

Results of the European Glaucoma Prevention Study

The European Glaucoma Prevention Study (EGPS) Group*

Objective: The European Glaucoma Prevention Study (EGPS) seeks to evaluate the efficacy of reduction of intraocular pressure (IOP) by dorzolamide in preventing or delaying primary open-angle glaucoma (POAG) in patients affected by ocular hypertension (OHT).

Design: Randomized, double-masked, controlled clinical trial.

Participants: One thousand eighty-one patients (age, ≥ 30 years) were enrolled by 18 European centers. The patients fulfilled a series of inclusion criteria, including: IOP 22 to 29 mmHg; 2 normal and reliable visual fields (on the basis of mean deviation and corrected pattern standard deviation or corrected loss variance of standard 30/II Humphrey or Octopus perimetry); normal optic disc as determined by the Optic Disc Reading Center.

Intervention: Patients were randomized to treatment with dorzolamide or placebo (the vehicle of dorzolamide).

Main Outcome Measures: Efficacy end points were visual field, optic disc changes, or both. A visual field change during follow-up had to be confirmed by 2 further positive tests. Optic disc change was defined on the basis of the agreement of 2 of 3 independent observers evaluating optic disc stereo slides. The safety end point was an IOP of more than 35 mmHg on 2 consecutive examinations.

Results: During the course of the study, the mean percent reduction in IOP in the dorzolamide group was 15% after 6 months and 22% after 5 years. Mean IOP declined by 9% after 6 months and by 19% after 5 years in the placebo group. At 60 months, the cumulative probability of converting to an efficacy end point was 13.4% in the dorzolamide group and 14.1% in the placebo group (hazard ratio, 0.86; 95% confidence interval [CI], 0.58–1.26; $P = 0.45$). The cumulative probability of developing an efficacy or a safety end point was 13.7% in the dorzolamide group and 16.4% in the placebo group (hazard ratio, 0.73; 95% CI, 0.51–1.06; $P = 0.1$).

Conclusions: Dorzolamide reduced IOP by 15% to 22% throughout the 5 years of the trial. However, the EGPS failed to detect a statistically significant difference between medical therapy and placebo in reducing the incidence of POAG among a large population of OHT patients at moderate risk for developing POAG, because placebo also significantly and consistently lowered IOP. *Ophthalmology* 2005;112:366–375 © 2005 by the American Academy of Ophthalmology.

Prevention of glaucomatous damage remains one of the major goals in ophthalmology. At present, the therapeutic strategies largely are based on a medical or a surgical approach aimed at decreasing intraocular pressure (IOP). Ocular hypertension in fact has been recognized as the most important risk factor for the development of primary open-angle glaucoma (POAG)^{1–5} and, as of today, the only factor that can be controlled medically or surgically. Among other risk factors, such as age, race,³ family history,^{5,6} and low diastolic perfusion pressure,^{4,5,7} which are deemed important in the genesis of the disease, only the last one hypothetically can benefit from a multidisciplinary therapeutic

approach. Because elevated IOP is associated with the development of glaucoma^{1,2,8} and topical therapy is capable of reducing IOP, it is conceivable that topical IOP-lowering therapy may protect against the development of glaucoma. This hypothesis has been supported by the Ocular Hypertension Treatment Study (OHTS), which has shown that a 20% IOP reduction from baseline achieved by topical medical therapy may delay or prevent the onset of POAG over the course of 5 years in individuals with elevated IOP.⁹ A number of drugs have been demonstrated to be effective in lowering IOP. Among those, traditional categories include β -blockers, parasympathetic agonists, systemic carbonic anhydrase inhibitors, and sympathetic agonists. Newer categories effective in reducing IOP include prostaglandin analogs, α^2 agonists, and topical carbonic anhydrase inhibitors. Although all of these drugs are capable of reducing IOP, at the time the European Glaucoma Prevention Study (EGPS) was designed clear evidence of their own specific efficacy in reducing the incidence of glaucoma did not exist.^{10–12}

On the basis of these observations, we designed the EGPS, an investigator-initiated trial, to test the hypothesis

Originally received: May 18, 2004.

Accepted: November 15, 2004.

Manuscript no. 240378.

Supported by The European Commission, Brussels, Belgium (BIOMED II program, contract no.: BMH4-CT-96-1598), and Merck & Co., Inc., Whitehouse Station, New Jersey.

Correspondence to Stefano Miglior, MD, Università di Milano Bicocca, Policlinico di Monza, Via Amati 111, 20052 Monza (Mi), Italy. E-mail: stefano.miglior@unimib.it.

*See "Appendix" for a list of the group's members, and "Acknowledgments" for writing committee identification.

that the onset of POAG (defined on the basis of visual field loss, optic disc change, or both) can be prevented or delayed in patients with increased IOP by means of medical hypotensive therapy. Secondary aims of the EGPS were to obtain information about the natural history of ocular hypertension (OHT) and the identification of risk factors in the onset of POAG. The protocol was submitted to, approved by, and received funding from the BIOMED II Program of the European Commission. At the time the study was designed and approved (June 1995), commercially available medications for OHT in the 4 European countries participating in the study were limited to topical β -blockers, dorzolamide, and older drugs, including oral carbonic anhydrase inhibitors and parasympathetic and sympathetic agonists.

The hypotensive drug selected for use in the EGPS was dorzolamide. Clinical studies in humans have demonstrated that dorzolamide is well tolerated and possesses good IOP-lowering activity.¹³⁻¹⁹ Three times daily administration of 2% dorzolamide results in a substantial mean percent decrease in IOP of 18% to 22%¹⁸ and of 14% to 20%¹⁹ throughout the day. As soon as the study was approved by the European Commission, the manufacturer of dorzolamide (Merck & Co., Inc., Whitehouse Station, NJ) was approached and agreed to participate in the study by providing the study drug and any additional support.

In this article, we describe the efficacy of medical treatment (by topical dorzolamide) as compared with placebo in delaying or preventing the onset of POAG in OHT patients. Analyses on prognostic and predictive factors will be the subject of future articles.

Patients and Methods

The EGPS was a multicenter, randomized, double-masked, placebo-controlled clinical trial. The design and methods of the EGPS were described previously²⁰ and are summarized as follows.

Study Organization

The EGPS organization consisted of 18 centers distributed in 4 European countries: Belgium, Germany, Italy, and Portugal, listed at the end of this article. The Coordinating Center was responsible for eligibility confirmation, end point confirmation, quality assurance, and data processing. The Data Management and Statistical Analysis Center was responsible for epidemiologic and biostatistical input, data management and analysis, and report preparation. A centralized optic disc archiving center provided the optic disc stereo slides of each participant to the Optic Disc Reading Committee, which was composed of 3 independent, certified evaluators.²¹ Visual field assessment at enrollment was performed at each study center by the local investigator. The assessment of visual field end points was performed at the Coordinating Center. The Steering Committee was composed of the principal investigators from each of the 4 participating countries, the biostatistician responsible for the data management and biostatistical center, an American glaucoma specialist, and a representative from Merck.

