A Phase III Study of Subconjunctival Human Anti–Transforming Growth Factor β_2 Monoclonal Antibody (CAT-152) to Prevent Scarring after First-Time Trabeculectomy

*CAT-152 0102 Trabeculectomy Study Group**

Objective: To evaluate CAT-152 (lerdelimumab), a monoclonal antibody to transforming growth factor-β_2 (TGF-β_2), in preventing the progression of fibrosis in patients undergoing first-time trabeculectomy for primary open-angle (POAG) or chronic angle-closure glaucoma (CACG).

Design: Randomized, double-masked, multicenter, placebo-controlled trial.

Participants: Individuals with a diagnosis of POAG, CACG, pseudoexfoliative glaucoma (PEXG), or pigmentary glaucoma (PG), with a recorded intraocular pressure (IOP) of more than 21 mmHg, visual field or optic disc changes characteristic of glaucoma, and taking the maximum tolerated dose of medication.

Intervention: Patients received unilateral trabeculectomy with either 4 subconjunctival injections of CAT-152 (100 μg in 100 μl phosphate buffer) or 4 placebo injections, administered immediately before and on completion of trabeculectomy, and on the first day and at 1 week after surgery. Patients were followed up for 12 months after surgery.

Main Outcome Measures: The primary outcome measure was treatment success in the study eye (unmedicated IOP of 6–16 mmHg inclusive), at the 6- and 12-month follow-up. Secondary outcome measures were the incidence of postoperative intervention with 5-fluorouracil (5-FU); incidence of surgical failure; time to surgical failure; and incidence of vascularity, microcysts, and encapsulation or demarcation of the bleb site.

Results: Of the 388 patients evaluated in the trial, 81% (n = 274) had either POAG or CACG, combined into a single set (POAG/CACG) analyzed by intent-to-treat (ITT) criteria. Separate ITT analyses were carried out for all participants (+PEXG/PG group), with similar results. The treatment success rate was 60% in the CAT-152 group and 68% in the placebo group ($P = 0.23$). No statistically significant differences emerged in the secondary end points. Patients requiring 5-FU for postsurgical management were more likely to be treatment failures ($P = 0.0003$). Patients with a primary diagnosis of PG (n = 49) had a higher success rate than those with other diagnoses ($P = 0.0077$). Administration of CAT-152 was not associated with an increased incidence of adverse events. The immunogenicity of CAT-152 was very low.

Conclusions: At the dose level and regimen studied, there was no difference between CAT-152 and placebo in preventing the failure of primary trabeculectomy. The safety profile of CAT-152 was similar to that of placebo.
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Since its popularization by Cairns in 1970,[1] trabeculectomy, or guarded glaucoma filtration surgery, has become the mainstay of surgical treatment for medically uncontrolled glaucoma. In this procedure, a fistula drains aqueous humor from the anterior chamber of the eye to a bleb created between the conjunctiva and the sclera, from which the fluid is absorbed by the vasculature. In this way, intraocular pressure (IOP) can be decreased to levels that can lessen or prevent further progression of visual field loss.[2] Success of the surgery depends on maintenance of the integrity of the created fistula and bleb. In the long term, however, trabeculectomy fails to lower IOP sufficiently in a sizable proportion of eyes. Progressive surgical failure results from fibroblast proliferation and collagen deposition in the subconjunctival tissues at the site of the filtration bleb. Scarring of the conjunctiva can cause adhesion to the un-

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derlying episcleral tissue, resealing the bleb, or the bleb can become encapsulated by dense fibrotic tissue that prevents aqueous outflow. Eventually, scarring and encapsulation of the bleb results in poor IOP control.[3–6]

The fibroblast has a central role in the scarring process and the failure of the filtration bleb,[7] and thus, most efforts to suppress scarring have concentrated on this cell type. Adjunctive antiscarring agents such as 5-fluorouracil (5-FU) and mitomycin C (MMC) interfere with cellular (including fibroblast) proliferation, and the use of such antimitotic drugs has increased in recent decades as physicians attempt to improve the results of glaucoma filtration surgery.[8–11] This approach has met with some success; however, the nonspecific mechanism of these antiproliferative drugs results in nonspecific cell death,[12,13] occasionally with severe and potentially blinding complications.[14–16] Moreover, the response of individual patients to these agents can be idiosyncratic, making dose titration difficult. Thus, more predictable, specific, and effective antiscarring agents are desirable to improve surgical outcome.

A more targeted approach is to prevent the proliferation of fibroblasts and activation of scarring using antibodies directed to specific cytokines. Transforming growth factor-β (TGF-β) is a key cytokine in the process of tissue repair and has been found to be one of the most potent stimulators of scarring in the eye.[7,17–20] In humans, TGF-β is present in 3 isoforms. Of these, TGF-β_2 is the predominant ocular isoform and a potent stimulator of the conjunctival scarring response.[17,18,21–24] Importantly, TGF-β_2 is the most potent growth factor in aqueous humor for stimulation of Tenon's capsule fibroblasts,[7] and it is found in significantly higher concentrations in the aqueous humor from patients with glaucoma (Invest Ophthalmol Vis Sci 37: S152, 1996; Invest Ophthalmol Vis Sci 37:S27, 1996; Invest Ophthalmol Vis Sci 3:S27, 1996).[25,26]

CAT-152 (lerdelimumab) is a fully human, monoclonal immunoglobulin G4 antibody that specifically and potently neutralizes human TGF-β_2 and has been designed for potential therapeutic use as an inhibitor of scarring.[27] In a rabbit model of glaucoma filtration surgery, subconjunctival injections of CAT-152 improved bleb survival.[19,28] Previous phase I[29] and phase II (Broadway et al, unpublished data) clinical studies in patients undergoing trabeculectomy for primary glaucoma found that CAT-152 treatment was safe, well-tolerated, and effective in maintaining bleb survival and lowered IOP after trabeculectomy. On the basis of these positive findings, a phase III trial of CAT-152 as an adjunct to trabeculectomy was undertaken.

