14%)	168 (74.34%)		71 (19.83%)	21 (20.39%)	
Current treatment duration (months)	7.28 (8.40)	19.23 (14.23)	<0.0001	5.57 (7.84)	15.56 (15.25)	<0.0001
Time of IOP measure						
0-8h	15 (1.48%)	3 (1.33%)		5 (1.4%)	0 (0%)	
8-12h	416 (40.99%)	108 (47.79%)		143 (39.94%)	53 (51.46%)	
12-16h	333 (32.81%)	68 (30.09%)	0.2996	102 (28.49%)	30 (29.13%)	0.1156
16-20h	251 (24.73%)	47 (20.80%)		107 (29.89%)	20 (19.42%)	
20-24h	0 (0%)	0 (0%)		1 (0.28%)	0 (0%)	
IOP (mmHg)						
At diagnosis	24.88 (±3.25)	25.03 (±3.15)	0.7325	25.18 (±3.47)	25.02 (±2.92)	0.5387
Previous treatment	22.62 (±3.78)	22.86 (±4.00)	0.3853	22.36 (±3.58)	23.26 (±3.76)	0.5705
Targeted value at present visit	17.64 (±2.01)	17.55 (±1.89)	0.0264	17.41 (±1.94)	17.89 (±2.07)	0.0298

Table 3: Treatment responses

Parameter	Time since last dose <24h			Time since last dose >24h		
	Travoprost	**Latanoprost**	***p*-value**	**Travoprost**	**Latanoprost**	***p*-value**
IOP (mmHg) overall	16.72 (±2.58)	17.38 (±2.88)	0.0007	16.76 (±2.78)	17.80 (±3.38)	0.0016
-12h00	16.77 (±2.66)	17.19 (±3.13)	0.1534	na	na	na
12h00-16h00	16.79 (±2.63)	17.51 (±2.97)	0.0503	na	na	na
16h00+	16.55 (±2.35)	17.67 (±2.02)	0.0025	na	na	na
IOP < 20 mmHg overall	894 (88.78%)	180 (81.08%)	0.0018	308 (88.00%)	71 (69.61%)	<0.0001
-12h00	370 (86.85%)	91 (81.98%)	0.1896	na	na	na
12h00-16h00	291 (88.18%)	52 (80.00%)	0.0745	na	na	na
16h00+	233 (92.83%)	37 (80.43%)	0.0209	na	na	na
IOP < 17.5 mmHg overall	652 (64.75%)	122 (54.95%)	0.0062	227 (64.86%)	55 (53.92%)	0.0448
-12h00	268 (62.91%)	65 (58.56%)	0.4001	na	na	na
12h00-16h00	218 (66.06%)	36 (55.38%)	0.1006	na	na	na
16h00+	166 (66.14%)	21 (45.65%)	0.0082	na	na	na
IOP < 15 mmHg overall	178 (17.68%)	28 (12.61%)	0.0675	65 (18.57%)	20 (19.61%)	0.8137
-12h00	78 (18.31%)	17 (15.32%)	0.4615	na	na	na
12h00-16h00	56 (16.97%)	9 (13.85%)	0.5347	na	na	na
16h00+	44 (17.53%)	2 (4.35%)	0.0231	na	na	na
IOP<targeted value overall	812 (81.85%)	148 (67.27%)	<0.0001	267 (78.53%)	69 (68.32%)	0.0344
-12h00	339 (80.52%)	76 (69.72%)	0.0148	na	na	na
12h00-16h00	264 (81.48%)	44 (67.69%)	0.0125	na	na	na
16h00+	209 (84.62%)	28 (60.87%)	0.0002	na	na	na
Complementary examinations	529 (54.09%)	127 (56.70%)	0.4797	166 (48.68%)	51 (52.04%)	0.5576
Surgery	9 (0.98%)	2 (0.95%)	1.00	3 (0.92%)	0 (0%)	1.00
Laser treatment	8 (0.87%)	1 (0.48%)	1.00	2 (0.62%)	0 (0%)	1.00

na: not available, because sample size too small.

Table 4: Results adjusted by propensity score

Parameter	Time since last dose <24h			Time since last dose >24h		
	Travoprost	**Latanoprost**	***p*-value**	**Travoprost**	**Latanoprost**	***p*-value**
IOP (mmHg) overall	16.65	17.64	<0.0001	16.71	17.54	0.0289
-12h00	16.69	17.33	0.0301	na	na	na
12h00-16h00	16.74	17.75	0.0069	na	na	na
16h00+	16.51	17.85	0.0027	na	na	na
IOP < 20 mmHg overall	89.87%	77.91%	<0.0001	88.19%	74.70%	0.0101
-12h00	87.29%	79.21%	0.0569	na	na	na
12h00-16h00	88.63%	76.44%	0.024	na	na	na
16h00+	92.88%	78.00%	0.0128	na	na	na
IOP < 17.5 mmHg overall	65.61%	50.42%	0.0004	64.50%	58.07%	0.3324
-12h00	63.69%	56.57%	0.1456	na	na	na
12h00-16h00	66.00%	51.82%	0.1482	na	na	na
16h00+	66.79%	42.88%	0.0038	na	na	na
IOP < 15 mmHg overall	17.89%	9.24%	0.0154	19.02%	18.03%	0.8444
-12h00	18.81%	14.77%	0.5107	na	na	na
12h00-16h00	17.21%	12.42%	0.3434	na	na	na
16h00+	17.69%	4.12%	0.0225	na	na	na
IOP < targeted value overall	82.60%	63.45%	<0.0001	79.20%	71.80%	0.1949
-12h00	80.80%	68.46%	0.0118	na	na	na
12h00-16h00	81.79%	64.53%	0.0077	na	na	na
16h00+	84.99%	56.97%	0.0005	na	na	na
Complementary examinations	53.91%	55.13%	0.7783	47.40%	48.49%	0.8711
Surgery	*	*	*	*	*	*
Laser treatment	*	*	*	*	*	*

na: not available because sample size too small.

*** adjustment not stable due to too few events.**