The study protocol was approved by the ethical review committees of each center. The ethical conduct of the study and the information concerning adverse and beneficial treatment effects were monitored by a Data and Safety Monitoring Committee (DSMC). Only the DSMC was aware of evidence of treatment effects (in terms of knowing the study results in the 2 arms) during

the course of the study. For the interim analyses, the DSMC was assisted by an unmasked statistician (a nonvoting member of the DSMC) who was otherwise uninvolved in this study.

Study Protocol

The eligibility criteria included age between 30 and 80 years, a qualifying IOP between 22 and 29 mmHg in at least 1 eye (without therapy or after a washout of at least 3 weeks from previously used drugs), gonioscopically open angles, 2 normal and reliable visual field tests per eye as determined by the local investigator, and normal optic discs seen at clinical examination and on stereoscopic photographs as determined by the 3 independent evaluators of the Optic Disc Reading Center. Exclusion criteria included a visual acuity of worse than 20/40 in either eye, previous intraocular surgery, or any sign of diabetic retinopathy or other diseases capable of causing visual field loss or optic disc deterioration. Informed consent, prepared according to the ethical review committees' regulations, was obtained from each participant. Eligible patients were consecutive cases from clinic populations.

Methods

The patients were randomized into 2 groups: active therapy (dorzolamide) and placebo (which was the vehicle of the active therapy). The placebo was a sterile, isotonic, buffered, slightly viscous, aqueous solution with a pH of approximately 5.6 and an osmolality of 260 to 330 milliosmoles. Ingredients were hydroxyethyl cellulose, mannitol, sodium citrate dihydrate, hydrochloric acid (to adjust pH), and water. Benzalkonium chloride 0.0075% was added as a preservative.

Randomization was obtained at the Coordinating Center. Each clinical center had its own randomization list that was stratified for pseudoexfoliation, pigmentary dispersion syndrome, and diabetes mellitus. Bottles of drug and placebo were given to each center according to the randomization list. Patients were given a bottle marked with a code label. The administration of the drug (or placebo) was the same in both cases and corresponded to the recommended dosage and administration of the active drug (3 times daily). The bottles of active therapy and of placebo were identical in appearance. At each study visit, the patient received enough drug (or placebo) for a 6-month period. Patients were checked at a 6-month interval, at which time they were queried about any missed doses. The allocation code was secured at the Coordinating Center at the office of the Project Coordinator.

Whenever the treatment had to be interrupted, whether because of allergy or other unspecific ocular problems, it was started again after the resolution of the problem itself.

Masking. The EGPS was a double-masked study. Neither the patients nor the investigators visiting or testing the patients knew the group to which they belonged (therapy or control). The evaluation of visual field and optic disc photographs also was performed in a masked fashion.

Study Visit. The baseline and follow-up visits included the assessment of refraction and visual acuity using the procedure routinely used at each given office; Goldmann applanation tonometry performed and recorded by a single investigator between 8:00 and 11:00 AM (i.e., at least 1 but not more than 3 hours after the last dose of study medication); complete ophthalmologic examination, automated static perimetry with a Humphrey or Octopus instrument using a central 30° program with threshold double-crossing strategy; and color slide stereophotography of the optic disc. Gonioscopy was performed at the end of the visit after resolution of mydriasis.

Follow-up visits included an assessment of compliance, checking for possible side effects, and the occurrence of adverse effects.

Central Corneal Thickness Measurements. Although not included in the original protocol of the study, central corneal thickness measurements were taken during the trial in a large sample of the patients: 429 in the dorzolamide group (80.0%) and 425 in the placebo group (78.5%). It was performed using the same pachymeter used in the OHTS (DGH-500 Pachte; DGH Technologies, Exton, PA),²² following a standard procedure in all the centers that included the use of topical anesthesia and the acquisition of 5 measurements in both eyes. The average of the mean of the 5 measurements of the 2 eyes was considered for the analysis. When only 1 eye was included in the study, the mean of the 5 measurements of that eye was considered for the analysis.

Study End Points

The EGPS criteria for the onset of POAG were defined as the occurrence of a worsening of the visual field or a progressive change in the optic disc appearance, or both. A safety end point was defined as an increase of IOP above ethically unacceptable values (in agreement with the ethical review committees). Patients meeting any of these 3 end points were reviewed, and a decision of agreement or disagreement was made at the Central Coordinating Center.

Worsening of visual field was reached when at least 1 of the following criteria was met: (1) 3 or more horizontally or vertically adjacent points that differ 5 dB or more from baseline, (2) 2 or more horizontally or vertically adjacent points that differ 10 dB or more from baseline, (3) a difference of 10 dB or more across the nasal horizontal meridian at 2 or more adjacent points. The loss could not be attributable to other pathologic features.

The sensitivity loss was defined relative to the baseline (normal) values of each patient. The superior and inferior rows of the physiologic blind spot were excluded from the field evaluation.

To meet the criteria that defined the occurrence of the visual field end point, the patient had to repeat the visual field test within 30 days. If the defect was confirmed in the same test locations, the patient had to repeat a third visual field test. If again the defect was confirmed, the visual field end point was considered to be met. The 3 visual field tests had to be consecutive and had to be performed within 3 months. In case of questionable worsening, the patient continued the study and repeated the visual field at the next follow-up visit.

Worsening of the optic disc was defined as a visually recognizable (on stereo photographs) narrowing of the neuroretinal rim area (localized or diffuse) not attributable to photographic artifacts. This was detected by comparing follow-up stereoscopic optic disc slides with baseline stereoscopic optic disc slides. An optic disc end point was reached when 2 of 3 optic disc evaluators independently determined worsening. If the worsening appeared to be questionable, the patient continued in the study and pictures were taken again at the next follow-up visit. All the evaluations of each optic disc evaluator were sent to the Central Coordinating Center, which assessed the consensus agreement or disagreement between the 3 independent evaluations. The repeatability and reproducibility of the consensus agreement between the 3 independent readers were excellent both at the beginning of the study and when a change in the readership occurred.²¹

A safety end point was met whenever IOP increased to 35 mmHg or more in the same eye on 2 separate occasions within 1 week.

Quality Assurance

The EGPS was conducted according to Good Clinical Practice (Note for Guidance on Good Clinical Practice. CPMP/International Conference on Harmonization of Technical Requirements

for Registration of Pharmaceuticals for Human Use [ICH]/135/95. 1996). The occurrence of end points was assessed independently at the Coordinating Center, which also monitored data quality and adherence to protocol. Collected data (case report forms [CRFs]) were sent for review to the Coordinating Center, where they were processed to ensure a standard quality of the forms ready for input into the database. This process included the production of queries to be sent back to the original study center to be corrected for missing, invalid, or questionable data. Monitoring of the data collection flow, as well as of optic disc flow between the 3 evaluators, was performed on a monthly basis.