Patients and Methods

Study Design

This multicenter, double-masked, randomized, placebo-controlled trial examined the use of a human monoclonal antibody to TGF-β_2 (CAT-152) as an adjunct to first-time trabeculectomy. Each patient was treated in 1 eye. Patients were enrolled at 36 sites in 6 countries. The study conformed with the principles of the Declaration of Helsinki, with the good clinical practice protocols of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, and with the laws of the countries where it was conducted. Institutional review board or ethics committee approval was obtained at all sites, and each patient provided signed informed consent before study entry.

Patient Selection

Men and women (≥18 years of age) were selected on the basis of requiring first-time trabeculectomy. For inclusion in the primary analysis set, patients needed: a diagnosis of primary open-angle glaucoma (POAG) or chronic angle closure glaucoma (CACG); a recorded IOP of more than 21 mmHg by Goldmann applanation tonometry; visual field or optic disc changes characteristic of glaucoma; and to have been taking the maximum tolerated dosage of antiglaucoma medication. Exclusion criteria included: discernable congenital abnormality of the anterior chamber angle; secondary glaucoma other than pseudoexfoliation (PEXG) or pigmentary glaucoma (PG); disease in the study eye that could affect IOP or its measurement; vitreous in the anterior chamber; posterior capsular opacity; uveitis or history of uveitis; intraocular neovascularization; proliferative retinopathy or severe nonproliferative diabetic retinopathy; being at high risk for yttrium–aluminum–garnet laser treatment; or any ocular or medical condition that could interfere with the assessment of the effect of the study medication. Treatment histories resulting in exclusion included previous conjunctival incisional surgery in the study eye; laser treatment in the study eye within 90 days before trabeculectomy; clear corneal phacoemulsification performed within 1 year of surgery; use of antimetabolites or systemic steroids within 90 days of surgery; treatment with cancer chemotherapy within 6 weeks of surgery; use of any investigational drug within 4 weeks of surgery; or previous use of CAT-152. Women of childbearing age were excluded if pregnant or not using contraception. Because the focus of this trial was on patients with POAG or CACG, trial recruitment ended when the target number of patients with POAG or CACG had been recruited. The PEXG or PG patients did not count toward the recruitment target and were included until recruitment was completed.

Randomization and Treatment

The risks of subconjunctival injections of sterile buffered saline were considered minimal, and thus, a placebo-injection control group was deemed ethical. An interactive voice-response system provided centralized randomization control on a site-specific basis. Individual patient enrollment information was entered by telephone (using secure password protection), and in response, the site immediately received the treatment number assignment via fax. Study treatments were allocated using a dynamic balancing algorithm. Investigators, patients, outcome assessors, and data analysts were masked throughout the study. The investigator could break the code only in an emergency within the first 30 days after the final dose was administered. Thereafter, the code could be broken only by the medical monitor. Placebo vials and contents were indistinguishable from those of CAT-152; labels on the vials detailed the randomly assigned treatment number but did not identify treatment group.

Immediately before surgery, a single subconjunctival injection of 100 μl CAT-152 (or placebo) was given approximately 10 mm from the limbus in the same quadrant as the surgical site and filtration bleb. A trabeculectomy modified from Cairn's original description[1] then was performed under either local or general anesthesia. After surgery (in the operating room), steroid and antibiotic injections were given inferiorly, followed by the second subconjunctival injection of CAT-152 or placebo (100 μl). Topical

steroids and antibiotics were prescribed according to local practice. Cycloplegics were not used routinely unless clinically indicated. On the day after surgery, patients were assessed and administered the third injection of CAT-152 or placebo (100 μl). At 7 ($\pm$2) days after surgery, patients were evaluated and administered the fourth and final antibody or placebo injection (100 μl) within 5 mm of the bleb. It was not possible to standardize the surgical procedures and postoperative medications rigidly, but each site attempted to follow a common procedure. Oral acetazolamide and all topical treatments used in the study eye to control IOP before the trabeculectomy were discontinued at the time of surgery.

From days 1 through 14, massage and suture release and lysis were permitted for high IOP. After day 14, massage, needling, suture release and lysis, and 5-FU injections (if IOP was 17 mmHg or more) were allowed. Administration of MMC was not allowed, and investigators were encouraged to minimize 5-FU use. Topical antiglaucoma medications were permitted if the IOP (mean of 2 readings) exceeded 21 mmHg.

