

FINAL REPORT

This is the final report of the European Multicentre, interventional, 2-year prospective, randomized, Single Blinded/Masked, parallel group study to compare the quality of 24-hour IOP control obtained after 3 and 24 months of therapy with the combined administration of Combigan in the morning and Ganfort in the evening versus Latanoprost administered once in the evening, in high risk newly diagnosed untreated patients with primary open-angle glaucoma (POAG), or exfoliative glaucoma (XFG).

Study Objectives

The objectives of this trial were:

- To compare for the first time the quality of 24-hour IOP control obtained after **3 and 24 months** of therapy with the combined administration of Combigan in the morning and Ganfort in the evening versus latanoprost administered once in the evening, in high risk newly diagnosed untreated patients with primary open-angle glaucoma (POAG), or exfoliative glaucoma (XFG) with IOP equal to or greater than 27 mm Hg and a visual field defect with an MD of at least -5 dB.
- To identify the best long-term **24-hour IOP predictors** for progression (e.g. determine the value of peak, mean or fluctuation of IOP over 24 hours).
- The study will correlate for the first time **level of 24-hour IOP** and **progression rate**, thus allowing the determination of a "safe" 24-hour IOP level with which nearly all at-risk XFG and POAG patients will not progress.

- The study will identify the **long-term 24-hr IOP efficacy** of the 2 selected therapeutic regimens in a group of at-risk glaucoma patients (high baseline IOP and POAG, or XFG).

Study Population

Based on sample size calculation, 72 glaucoma patients should be included by the two centers in Europe (Milan, Thessaloniki). We considered a 20%-drop-out rate during the study. Therefore a total of 60 patients should conclude the study.

Each Arm was composed of 30 randomized subjects (total = 60). Subjects were scheduled for 6 visits (Baseline, 3 Months, 6 Months, 12 Months, 18 Months, 24 Months). At each visit, Intraocular Pressure (IOP) was measured at 6 different times of the day (02:00, 06:00, 10:00, 14:00, 18:00 and 22:00). A Visual Field (VF) test was also performed (24-2 SITA-Standard) in the test eye at each visit. Central Corneal Thickness (CCT) was measured at the Baseline visit. For Arm A, all subjects attended the second and third visit, 29 the fourth, 28 the fifth and 27 the last visit. Reasons for not completing the study were related to the “unsafe” patient’s clinical conditions (i.e. IOP and/or VF) that, on the basis of P.I.’s opinion, required surgery (2 patients) and treatment side effects (moderate hyperaemia, probably treatment related). For Arm B, all subjects attended the second visit, 29 the third, 28 the fourth and the fifth and 25 the last visit. Again, reasons for not completing the study included “unsafe” IOP levels (3 patients) and treatment side effects (hyperaemia 1 patient and another patient with punctate superficial keratitis). Only subject LT01 (arm A) was missing the Visual Field data at 6 months, despite attending the visit.

Summary statistics are reported in **Table 1**.

	Arm A	Arm B
Baseline Age (years)	67 ± 10	62 ± 11
Baseline MD (dB)	-5.3 ± 4.2	-4.7 ± 3.6
Baseline Average IOP (mmHg)	28.5 ± 2.6	28.6 ± 1.4
Baseline IOP Fluctuation (mmHg)	2.5 ± 0.8	2.2 ± 1
Treated IOP (mmHg)	19.2 ± 2.2	17.2 ± 2.2
Treated IOP Fluctuations (mmHg)	1.6 ± 0.5	1.9 ± 0.9

Table 1. Summary statistics reported as Mean ± Standard Deviation

IOP analysis

IOP values between the two groups were compared at the same time of the day at different visits (see **Figure 1**). For the statistical analysis, we used a multivariate linear mixed model that had the Arm, the Visit and the Time of day as predictors and the IOP as the response variable. Two and three way interactions were used to obtain estimates at each time and each visit for both arms. Random effects were used to account for repeated measurements on the same subject over time (multiple IOP values per day and multiple Visits per subject). This framework allowed us to deal with missing values, since mixed models do not require the exclusion of incomplete data series.

Subjects in Arm A had overall higher IOP values. Pairwise differences were significant at Time 14:00 at 3, 6, 12 and 18 months, at Time 10:00 at 3, 12 and 18 months and at Time 18:00 at 24 months (see **Figure 1**). No significant differences were detected at Baseline. By removing the

Time term in the model we could also compare average IOP between the two Arms at different Visits. We found a significant difference at all study visits favouring Arm B: at 3 Months (1.6 [0.2 – 2.8] mmHg; Mean Difference [95% CIs]; $p = 0.01$), at 6 Months (1.5 [0.1 – 2.6]; $p = 0.02$), at 12 Months (1.6 [0.1 – 2.7]; $p = 0.02$) and at 24 Months (1.5 [0.1 – 2.7]; $p = 0.02$).