The input of the CRFs in the database was performed at the Data Management and Statistical Analysis Center. Single entry of all variables with a double check for all variables was attained for each CRF.²³ This procedure was performed by 2 independent, certified persons. This process consisted of 2 separate steps. The first, performed automatically by a dedicated computer check program, allowed inconsistent or outlying data to be identified, checked, and eventually corrected if required. The second step was performed separately by the 2 independent evaluators by comparing the data stored in the computer with the data reported in the CRFs. During this step, data that were entered incorrectly were corrected immediately.

Statistical Design

Sample Size. A sample size of 1081 patients initially was calculated to assure a statistical power of 80% to detect, with the log-rank test, a difference between groups of 5% at 2.5 years in the proportion of events (from 12.5% in the placebo group to 7.5% in the treated group), assuming a 10% rate of dropouts, with a 0.05 type 1 error (1 tailed) and a follow-up time of 2.5 years. The number of end points required to meet the initial statistical assumptions was 78. Shortly after the initiation of the study, the Steering Committee decided to adopt a more conservative 2-sided test, still maintaining the same power and type 1 error. Therefore, 101 end points needed to be reached. Moreover, given the observed lower than expected overall event rate, the Steering Committee decided to prolong the observation time until the requested number of end points was reached in patients currently enrolled in the study, or until 5 years of follow-up was completed for each patient. With these estimates, even assuming a 5-year event rate of 20% in the placebo group and 12% in the treated group (which is smaller than what was assumed), the study would have maintained the same power even with a dropout rate of up to 36%.²⁴

The projections on visual field loss, optic disc changes (end points), or both were based on the incidence rates for individuals older than 40 years of age with similar levels of IOP reported in the Collaborative Glaucoma Study (1-year incidence rate of 5%),²⁵ as well as the results of Epstein et al¹⁰ (1-year incidence rate of 5%), Kass et al¹¹ (1-year incidence rate of 3.2%), and Schulzer et al¹² (1-year incidence rate of 4.7%).

Analysis. The intention-to-treat approach was used for efficacy and safety analysis. That is, all randomized patients were included in all analyses, with the exception of patients violating major entry criteria (i.e., having glaucoma at the study beginning). Patients who reached the safety end point and patients lost to follow-up also were included in the analysis of all available data: they were considered censored at the time of reaching the safety end point or loss to follow-up.

All statistical tests (log rank, Cox proportional hazards regression model) were 2-sided and were performed at the 5% significance level. The primary efficacy variable was the length of time to develop glaucomatous damage, that is, the time from randomization to first confirmed occurrence of a worsened visual field or a worsened optic disc. A secondary efficacy variable, the length of

time to develop a safety end point, was added by the Steering Committee after the publication of the OHTS and Early Manifest Glaucoma Trial (EMGT) results,^{9,26} but before unmasking of the trial. The difference between treatment groups with respect to both primary and secondary variables was assessed using survival analysis.

Intraocular pressure was the average of the right and left eyes. When only 1 eye was included in the study (238 patients), its IOP was considered for the analysis. It was calculated as the mean (and standard deviation [SD]) of the IOPs of the patients actively in the study, as well as of the last observation carried forward. It was also calculated as the last observation before withdrawing in the group of patients who withdrew from the study.

The DSMC approved the termination of the study when the last patient performed the last follow-up visit as soon as 101 efficacy end points were reached among patients within the study, as specified in the original protocol.

Results

The enrollment of the patients lasted from January 1997 through May 1999. A total of 1081 patients were enrolled. However, because of the enrollment of 4 patients with glaucoma (i.e., major protocol violators), the overall number of the randomized patients included in the intention-to-treat analysis was reduced to 1077 (including 2 patients younger than 30 years).

The details concerning the baseline description of the participants were provided in the previously published article.²⁰ In addition, the mean corneal thickness was 574 μm (SD, 39.0 μm) in the dorzolamide group and 570 μm (SD, 37.8 μm) in the placebo group ($P = 0.2$, t test).

Follow-up

The flowchart of the participant progress is shown in Figure 1. The percentage of patients who discontinued for any reason was 35.6% in the dorzolamide group and 24.7% in the placebo group (30.1%, overall). The reasons for discontinuation are summarized in Table 1. When discontinued patients were excluded from the analysis, 99% or more of scheduled study visits were performed in both

groups. The median duration of follow-up for all the patients enrolled was 55.3 months (55.0 and 55.6 months in the dorzolamide and placebo groups, respectively). Technically acceptable visual field tests and stereoscopic optic disc photographs suitable for analysis were obtained in 99% and 95% of the follow-up visits, respectively. A total of 3591 and 3987 follow-up CRFs were received for the dorzolamide and placebo groups, respectively.

Intraocular Pressure Reduction

The baseline and follow-up IOP for the dorzolamide and the placebo groups are reported in Table 2. Mean IOP at baseline (23.4 mmHg and 23.5 mmHg for the dorzolamide and placebo groups, respectively) was not significantly different. The mean value of IOP averaged across the follow-up visits was 19.3 mmHg for the dorzolamide group and 20.4 mmHg for the placebo group, the difference being significantly different ($P < 0.0001$). The mean percent reduction in IOP from baseline in observed cases was 14.5% for the dorzolamide group at 6 months, which progressively increased to 22.1% at 5 years ($P < 0.0001$). The mean percent reduction in IOP from baseline in observed cases was 9.3% for the placebo group at 6 months, which progressively increased to 18.7% at 5 years ($P < 0.0001$; Fig 2).

In the last observation carried forward analysis (Fig 3), IOP dropped by 13.1% (SD, 11%) and 8.6% (SD, 11.3%) in the dorzolamide and placebo groups, respectively, at 6 months, and by 17.9% (SD, 14.1%) and 13.7% (SD, 15.9%) in the dorzolamide and placebo groups, respectively, at the end of the study (the difference was statistically significant, $P < 0.0001$).