Study Assessments and End Points

Study Assessments. After giving signed informed consent, patients were screened for eligibility within 90 days of surgery, usually on the day of presentation to the clinic. Presurgical assessments were carried out on the day before or the day of surgery and included physical examination, vital signs, pregnancy testing, the presence of antibodies to CAT-152, and any adverse events. An ophthalmic history was obtained, and both eyes were examined by slit-lamp biomicroscopy (cells and flare were not assessed in the nonstudy eye) and were measured for visual acuity and IOP. The IOP measurements were read to the nearest 1 mmHg, and repeated measurements were obtained until 2 were obtained that were no more than 1 mmHg apart. If only a single IOP measurement was available, it was used. When there were 2 measurements more than 1 mm Hg apart, the mean of the 2 measurements was used. On the first and seventh days after surgery, investigators graded the technical success of the surgery, assessed the bleb site, examined the eye by funduscopy and slit-lamp biomicroscopy, and measured visual acuity and IOP. Concomitant medications or interventions were noted, as were adverse events in either eye. Study eyes, interventions, and adverse events similarly were evaluated on day 14, and the bleb site was photographed. On day 28 and at month 3, the same evaluation protocol was followed, but without bleb photography and with the addition of testing for antibodies to TGF-β_2. At 6 months after surgery, the standard evaluation was accompanied by cataract grading (Lens Opacities Classification System III), and no testing for antibodies for TGF-β_2 was carried out. At the final visit at month 12 (or when a patient exited the study), patients underwent a physical examination, were tested for antibodies to TGF-β_2, and were evaluated for adverse events, interventions, and concomitant medications. Both eyes were examined by funduscopy and slit-lamp biomicroscopy and were tested for visual acuity and IOP, and visual fields were determined. In the study eyes, the bleb site and disc were photographed, cataracts were graded, and the bleb site was evaluated for vascularity, microcysts, and encapsulation or demarcation.

Efficacy End Points. The primary efficacy end point, treatment success, was defined as an IOP of 6 to 16 mmHg (inclusive), at both the month 6 and month 12 follow-up visits. Because any use of antiglaucoma medication would lower IOP and potentially would shift a treatment failure into a treatment success, the assessment was made using the most recent off-medication IOP before months 6 and 12. Measurements obtained immediately after a postsurgery intervention, at any time after repeat surgery, while taking antiglaucoma medication, or during a period after stopping medications that could affect IOP were excluded. Patients missing IOP measurements at either months 6 or 12 were considered treatment failures.

In addition to the primary outcome variable, several secondary efficacy outcomes were assessed. Postoperative intervention with 5-FU was assessed. Surgical failure was defined as repeat surgery in the study eye or administration of antiglaucoma medication for more than 7 days at or after month 3 (excluding topical medications in the nonstudy eye). Repeat surgery included any procedure creating a new drainage pathway distinct from the sclerotomy created as part of the study-related trabeculectomy. Patients who withdrew early from the trial were counted as surgical failures. The time to surgical failure was the duration from completion of surgery to the first event that rendered a patient a surgical failure. The changes in the patients' IOP were measured and recorded at the follow-up visits.

Safety End Points. Safety assessments included detailed ophthalmic examinations (slit-lamp biomicroscopy, visual acuity, visual field, funduscopy) with specific attention to evidence of uveitis (flare and cells), hypotony, bleb leaks, allergic reaction, unexplained poor vision, corneal changes, and retinal changes. Other safety assessments included physical examination, adverse events, laboratory tests (hematology, biochemistry, and for antibodies to CAT-152), and recording of prior and concomitant medications. Any clinically significant abnormalities observed in the nonstudy eye were recorded as adverse events.

Statistical Analyses

The null hypothesis stated that there was no difference in the number of patients treated successfully between the CAT-152 and placebo groups. To determine the number of patients required, the following was assumed: one primary variable for analysis (treatment success), that the results of treatment could be either better or worse than placebo, that the placebo would be effective in 25% of cases, and that the minimum treatment effect that would be considered clinically relevant would be at least 20% different than placebo. The primary intention of the study was examination of patients with POAG or CCAG, of which a total of 256 was estimated to be required for a 5% type I error and a 10% type II error (i.e., 90% power). The primary analyses were conducted by intent-to-treat (ITT) criteria on a data set that included all patients with POAG or CACG who received study medication and surgery (POAG/CACG group) and included 274 patients. A secondary study goal was to explore the effect of treatment on patients with PEXG or PG. The expected outcome for these latter patients was unknown because of insufficient data from previous investigations with CAT-152. Patients with PEXG or PG therefore were excluded from the primary ITT analysis, but they were included in an expanded ITT analysis set that included all patients who underwent surgery and received study medication (+PEXG/PG group). The safety analysis set included all patients who were randomized and received any study medication. The disposition of all patients is shown in Figure 1. Statistical analyses were conducted using SAS software version 8.2 (SAS Institute, Cary, NC). Statistical comparisons were made using the Cochran-Mantel-Haenszel test or logistic regression analyses.