When the IOP values under treatment (independently of the Visit and Time) were compared to Baseline, there was a significant difference between Arm A and Arm B ($p = 0.018$) in terms of absolute IOP values, and a significant difference was found in terms of percentage reduction ($p = 0.025$), treatment in Arm A being slightly less effective (34% reduction) compared to Arm B (38% reduction).

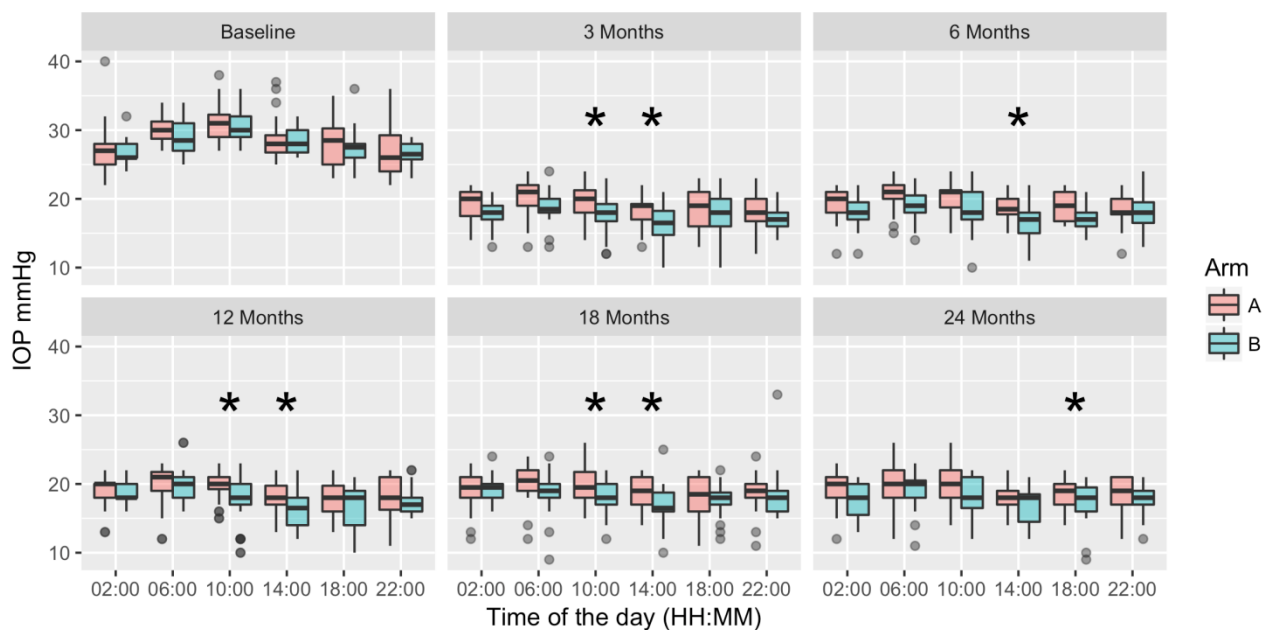


Figure 1. Box-plots representing the IOP values at different times of the day in the two arms at different visits. Asterisks indicate significant pairwise differences between the two arms of the study.

Visual field progression analysis

For this analysis, the Mean Deviation (MD) value of the 24-2 visual field was used to assess progression. We investigated the effect of different predictors using linear mixed models with subject random effects. The MD was the response variable and Time (in months) was included as a continuous predictor. Interactions between Time and the predictor of interest (IOP average, IOP fluctuation and treatment Arm) were used to model the effect of such predictors on the Rate of progression (RoP, coefficient of Time in the model). Random intercepts and slopes were used to model the progression of each subject. Average IOP was calculated for each visit as the average at across all times of the day.

IOP fluctuations were calculated as the standard deviation of the IOP measurements within a day for each visit. Therefore, for IOP average and IOP fluctuation we had a value for each visit. This model does not account for lag effects but considers each IOP average or fluctuation value per visit to be a stable estimate of a reasonably large period of time around (before and after) that visit. Measures at baseline were discarded for this analysis. There was no significant difference between the two groups in terms of IOP fluctuation (see Table 1 and 2; $p = 0.1$).

The Rate of Progression (RoP) for Arm A (-0.06 [-0.11, -0.01] db/month) and Arm B (-0.05 [-0.099, -0.001] dB/month) were similar ($p = 0.8$). No significant effect in the RoP was observed for IOP average ($p = 0.95$). However, a significant effect was observed for the IOP fluctuation (-0.07 [-0.12, -0.03] (dB/month)/mmHg; $p = 0.002$; see Table 2 and Figure 2).