Efficacy End Points

A reproducible visual field or optic disc change developed in a total of 110 patients as a result of POAG ($n = 106$) or other reasons ($n = 4$), including retinal vein occlusion, cataract, and testing artifacts. Table 1 summarizes the distribution of end points in this study. Of the 345 patients who completed the study in the dorzolamide group, 46 reached an efficacy end point and 1 reached a safety end point, whereas of the 407 patients who completed the study in the placebo group, 60 reached an efficacy end point and 12 reached a safety end point. At the completion of the study, the cumulative probability of developing an efficacy end point was

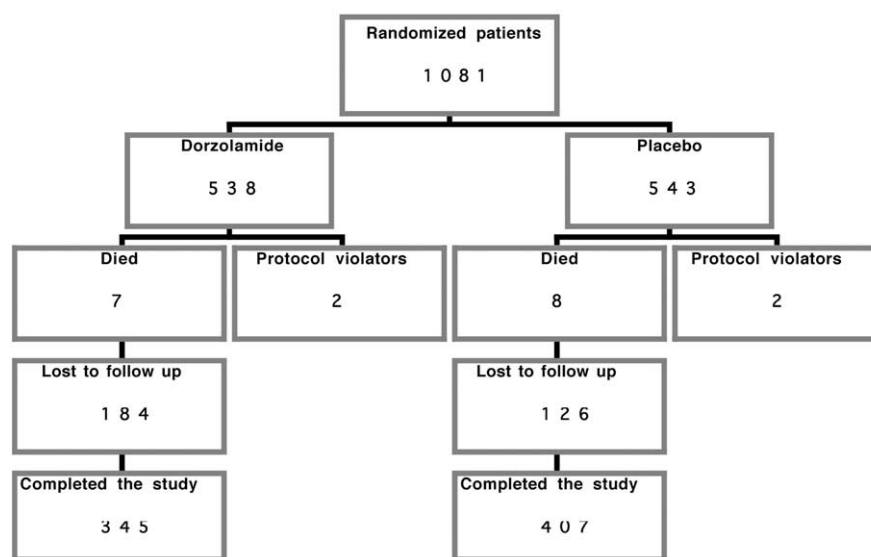


Figure 1. Flowchart of participant progress in the European Glaucoma Prevention Study.

Table 1. Progress and Outcome of Study Participants

	Dorzolamide		Placebo		Total	
	n	%	n	%	n	%
End of study	298	55.6	335	61.9	633	58.8
Adverse events	116	21.7	51	9.4	167	15.5
Lost to follow-up	27	5.0	23	4.3	50	4.6
Deviation from protocol	11	2.1	5	0.9	16	1.5
Withdrew from study	35	6.5	53	9.8	88	8.2
ODP/VF end point other than POAG	2	0.4	2	0.4	4	0.4
ODP end point	20	3.7	22	4.1	42	3.9
VF end point	26	4.9	38	7.0	64	5.9
Safety end point (IOP \geq 35 mmHg)	1	0.2	12	2.2	13	1.2
All	536	100.0	541	100.0	1077	100.0

IOP = intraocular pressure; ODP = optic disc photograph; POAG = primary open-angle glaucoma; VF = visual field.

13.4% in the dorzolamide group and 14.1% in the placebo group; the difference was not statistically significant (hazard ratio, 0.86 and 95% confidence interval [CI], 0.58–1.26, Mantel-Haenszel log-rank test; $P = 0.45$; Fig 4). When the patients who reached a safety end point were added to those who reached an efficacy end point, the cumulative probability of developing any end point was 13.7% in the dorzolamide group and 16.4% in the placebo group; the difference was not statistically significant (hazard ratio, 0.73 and 95% CI, 0.51–1.06, Mantel-Haenszel log-rank test; $P = 0.1$; Fig 5). No difference in the 2 arms was found when the analysis was performed stratifying by pseudoexfoliation, pigmentary dispersion syndrome, and diabetic patients. For primary analysis, the hazard ratio was 0.86 and the 95% CI was 0.59–1.27 ($P = 0.45$). For the analysis that included the safety end points, the hazard ratio was 0.74 and the 95% CI was 0.51–1.06 ($P = 0.1$).

Safety

Serious adverse events not related to the study drug were reported at 124 (3.4%) and 181 (4.5%) study visits in the dorzolamide and placebo groups, respectively. Seven and 8 patients died during follow-up in the dorzolamide and placebo groups, respectively. Ocular adverse events related to the study drug were reported at 819 (22.8%) and 258 (6.5%) study visits in the dorzolamide and placebo groups, respectively. Of these ocular adverse events, 463 (12.9%) in the dorzolamide group and 107 (2.7%) in the placebo group were ocular burning or stinging at the time of instillation of

the study drug, and 100 (2.8%) in the dorzolamide group and 7 (0.1%) in the placebo group were taste disorders.

Discussion

At the time the EGPS was designed, there was no clear clinical evidence concerning the relationship between pressure reduction and conversion to POAG.²⁷ Management of OHT patients mainly was based on clinical experience or the results of conflicting clinical studies. The recently published results of the OHTS have shown that it is possible to prevent or delay the development of POAG in OHT patients by achieving an 18% net IOP reduction from baseline maintained for at least 5 years.⁹

The EGPS failed to confirm the results of the OHTS in the primary analysis, which included only the efficacy end points, and in the secondary analysis, which also included the safety end points. The secondary analysis included the safety end points because, based on the OHTS and EMGT results, one can consider an increase of IOP exceeding 35 mmHg on at least 2 occasions as a surrogate end point for POAG.^{28,29}

Reasons for these findings should not be sought primarily in possible differences between the 2 randomized pop-

Table 2. Mean Intraocular Pressure (mmHg) in the Dorzolamide and Placebo Groups by Length of Follow-up

	Dorzolamide			Placebo		
	n	Mean	Standard Deviation	n	Mean	Standard Deviation
IOP baseline	536	23.4	1.53	540	23.5	1.68
IOP 6 mos	484	20.0	2.69	492	21.3	2.98
IOP 12 mos	453	19.7	2.88	475	21.0	3.41
IOP 18 mos	415	19.4	3.00	455	20.7	3.48
IOP 24 mos	391	19.1	2.85	447	20.4	3.35
IOP 30 mos	365	18.8	2.84	421	20.1	3.47
IOP 36 mos	356	18.7	2.87	401	19.9	3.74
IOP 42 mos	333	18.5	2.99	378	19.6	3.48
IOP 48 mos	311	18.2	3.02	364	19.3	3.56
IOP 54 mos	290	17.9	3.08	328	19.1	3.60
IOP 60 mos	192	18.2	3.45	217	19.1	3.71

IOP = intraocular pressure.

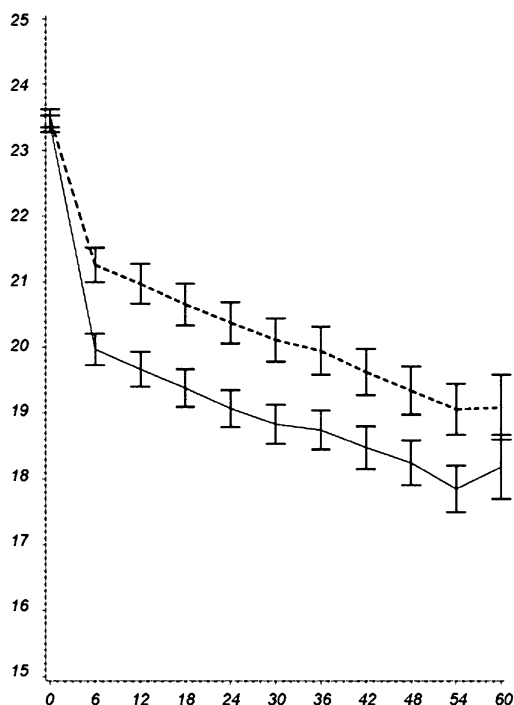


Figure 2. Mean intraocular pressure (IOP; 95% confidence intervals) at baseline and follow-up for the medication and placebo groups. Results for each participant's right and left eye were averaged to calculate a mean. The numbers of participants completing each follow-up visit are shown at the bottom. The solid line represents the dorzolamide group and the dotted line the placebo group. x-axis = months from randomization; y-axis = IOP.