Results

Study Population

A total of 354 patients consented to enter the study; 343 were randomized to receive either placebo or CAT-152; 96% (n = 330) of the randomized patients completed the trial (Fig 1). The ITT

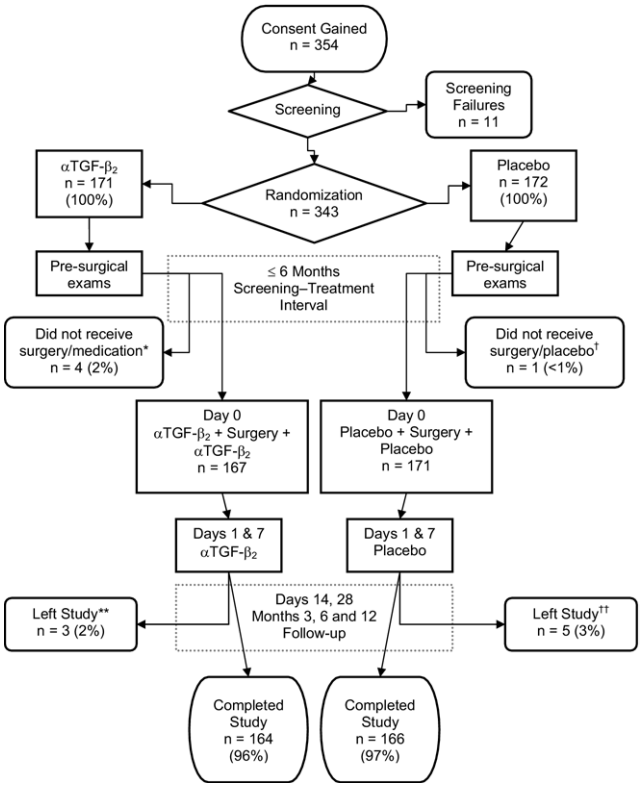

Figure 1. Flow chart detailing patient disposition. TGF-β_2 = transforming growth factor β_2. *One patient withdrew, and 2 patients lost medical eligibility. †One patient withdrew. **One patient missed 12-month follow-up, and 2 patients had unrelated adverse events. ††One patient missed 12-month follow-up, 2 patients died of unrelated causes, 1 patient had increased IOP, and 1 patient had an unrelated adverse event.

analyses were conducted using the data from 2 sets of patients: (1) those diagnosed with POAG or CACG (POAG/CACG group; n = 274); and (2) patients diagnosed with POAG, CACG, PEXG, or PG (+PEXG/PG group; n = 338). Analysis of the safety of CAT-152 was carried out on all patients treated (safety group; n = 338). (The safety group is identical to the +PEXG/PG group, except for 1 patient randomized to CAT-152 who actually received placebo.) The groups of patients used for analysis are shown in Table 1. The treated patients' demographic data are shown in Tables 2 and 3 (the latter available at http://aaojournal.org), which include the distribution of ocular comorbidities affecting more than 1 treated eye. Because the POAG/CACG analysis group comprised most of the study population, and this was the planned primary analysis population for this study, their results are detailed below. As a rule, the results did not vary between analysis groups, but specific mention is made of the instances where results differed between analysis groups.

Efficacy

Treatment Success. Treatment success, the primary measure of efficacy, was defined as an IOP in the study eye ranging from 6 to 16 mmHg (inclusive), measured without concomitant glaucoma medication at both the month 6 and month 12 follow-up visits. There was no evidence of a difference between the groups in terms of treatment success. In the CAT-152 group, 81 patients (60%) had a successful outcome, compared with 94 patients (68%) in the placebo group (P = 0.2294; odds ratio, 0.73; 95% confidence interval, 0.44–1.21). It is possible that including patients in the success group who met the IOP criteria but who were using glaucoma medications might have revealed a difference between the treatment groups. This was carried out and resulted in virtually no change in success rates. A difference of less than 1% was seen in both treatment arms (on or off medication: CAT-152, n = 82 [29.93%] and placebo, n = 95 [34.67%]; off medication only: n = 81 [29.56%] and n = 94 [34.31%], respectively).

Examination of the data overall showed there was some variation in success rates in different countries; for example, Belgium (79%) and The Netherlands (74%) had the highest overall success rates. For the POAG/CACG group, by logistic regression analysis, there was no treatment effect (P = 0.22) or center effect (P = 0.34), or treatment-by-center interaction (P = 0.78) identified, and thus, no evidence of differences between the treatment groups or the overall success rate in individual countries was seen. Patients in Belgium (81%) and The Netherlands (88%) showed higher success rates overall but, again, showed no evidence of any difference between CAT-152 and placebo groups.

From the +PEXG/PG group analysis, there was no evidence of any difference between the treatment groups, but PG patients were more likely to be successes compared with those with other diagnoses (P = 0.0077). These data also showed a statistically significant difference in response rate by country (P = 0.018). The success rate was lower in Sweden, where 14 patients had a primary diagnosis of PEXG, 2 patients had a primary diagnosis of POAG or CACG, and 1 patient had a primary diagnosis of PG. (Sweden was not included in the POAG/CACG analysis for country effect mentioned above because of the small number of patients.) Belgium and The Netherlands still contributed the highest success rates overall.