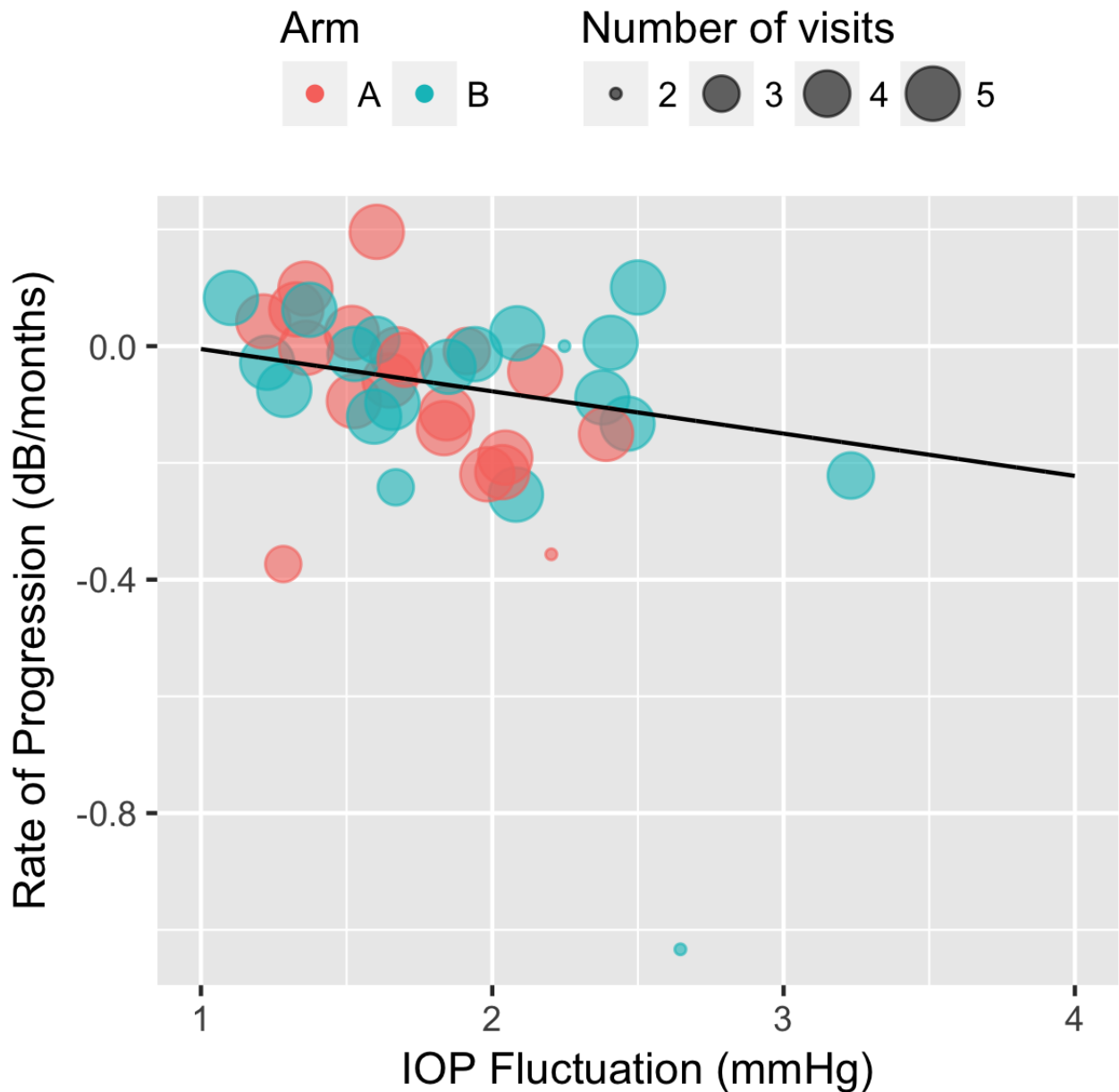


Figure 2. The dots represent the mean Rate of Progression (RoP) for each subject. The solid black line represents the estimate from the multivariate mixed model based on the IOP fluctuation. For this graph, the IOP fluctuation for each subject (dots) is reported as the mean value across all the visits. The size of the dot indicates the number of visits that were available to calculate the RoP for each subject.

Conclusions

The findings of this clinical trial including patients at high risk of progression indicate that lowering IOP with the combination of Combigan (once in the morning) and Ganfort (once in the evening), Arm B, obtains clinically and statistically significant better IOP profiles as compared with the standard monotherapy (latanoprost), Arm A. This difference is, on average, around 2 mmHg (first study objective). Morning and early afternoon are the moments when the differences between the 2 therapeutic schemes are more relevant. Both treatments are very effective in reducing IOP, with an average effect ranging between 30 and 40%. This is probably the reason why, at least with a follow-up of 2 years, we were not able to find a significant effect of the better IOP lowering shown in group B on the VF progression. However, IOP fluctuations were a significant predictor of VF progression (second study objective). The results of this study support the idea of treating from the beginning this particular phenotype of patients - presenting with a high IOP at baseline and with a mild to moderate glaucoma - with a “more aggressive” approach.