Numbers of Participants Completing Each Follow-up Visit

	0	6	12	18	24	30	36	42	48	54	60
Dorzolamide	536	484	453	415	391	365	356	333	311	290	192
Placebo	541	492	475	455	447	421	401	378	364	328	217

ulations or in specific biases related to the knowledge of the clinical features of the patients. The EGPS was a placebo-controlled double-masked trial. Its design allowed for a better control of potential biases, such as unmasked patients and investigators. Moreover, it promoted a comparable attitude toward the study of the patients in both the treated and untreated groups and eliminated complicated procedures that are otherwise necessary to avoid unmasking.³⁰ As previously published,²⁰ randomization in the EGPS was achieved with no imbalance between the 2 arms in any clinical variable or in corneal thickness, although this latter evaluation was performed after the trial was already ongoing and in approximately 80% of the participants. It is particularly important that the 2 arms did not show any relevant imbalance for clinically relevant variables, such as the history of ocular hypotensive medical treatment, self-reported ocular and systemic conditions, and treatment for systemic conditions. An imbalance of these conditions, particularly concerning the patients reporting previous ocular therapy with hypotensive medication, could have introduced a potentially relevant selection bias, with a possible impact on the outcome of the study.²⁰

During the study, more patients receiving dorzolamide than those receiving the placebo reported ocular burning or stinging and taste disorder, 2 well-known side effects of dorzolamide, thus potentially unmasking some of the patients and investigators to the therapy being taken. However, because the assessment of visual field and optic disc end points was carried out by centralized committees who were masked to the patients (who were known to them only by allocation number), any potential bias from unmasking because of dorzolamide side effects probably was eliminated.

The EGPS could not confirm the OHTS results, although the actively treated arm had a mean IOP reduction ranging between approximately 15% to 22% throughout the 5 years of the trial. Thus, the IOP effect of dorzolamide in the EGPS was consistent with that previously reported in much shorter trials that observed an IOP reduction ranging between 14% and 23%.^{18,19,31} In fact, the recently published Guidelines of the European Glaucoma Society describe the IOP-lowering effect of topical carbonic anhydrase inhibitors such as dorzolamide as being approximately 15% to 20%.³²

Interpretation of the results of the EGPS then should be based on other observations. A clinically relevant and sus-

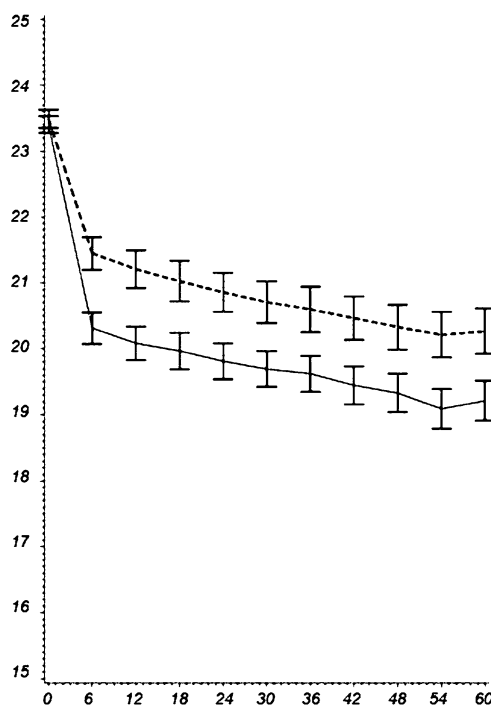


Figure 3. Mean intraocular pressure (IOP [mmHg]; 95% confidence intervals) at baseline and follow-up for the medication and placebo groups using the last observation carried forward analysis. Each participant's right and left eye was averaged to calculate the mean. The solid line corresponds to the dorzolamide group, and the dotted line to the placebo group. x-axis = months from randomization; y-axis = IOP.

Numbers of Participants Completing Each Follow-up Visit

	0	6	12	18	24	30	36	42	48	54	60
Dorzolamide	536	484	453	415	391	365	356	333	311	290	192
Placebo	541	492	475	455	447	421	401	378	364	328	217

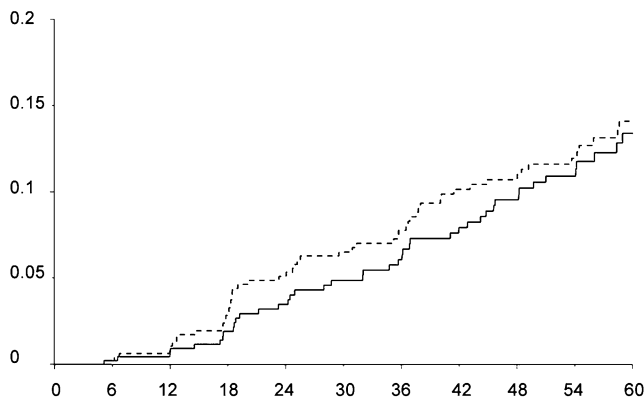


Figure 4. Kaplan–Meier plot of the cumulative probability of developing an efficacy end point by randomization group. The number of patients at risk are those who had not developed efficacy end points at the beginning of each 6-month period. Participants who did not develop efficacy end points and withdrew before the end of the study or who died are censored from the interval of their last completed visit. The number of events was 46 of 536 and 60 of 541 in the dorzolamide and placebo groups, respectively (chi-square log-rank test, 0.5526; $P = 0.4572$). The solid line corresponds to the dorzolamide group and the dotted line corresponds to the placebo group. x-axis = months from randomization; y-axis = proportion of patients developing an efficacy end point.

Patients at Risk

	6	12	18	24	30	36	42	48	54	60
Dorzolamide	537	466	417	388	353	331	307	290	272	208
Placebo	541	483	456	433	408	384	359	328	304	241

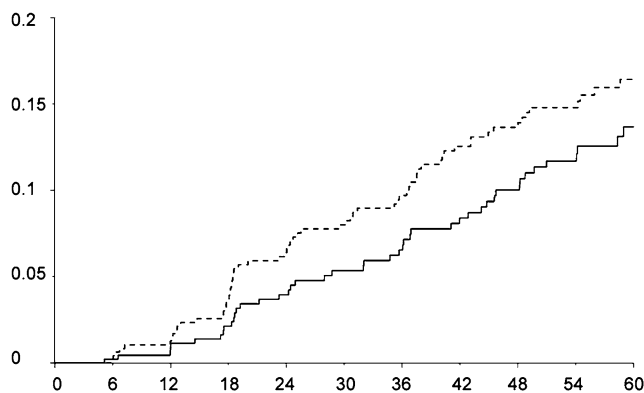


Figure 5. Kaplan–Meier plot of the cumulative probability of developing an efficacy end point or a safety end point by randomization group. The number of patients at risk are those who had not developed efficacy or safety end points at the beginning of each 6-month period. Participants who did not develop efficacy or safety end points and withdrew before the end of the study or who died are censored from the interval of their last completed visit. The number of events was 47 of 536 and 72 of 541 in the dorzolamide and placebo groups, respectively (chi-square log-rank test, 2.7217; $P = 0.099$). The solid line corresponds to the dorzolamide group and the dotted line corresponds to the placebo group. x-axis = months from randomization; y-axis = proportion of patients developing an efficacy or safety end point.