5-Fluorouracil Use and Postsurgical Interventions. Although MMC use was prohibited in this study, investigators were allowed to use 5-FU at their discretion after day 14. Because 5-FU is used to prevent incipient scarring, its use is an indirect measure of the success of CAT-152 treatment, which, if successful, would obviate the necessity for 5-FU administration. There was no evidence of a difference between the CAT-152 and placebo groups in the postoperative use of 5-FU in the POAG/CCAG analysis group (P =

Table 1. Analysis Groups

	CAT-152 (n = 171)		Placebo (n = 172)		Total (n = 343)	
	n	%	*n*	%	*n*	%
Total randomized	171	100	172	100	343	100
POAG/CACG group	135	79	139	81	274	80
+PEXG/PG group	167	98	171	99	338	99
Safety set	166	98	172	99	338	99

CACG = chronic angle-closure glaucoma; PEXG = pseudoexfoliative glaucoma; PG = pigmentary glaucoma; POAG = primary open-angle glaucoma.

Table 2. Demographic Characteristics for All Participants

	CAT-152 (n = 167)	Placebo (n = 171)	Total (n = 338)
Age (yrs)			
No.	167	171	338
Mean	65.6	66.3	66.0
Median	66.0	68.0	67.0
Range	34–85	28–83	28–85
Ethnic origin (n, %)			
White	164 (98)	166 (97)	330 (98)
Black*	1 (0.60)	4 (2.3)	5 (1.5)
Indian subcontinent†	2 (1.2)	1 (0.58)	3 (0.89)
Gender (n, %)			
Male	8 (52)	85 (50)	173 (51)
Female	79 (48)	86 (50)	165 (49)
Diagnosis (n, %)			
POAG	127 (76)	135 (79)	262 (78)
CACG	8 (4.8)	4 (2.3)	12 (3.6)
PEXG	27 (16)	22 (13)	49 (14)
PG	5 (3.0)	10 (5.8)	15 (4.4)
Years since diagnosis			
Mean	7.1	6.3	6.7
Median	5.4	4.8	5.1
Range	0–38	0–36	0–38
IOP at listing for surgery (mmHg; taking medication)			
Mean	24.6	23.5	24
SD	7.2	6.1	6.7
Median	23.5	22	23
Range	13–60	11–45	11–60
Highest recorded preoperative IOP (mmHg)			
Mean	34.0	32.3	33.2
SD	9.2	8	9
Median	32	30	30
Range	21–71	19–60	19–71
Previous eye surgeries (n)			
Cataract extraction	7	8	15
Iridotomy	8	12	20
Trabeculoplasty	28	36	64
Prior IOP-lowering medication use (n, %)‡			
β-blocking agents	116 (70)	127 (74)	243 (72)
Carbonic anhydrase inhibitors (systemic or topical)	56 (34)	54 (31)	110 (33)
Parasympathomimetics	13 (7.8)	4 (2.3)	17 (5.0)
Prostaglandin analogs	132 (80)	128 (74)	260 (77)
Sympathomimetics	49 (30)	54 (31)	103 (30)
Total	164 (99)	169 (98)	333 (99)

CACG = chronic angle-closure glaucoma; IOP = intraocular pressure; PEXG = pseudoexfoliative glaucoma; PG = pigmentary glaucoma; POAG = primary open-angle glaucoma; SD = standard deviation.
*Includes black Caribbean and African.
†Includes Indian, Pakistani, and Bangladeshi.
‡Both topical and systemic.

0.497; Table 4), indicating that treatment with CAT-152 did not affect how investigators perceived the incidence of incipient scarring. Detailed examination showed a similar pattern of 5-FU administration between the CAT-152 and placebo groups. As expected, patients requiring 5-FU were less likely to be treatment successes than those who did not ($P = 0.0003$), whether in the CAT-152 group or placebo group.

Most postsurgical interventions, including 5-FU administration, occurred within the first 3 months. Overall, 74 (55%) of 135 patients in the CAT-152 group and 75 (54%) of 139 patients in the placebo group required any postsurgical interventions, and there were no differences between the groups in the reasons for the interventions. Needling without 5-FU was more common in the CAT-152 group than in the placebo group (15/135 patients [11%]

Table 4. Postoperative Use of 5-Fluorouracil in Those with either Primary Open-Angle Glaucoma or Chronic Angle-Closure Glaucoma

Postoperative Use of 5-Fluorouracil	CAT-152 (n = 135), n (%)	Placebo (n = 139), n (%)	*P* Value*
Yes	27 (20)	23 (17)	0.497
No	108 (80)	116 (83)	

Odds ratio (CAT-152:placebo), 1.25; 95% confidence interval, 0.65–2.41. Relative risk (CAT-152:placebo), 1.18; 95% confidence interval, 0.73–1.90.
*Cochran–Mantel–Haenszel test, controlling for pooled centers.

Table 5. Incidence of Surgical Failure in Those with either Primary Open-Angle Glaucoma or Chronic Angle-Closure Glaucoma

	CAT-152 (n = 135), n (%)	Placebo (n = 139), n (%)	P Value*
Surgical success	113 (84)	121 (87)	0.437
Surgical failure†	22 (16)	18 (13)	
Repeat surgery	0 (0)	2 (1.4)	
Application of topical antiglaucoma medication	22 (16)	16 (12)	
Early withdrawal	0 (0)	0 (0)	

Odds ratio (CAT-152:placebo), 1.30; 95% confidence interval, 0.67–2.55. Relative risk (CAT-152:placebo), 1.26; 95% confidence interval, 0.71–2.24.
*Cochran-Mantel-Haenszel test, controlling for pooled centers.
†Patients were assigned a primary reason for surgical failure based on the first occurrence of any failure criteria. If a patient first failed on the same day for more than 1 reason, the hierarchy presented here (ranking top to bottom) was used to assign reason for failure.

vs. 5/139 [4%], respectively; $P<0.05$). Of these, 6 (40%) taking CAT-152 and 3 (60%) taking placebo were successes. The numbers are obviously too small to draw any reliable conclusions. There was a slightly greater number of patients receiving 5-FU administration without needling in the CAT-152 group (21/135 patients [16%]) than in the placebo group (13/139 patients [9%]).

Surgical Failure. The causes of surgical failure are detailed in Table 5 for the POAG/CACG analysis group. No difference between treatment groups was observed in the overall incidence of surgical failure or in the causes of failure. Furthermore, by Kaplan-Meier analysis, the time to first surgical failure was virtually identical between the treatment groups for the first year. No patient receiving placebo failed after week 40, and 4 patients in the CAT-152 group failed between weeks 52 and 56. There were no failures in the CAT-152 group beyond 56 weeks, the end of the follow-up period. Sensitivity analyses that excluded patients using antiglaucoma medications at the time of surgery and ongoing at or after month 3 continued to show no statistically significant difference between the treatment groups (data not shown).

Intraocular Pressure. Intraocular pressure was measured for all patients shortly before surgery without washout of their antiglaucoma medications and at the follow-up visits at months 3, 6, and 12. For the treatment groups as a whole, trabeculectomy successfully lowered mean IOP in both the CAT-152 and placebo groups from approximately 22 mmHg before surgery to 12 to 13 mmHg at 3 months (including cases of surgical failure), after which time the mean IOP of both groups drifted upward. No clinically important difference between the treatment groups was observed in mean IOP over the course of the follow-up visits. The distribution of the magnitude of changes of IOP over time was similar between the treatment groups, as were the proportions of patients taking antiglaucoma medication (Fig 2, Table 6 [the latter available at http://aaojournal.org]).

Bleb Site Assessment. At each follow-up visit, the bleb sites were appraised by the investigators. Assessments of vascularity at the bleb site relative to surrounding conjunctiva were categorized as follows: no vessels; vessels equal to surrounding conjunctiva; moderate but significantly increased vascularity; and severe increase of vascularity.

The presence of microcysts, encapsulation, and demarcation each was categorized as follows: none; in one third of the filtering bleb; in two thirds of the filtering bleb; and in the entire filtering bleb. No clinically significant difference was seen between the CAT-152 and placebo groups on any measure at any time.

Surgical Procedure Success. On the day after surgery, investigators were required to grade the operative procedure. Most operations were technically successful with no complications (156/167 patients [94%] in the CAT-152 group and 157/171 patients

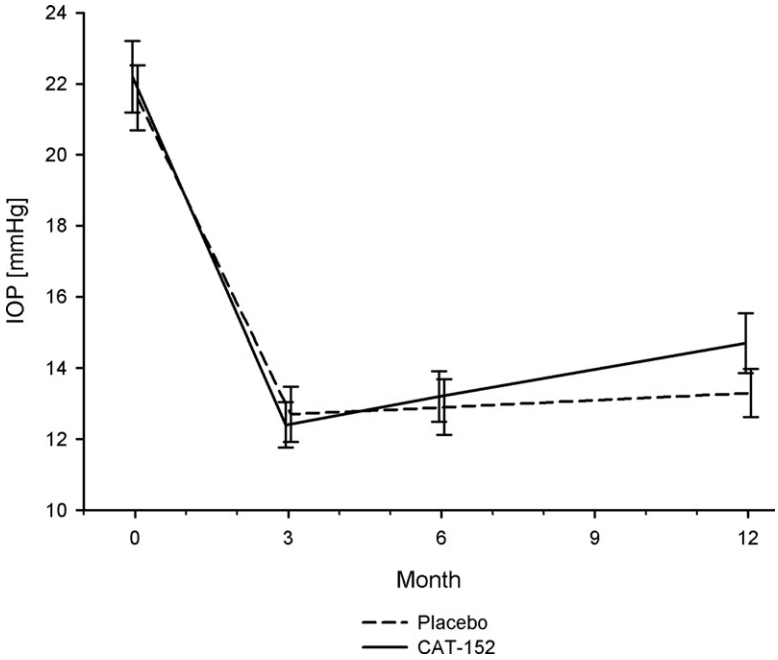

Figure 2. Graph showing the change in mean intraocular pressure (IOP) (± 95% confidence interval), on or off medication, over time by treatment group (primary open-angle glaucoma/chronic angle-closure glaucoma analysis group).

[91%] in the placebo group). The remaining operations were graded as successful with complications. No operation was unsuccessful.

Of the total enrolled, 75% had fornix-based flaps, and the rest had limbus-based flaps. In both treatment groups, those who had a limbus-based flap had a higher likelihood of success (fornix-based: CAT-152, 58 [56.31%] and placebo, 68 [66.97%]; limbus-based, 23 [71.88%] and 26 [70.27%], respectively).

Safety

There were no clinically important differences on any safety measure between patients receiving CAT-152 and placebo. Overall, there were 399 adverse events in 120 subjects receiving CAT-152 and 367 adverse events in 119 patients receiving placebo.