Patients at Risk

	6	12	18	24	30	36	42	48	54	60
Dorzolamide	537	466	417	388	353	331	307	290	272	208
Placebo	541	483	456	433	408	384	359	328	304	241

tained placebo effect of approximately 9% to 19% is probably the most striking result of the EGPS. Moreover, the placebo effect increased during the study, parallel to the increasing efficacy of dorzolamide. In fact, the mean IOP difference between the 2 treatment groups at each time point of the trial ranged between 1.1 and 1.3 mmHg (mean, 1.03 mmHg). Based on the findings of OHTS as well as on those of the EMGT, which addressed the clinical relevance of IOP reduction sustained over time as the major protective factor for the development or further progression of POAG, the small treatment difference between dorzolamide and placebo can explain the failure to detect a statistically significant protective effect of medical treatment in the EGPS.^{9,26,28,29} The EGPS in fact was powered to detect a much larger relative difference (40%) in the number of efficacy end points between the 2 arms, based on a greater expected difference in IOP reduction between dorzolamide and placebo. Although a difference of even greater magnitude (approximately 60%) in the number of end points between the 2 study arms was observed in the OHTS,⁹ this did not occur in the EGPS. It is worth noting that the protective effect of dorzolamide in the EGPS (hazard ratio, 0.86; 95% CI, 0.58–1.26) was consistent with the protective effect per millimeter of mercury of IOP lowering (approximately 12%) seen in the risk factor analysis of the EMGT.²⁹ However, this effect was far from being statistically significant in the EGPS.

To our knowledge, this is the first time such a meaningful and consistent placebo effect has been observed with long-term (5-year) treatment. In the recent literature, only 1 study comparing travoprost with placebo documented a placebo effect of approximately 5% to 11% over a 6-month period.³³ However in that study, the effect of placebo tended to decrease during the last period of the trial. In the EGPS, the major part of the effect was observed after 6 months. This could have been explained by a regression to the mean. However, there was a tendency toward an increasing IOP effect as the trial continued. We considered several explanations for this rather unexpected placebo effect. First, the placebo supplies could have contained some dorzolamide. We have confirmed that all placebo batches manufactured for this study were tested for the absence of dorzolamide before being released. Second, bottles containing dorzolamide could have been distributed to placebo patients. However, the effect occurred in all centers to a similar extent. It would be highly unlikely that this error would have been consistently made at all centers. Third, a true hypotensive effect of this placebo may be possible. We tend to think of a placebo as a truly inactive drug. In general medicine, a placebo per os usually consists of starch or dextrose and is coated and formed to resemble the active therapy. In contrast, in the EGPS, the placebo and active treatment eyedrops were of the same formulation except for the fact that the placebo did not contain dorzolamide. That is, the placebo was the vehicle of the active formulation. Thus, a placebo for a β -blocker would not be the same as the placebo for dorzolamide. In fact, the formulations of these vehicles are different, for example, with the latter being at a lower pH. If there were a true IOP-lowering effect of the placebo, this would help to explain the IOP effect that

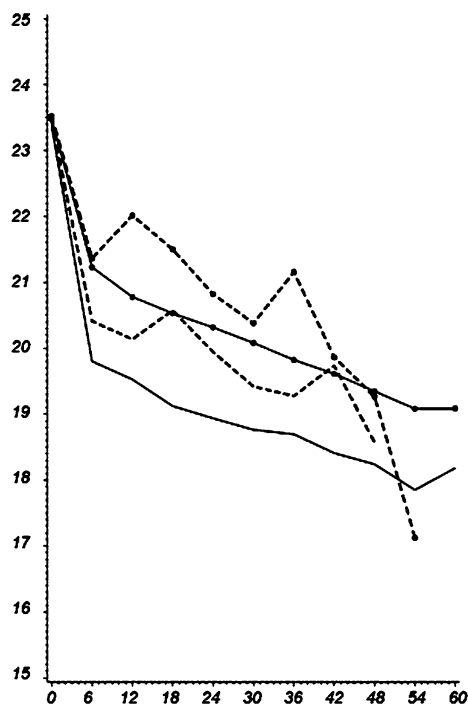


Figure 6. Mean intraocular pressure (IOP) at baseline and follow-up of participants in the study and participants withdrawn from the study, in the medication and placebo groups. Measurements of each participant's right and left eye were averaged to calculate a mean. The solid line corresponds to the patients in the dorzolamide group still in the study. The dotted line corresponds to the patients in the dorzolamide group who withdrew from the study. The solid line with solid circles corresponds to the patients in the placebo group still in the study. The dotted line with solid circles corresponds to the patients in the placebo group who withdrew from the study. x-axis = months from randomization; y-axis = IOP.

occurred in both the dorzolamide and placebo groups, because both treatments contained the vehicle. However, this hypothesis is not supported by the results of a previous clinical study that used the vehicle of dorzolamide as a placebo.³⁴

Conversely, the tendency for the increase in efficacy over time may be explained at least by a self-selection bias, with those patients with a higher IOP being more likely to withdraw from the trial. A comparative analysis of the mean IOP between the patients still in the study and those who voluntarily withdrew revealed a higher IOP level in the group of withdrawn patients (Fig 6). A smaller increase in the effect of placebo and dorzolamide over time was seen when the IOP analysis was performed using the last observation carried forward method, which includes the last IOP measurement obtained for each withdrawn patient in the analysis of each subsequent visit (Fig 3).

Given the remarkable efficacy of placebo, an a posteriori interpretation of the EGPS results should outline the limitation of the EGPS protocol, which did not require any target IOP reduction to be achieved during the trial. At the time the EGPS was designed, there were no clear data concerning a threshold value of expected beneficial reduction of IOP. The decision to not require a target pressure

was based on the possibility that patients achieving a treatment goal may have a less severe clinical situation (expecting an inherently better outcome) than patients who show a smaller reduction of IOP to treatment. Consequently, as was stated by Leske et al,³⁵ "comparison based on this controlled IOP group could show a beneficial effect of treatment, even if none existed." Although appropriate, such a statement may not have held true for the purposes of the EGPS.