In both groups, slightly more than half of the adverse events were in the study eye. Few patients reported adverse events that were at least possibly related to a study drug (10% in the CAT-152 group and 11% in the placebo group), and no serious adverse event was related to CAT-152 or placebo. Thirteen patients (7.8%) in the CAT-152 group and 17 patients (9.9%) in the placebo group experienced serious adverse events, none of which were possibly or probably related to study medication. Adverse events in the study eye tended to be mild in the CAT-152 group (6.6% of patients), with only 1.2% of patients reporting related events of moderate intensity and 1.2% of patients reporting related events of severe intensity. In the placebo group, 4.1% of patients reported related ocular adverse events of mild intensity, 3.5% reported related events of moderate intensity, and 1.2% reported related events of severe intensity. Of the patients reporting an adverse event, the surgery or study intervention was primarily the cause (67/120 patients in the CAT-152 group and 68/119 patients in the placebo group). The most common adverse events affecting the study eye from any cause are shown in Table 7 (available at http://aaojournal.org).

There was a slightly higher proportion of patients with protocol violations in the CAT-152 group (44/171 patients [26%]) compared with the placebo group (38/172 patients [22%]), largely because of differences in the administration of more than 100 μl of the study medication (CAT-152, n = 10 [6%]; placebo, n = 6 [3%]). Two of the patients receiving more than 100 μl CAT-152 experienced ophthalmic adverse events in the study eye: a mild inferior subconjunctival hemorrhage on the day of surgery and a mild conjunctival edema at 1 year after surgery. No difference was seen in efficacy or safety in those patients who received a dose of CAT-152 of more than 100 μl.

In very few patients (1–3 patients at any time point, or 0.58%–1.7%), antibodies developed to CAT-152 during the first 3 months after surgery. The production of antibodies to CAT-152 seemed to be sporadic and had no apparent effect on the overall efficacy or safety outcomes, partly because so few patients were involved.

Discussion

In this study, CAT-152, an antibody to TGF-β_2, was administered as an adjunctive treatment to delay or prevent scarring at the bleb site to patients receiving first-time trabeculectomy for intractable glaucoma. On the primary end point of treatment success (IOP lowering to the target range in the absence of medication or repeat surgery) and the secondary end points of success of surgery, time to surgical failure, IOP, and bleb site anatomic features, no statistically significant difference between the treatment and control groups was seen. The power of the trial was sufficient to have a 90% chance of detecting a 20% difference in treatment success, and thus, it is unlikely that a treatment effect was missed because of underpowering.

Previous studies in animals and humans had indicated that CAT-152 was effective in improving the long-term outcomes of trabeculectomy. In a rabbit model of glaucoma filtration surgery, preoperative and postoperative subconjunctival injections of CAT-152 have been shown to be well tolerated, to inhibit subconjunctival scarring effectively, and to improve bleb survival compared with placebo control.[19,28] The first clinical study of CAT-152 in patients undergoing trabeculectomy for primary glaucoma also showed that this treatment was safe and well-tolerated up to 3 years after surgery.[29] CAT-152 was shown to have a beneficial effect on IOP reduction compared with placebo at the 3- and 6- month follow-ups, and there was a strong trend for rate of filtration failure to be reduced up to 3 years after surgery. A subsequent randomized phase II study of CAT-152 used in conjunction with phacotrabeculectomy (Invest Ophthalmol Vis Sci 43:e-abstract 3331, 2002) confirmed that CAT-152 treatment resulted in a greater proportion of patients with IOP of no more than 21 mmHg and with a lower mean IOP for at least 1 year compared with placebo.

In the present larger, multicenter, randomized trial, these beneficial treatment effects of CAT-152 were, surprisingly, not replicated. Naturally, the question arises of what could account for this lack of a significant difference. One group of hypotheses revolves around the issues of study execution. In this regard, it is interesting to note that previous studies examining the effect of CAT-152 in humans had roughly the same rate of success as in this study in the treatment group, whereas the success rate in the placebo group was much lower (Table 8). The phase I trial of Siriwardena et al[29] and the larger phase II trial (Invest Ophthalmol Vis Sci 43:e-abstract 3331, 2002) had success rates in the placebo groups of 35% to 38%, which is substantially lower than the success rates of trabeculectomy with adjunctive 5-FU reported by other groups, which range from 70% to 80%.[8,30–32] It is possible that the encouraging results of the smaller early trials were misleading, in that a higher-risk cohort in whom higher levels of TGF-β are present (Invest Ophthalmol Vis Sci 37:S27, 1996) would be expected to respond better to the antibody.

Trabeculectomy outcomes can be affected by postoperative revision procedures, such as suture release and lysis or needling, or further application of 5-FU.[32–36] Such modifications were common and largely timed at the surgeons' discretion. The present study was larger than the previous ones examining CAT-152, and thus had more investigators and more countries involved, with a correspondingly greater chance of differences in surgical technique, postoperative care, and so forth, despite our attempts to maintain standard conditions. Although these sorts of vagaries affect many, if not most, international trials involving surgical procedures, there is little evidence that this affected the overall study findings, because the treatment groups were well balanced in each investigational center and each investigator had an equal chance of treating patients with CAT-152 or control.