Interestingly, although inconsistent with the OHTS results, the EGPS findings are in line with the results of 2 of the 4 published pre-OHTS trials that gave rise to controversial and inconsistent results concerning the effect of IOP-lowering treatment in OHT^{10-12,36} and with a recently published article by Kamal et al.³⁷ Two of these 3 trials were placebo controlled,^{36,37} and the other was not.¹² A significant IOP reduction from baseline, although of different magnitudes than that observed in the EGPS, was reported in the 2 placebo-controlled trials. None of the recently published long-term large clinical trials, such as the Collaborative Normal-Tension Glaucoma Study,³⁸ the Advanced Glaucoma Intervention Study,³⁹ the EMGT,²⁶ and the ongoing Collaborative Initial Glaucoma Treatment Study,^{40,41} evaluates OHT patients who are at risk of developing glaucoma. In addition, none of the above mentioned trials was placebo controlled.

Apart from the Collaborative Normal Tension Glaucoma Study, the Advanced Glaucoma Intervention Study, and the Collaborative Initial Glaucoma Treatment Study, whose protocols included a surgically treated arm and the achievement of well-defined target pressures, the EMGT compared a medical laser-treated arm versus an observation arm, without requiring any specific target pressure. The EGPS results then may support the need to replicate the EMGT findings with a placebo-controlled, double-masked, randomized clinical trial.

The incidence of efficacy end points (both visual field and optic disc progressive changes) was higher in the EGPS than in the OHTS⁹ (9.8% vs. 7.6%). The ratio between visual field and optic disc end points was 1.5 (64/42) in the EGPS, which was just the opposite of the OHTS⁹ (0.6; 44/69). This may be explained by the different definition of visual field end points adopted in the EGPS (which was based on a direct, quantitative, patient-based comparison between any follow-up examination and the baseline) as well as by the different assessment of optic disc changes in the 2 studies. Moreover, an interesting outcome of the EGPS is the equivalence of efficacy optic disc end points in the 2 arms (3.7% dorzolamide vs. 4.1% placebo), as compared with the greater incidence of visual field end points in the placebo group (4.9% dorzolamide vs. 7.0% placebo). Because the definition of optic disc changes was based on the agreement of 2 of 3 independent observers and did not need to be confirmed on the next follow-up evaluation, it is possible that an insufficient specificity was achieved. That is, a high rate of false positives may have occurred, thus diluting the actual rate of progressive disc changes. A possible bias related to an inconsistency of optic disc evaluations between the readers should be ruled out, because a reproducibility assessment was performed at the beginning

of the study and during the trial, when new evaluators were included in the optic disc photograph reading process.²¹

A possible limitation of the EGPS results may be the high dropout rate, which was 30.1% overall. The dropout rate was 9.3% within the first 6 months of the study and increased throughout the trial. It was higher (35.6%) in the dorzolamide group than in the placebo group (24.7%), which may be explained by the higher number of ocular side effects in the dorzolamide group. An additional explanation for such a high dropout rate may be the use of the placebo, which may create greater anxiety in the patients. In fact, the dropout rate observed in the EGPS is higher than that observed in the OHTS⁹ (24.5% including crossovers and end points not related to POAG), which was not placebo controlled, but consistent with those reported in previous placebo-controlled trials (dropout rates 28%,¹¹ 34%,³⁶ and 36%³⁷) with a 3-year or 5-year follow-up.

There were few safety concerns in the EGPS. As far as the serious adverse events not related to study drugs are concerned, they were few and slightly more frequent in the placebo group (4.5%) than in the dorzolamide group (3.4%). As far as the ocular side effects related to the study drugs are concerned, they were more common in the dorzolamide group than in the placebo group (22.8% vs. 6.5%). The most common of these side effects were ocular burning and stinging at the time of drug instillation (12.9% in the dorzolamide group and 2.7% in the placebo group) and taste disorder (2.8% in the dorzolamide group and 0.1% in the placebo group). Because these figures refer to a period of approximately 5 years, they are largely in agreement with previous reports (from studies lasting between 3 to 24 months) that documented an incidence of approximately 5% to 33% for ocular discomfort and 4% to 27% for taste perversion.^{16,18,19,31}

In conclusion, first, the EGPS failed to detect a protective effect of medical therapy (by means of dorzolamide) as compared with placebo for the development of POAG in OHT patients at moderate risk over a follow-up of approximately 5 years. This result can be explained mainly by a clinically significant effect of the placebo on IOP. However, although not statistically significant, the protective effect exerted by dorzolamide (hazard ratio, 0.86; with a mean 1.03-mmHg IOP difference between the dorzolamide-treated and the placebo-treated arms) is consistent with the results of the risk factor analysis of the EMGT, which attributed to each 1 mmHg of higher IOP a hazard ratio of 1.13 for the progression of POAG.

Second, in this study the pharmacologic component of the effect attributable to the active drug (the IOP-lowering effect of dorzolamide over the vehicle) was smaller than expected. However, the overall magnitude of the IOP-lowering effect of dorzolamide (15% to 22% throughout the 5 years of the study) was consistent with previously published studies.

Therefore, these results strongly support the need to evaluate or reevaluate the efficacy of long-term medical therapy of OHT, POAG, or both by means of placebo-controlled, double-masked, randomized clinical trials.

Acknowledgments. The EGPS Group acknowledges the members of the Writing Committee: Stefano Miglior, Thierry Zeyen,

Norbert Pfeiffer, Jose Cunha-Vaz, Valter Torri, and Ingrid Adamsons.

References

1. Anderson DR. Glaucoma: the damage caused by pressure. XLVI Edward Jackson memorial lecture. *Am J Ophthalmol* 1989;108:485-95.
2. American Academy of Ophthalmology Glaucoma Panel. Preferred Practice Pattern. Primary Open-Angle Glaucoma. San Francisco: American Academy of Ophthalmology; 1992.
3. Sommer A, Tielsch JM, Katz J, et al. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. *Arch Ophthalmol* 1991;109:1090-5.
4. Tielsch JM, Katz J, Sommer A, et al. Hypertension, perfusion pressure, and primary open angle glaucoma. A population-based assessment. *Arch Ophthalmol* 1995;113:216-21.
5. Leske C, Connell AM, Wu SY, et al. Risk factors for open-angle glaucoma. The Barbados Eye Study. *Arch Ophthalmol* 1995;113:918-24.
6. Tielsch JM, Katz J, Sommer A, et al. Family history and risk of primary open angle glaucoma. The Baltimore Eye Survey. *Arch Ophthalmol* 1994;112:69-73.
7. Bonomi L, Marchini G, Marraffa M, et al. Vascular risk factors for primary open angle glaucoma: the Egna-Neumarkt Study. *Ophthalmology* 2000;107:1287-93.
8. Ekstrom C. Elevated intraocular pressure and pseudoexfoliation of the lens capsule as risk factors for chronic open-angle glaucoma. A population-based five-year follow-up study. *Acta Ophthalmol* 1993;71:189-95.
9. Kass MA, Heuer DK, Higginbotham EJ et al. Ocular Hypertension Treatment Study Group. The Ocular Hypertension Treatment Study. A randomized trial determines that topical hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol* 2002;120:701-13.
10. Epstein DL, Krug JH Jr, Hertzmark E, et al. A long-term clinical trial of timolol therapy versus no treatment in the management of glaucoma suspects. *Ophthalmology* 1989;96:1460-7.
11. Kass MA, Gordon MO, Hoff MR, et al. Topical timolol administration reduces the incidence of glaucomatous damage in ocular hypertensive individuals. A randomized, double-masked, long-term clinical trial. *Arch Ophthalmol* 1989;107:1590-8.
12. Schulzer M, Drance SM, Douglas GR. A comparison of treated and untreated glaucoma suspects. *Ophthalmology* 1991;98:301-7.
13. Schuman JS. Antiglaucoma medications: a review of safety and tolerability issues related to their use. *Clin Ther* 2000;22:167-208.
14. Sugrue MF. Pharmacological and ocular hypotensive properties of topical carbonic anhydrase inhibitors. *Prog Retin Eye Res* 2000;19:87-112.
15. Pfeiffer N. Dorzolamide: development and clinical application of a topical carbonic anhydrase inhibitor. *Surv Ophthalmol* 1997;42:137-51.
16. Adamsons IA, Polis AB, Ostrov CS, Boyle JE, Dorzolamide Safety Study Group. Two-year safety study of dorzolamide as monotherapy and with timolol and pilocarpine. *J Glaucoma* 1998;7:395-401.
17. Stewart WC, Garrison PM. Beta-blocker-induced complications and the patient with glaucoma. Newer treatments to help reduce systemic adverse events. *Arch Intern Med* 1998;158:221-6.

18. Strahlman E, Tipping R, Vogel R, International Dorzolamide Study Group. A double-masked, randomized 1-year study comparing dorzolamide (Trusopt), timolol, and betaxolol. *Arch Ophthalmol* 1995;113:1009–16.
19. Rusk C, Sharpe E, Laurence J, et al, Dorzolamide Comparison Study Group. Comparison of the efficacy and safety of 2% dorzolamide and 0.5% betaxolol in the treatment of elevated intraocular pressure. *Clin Ther* 1998;20:454–66.
20. European Glaucoma Prevention Study (EGPS) Group. The European Glaucoma Prevention Study design and baseline description of the participants. *Ophthalmology* 2002;109:1612–21.
21. European Glaucoma Prevention Study (EGPS) Group. Reproducibility of evaluation of optic disc change for glaucoma with stereo optic disc photographs. *Ophthalmology* 2003;110:340–4.
22. Brandt JD, Beiser JA, Kass MA, Gordon MO, Ocular Hypertension Treatment Study (OHTS) Group. Central corneal thickness in the Ocular Hypertension Treatment Study (OHTS). *Ophthalmology* 2001;108:1779–88.
23. King DW, Lashley R. A quantifiable alternative to double data entry. *Control Clin Trials* 2000;21:94–102.
24. Freedman LS. Tables of the number of patients required in clinical trials using the logrank test. *Stat Med* 1982;1:121–9.
25. Armaly MF, Krueger DE, Maunder L, et al. Biostatistical analysis of the Collaborative Glaucoma Study. I. Summary report of the risk factors for glaucomatous visual-field defects. *Arch Ophthalmol* 1980;98:2163–71.
26. Heijl A, Leske MC, Bengtsson B, et al, Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol* 2002;120:1268–79.
27. Rossetti L, Marchetti I, Orzalesi N, et al. Randomized clinical trials on medical treatment of glaucoma. Are they appropriate to guide clinical practice? *Arch Ophthalmol* 1993;111:96–103.
28. Gordon MO, Beiser JA, Brandt JD, et al, Ocular Hypertension Treatment Study Group. The Ocular Hypertension Treatment Study. Baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol* 2002;120:714–20.
29. Leske MC, Heijl A, Hussein M, et al, Early Manifest Glaucoma Trial Group. Factors for glaucoma progression and the effect of treatment. The Early Manifest Glaucoma Trial. *Arch Ophthalmol* 2003;121:48–56.
30. Pocock SJ. *Sperimentazioni Cliniche. Approccio Pratico [Clinical Trials. A Practical Approach]*. Torino, Italy: Centro Scientifico Torinese; 1989:91–100.
31. Silver LH, Brinzolamide Primary Therapy Study Group. Clinical efficacy and safety of brinzolamide (Azopt), a new topical carbonic anhydrase inhibitor for primary open-angle glaucoma and ocular hypertension. *Am J Ophthalmol* 1998;126:400–8.
32. European Glaucoma Society. *Terminology and Guidelines for Glaucoma*. 2nd ed. Savona, Italy: Dogma Publishers; 2003.
33. Orengo-Nania S, Landry T, Von Tress M, et al, Travoprost Study Group. Evaluation of travoprost as adjunctive therapy in patients with uncontrolled intraocular pressure while using timolol 0.5%. *Am J Ophthalmol* 2001;132:860–8.
34. Strahlman E, Tipping R, Vogel R, Dorzolamide Dose-Response Study Group. A six-week dose-response study of the ocular hypotensive effect of dorzolamide with a one-year extension. *Am J Ophthalmol* 1996;122:183–94.
35. Leske MC, Heijl A, Hyman L, Bengtsson B, Early Manifest Glaucoma Trial Group. Early Manifest Glaucoma Trial: design and baseline data. *Ophthalmology* 1999;106:2144–53.
36. Heijl A, Bengtsson B. Long-term effects of timolol therapy in ocular hypertension: a double-masked, randomised trial. *Graefes Arch Clin Exp Ophthalmol* 2000;238:877–83.
37. Kamal D, Garway-Heath D, Ruben S, et al. Results of the betaxolol versus placebo treatment trial in the ocular hypertension. *Graefes Arch Clin Exp Ophthalmol* 2003;241:196–203.
38. Collaborative Normal-Tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. *Am J Ophthalmol* 1998;126:498–505.
39. AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. *Am J Ophthalmol* 2000;130:429–40.
40. Musch DC, Lichter PR, Guire KE, Standardi CL, CIGTS Study Group. The Collaborative Initial Glaucoma Treatment Study: study design, methods, and baseline characteristics of enrolled patients. *Ophthalmology* 1999;106:653–62.
41. Lichter PR, Musch DC, Gillespie BW, et al, CIGTS Study Group. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. *Ophthalmology* 2001;108:1943–53.

Appendix: The European Glaucoma Prevention Study (EGPS) Group

The composition of the members of the EGPS is reported in: The European Glaucoma Prevention Study Group. The European Glaucoma Prevention Study. Design and baseline description of the participants. *Ophthalmology* 2002;109:1612–21.

Marco Centofanti, MD, was added to the Ospedale Oftalmico, Rome. Thierry Zeyen is now at the University of Leuven. Stefano Miglior is now at the “Policlinico di Monza,” University of Milano Bicocca.