Table 8. CAT-152 Treatment Success across Studies with Human Subjects

	CAT-152			Placebo		
	Study I (n = 16)*	*Study II† (n = 36)*	*Study III‡ (n = 135)*	*Study I* (n = 8)*	*Study II† (n = 20)*	*Study III‡ (n = 139)*
Success rate (%)	56.3	61.0	60.0	37.5	35.0	68.0

*Siriwardena et al.[29]
†Broadway et al (unpublished).
‡Current study.

However, the implementation of postsurgical interventions might have varied among centers.

There is evidence from the present trial of variations in outcomes from different geographical areas. Outcomes in Belgium and The Netherlands (6 centers in total) often were better than those overall, and outcomes in some other countries sometimes were worse. A number of different factors could have contributed to this phenomenon, such as subject selection criteria and surgical and postoperative technique. Although this study was not designed to explore the reasons for such geographical variation, its existence points to a potential opportunity to improve the outcomes of trabeculectomy in general, should causative factors be elucidated. Patients with PG seemed to fare better than average after trabeculectomy (regardless of CAT-152 treatment), in accord with the survey of trabeculectomy results in the United Kingdom by Edmunds et al[37]; this suggests that further exploration of the effect that glaucoma diagnosis has on trabeculectomy outcomes could be fruitful. However, the number of patients with PG was small, and this observation, although suggestive, should be treated with caution.

A second group of hypotheses pertains to the treatment itself. Although there are compelling reasons to focus on TGF-β_2 as a target for modulating bleb healing and wound formation, it is conceivable that a monoclonal antibody directed against TGF-β_2 represents too narrow an approach in humans. Although TGF-β_2 activity seems to dominate in the human aqueous,[17,24] other isoforms of TGF-β also are involved, as are other factors that may mediate the effects of TGF. Possibly, the results of this trial point to a need for a more robust set of antibodies to interrupt the cascade of factors that result in scar formation. Alternatively, because patients with glaucoma seem to produce more TGF than normal patients (Invest Ophthalmol Vis Sci 37:S152, 1996; Invest Opthalmol Vis Sci 37:S27, 1996; Invest Ophthalmol Vis Sci 37:S27, 1996),[25] the CAT-152 may have been underdosed. The CAT-152 dosage and treatment regimen were developed from studies in the rabbit[19,28] and may not yet be optimal for humans. For example, the clearance rate of the human monoclonal antibody CAT-152 may be faster in humans than rabbits. Finally, the dosage was based on the study of Cordeiro et al.[19] A subsequent study by Mead et al[28] showed a significantly enhanced effect on bleb survival using long-term injection of CAT-152. This prolonged application is more in line with the prolonged use of antibiologics to neutralize cytokines.[38–40]

These data show that patients treated with 5-FU did not fare as well as those who did not require this intervention. The need for treatment with 5-FU is an early indicator of treatment failure, and thus, this observation indicates that 5-FU does not always succeed in preventing failure. However, the use of 5-FU itself can have an effect on the measure of treatment success, and there was a suggestive indication of an interaction of 5-FU use and CAT-152 treatment, in that 5-FU use in the CAT-152–treated patients improved treatment success more than in placebo-treated patients given 5-FU, although this trend did not attain statistical significance ($P = 0.1049$).

In conclusion, this study failed to find a difference in surgical success after the use of CAT-152 antibody to TGF-β_2. However, it is still possible in the future that an approach neutralizing TGF with a different regimen may be able to improve the prognosis of glaucoma filtration surgery.

References

1. Cairns JE. Trabeculectomy: preliminary report of a surgical method of reducing intra-ocular pressure in chronic simple glaucoma without sub-conjunctival drainage of aqueous humor. Bibl Ophthalmol 1970;81:143–53
2. 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.
3. Addicks EM, Quigley HA, Green WR. Histologic characteristics of filtering blebs in glaucomatous eyes. Arch Ophthalmol 1983;101:795–8.
4. Hitchings RA, Grierson I. Clinicopathological correlation in eyes with failed fistulizing surgery. Trans Ophthalmol Soc UK 1983;103:84–8.
5. Jay JL. Rational choice of therapy in primary open angle glaucoma. Eye 1992;6:243–7.
6. Migdal C, Gregory W, Hitchings R. Long-term functional outcome after early surgery compared with laser and medicine in open-angle glaucoma. Ophthalmology 1994;101:1651–6, discussion 1657.
7. Khaw PT, Occleston NL, Schultz G, et al. Activation and suppression of fibroblast function. Eye 1994;8:188–95.
8. Fluorouracil Filtering Surgery Study Group. Fluorouracil Filtering Surgery Study one-year follow-up. Am J Ophthalmol 1989;108:625–35.
9. Katz GJ, Higginbotham EJ, Lichter PR, et al. Mitomycin C versus 5-fluorouracil in high-risk glaucoma filtering surgery. Extended follow-up. Ophthalmology 1995;102:1263–9.
10. Kitazawa Y, Kawase K, Matsushita H, et al. Trabeculectomy with mitomycin. A comparative study with fluorouracil. Arch Ophthalmol 1991;109:1693–8.
11. Lamping KA, Belkin JK. 5-Fluorouracil and mitomycin C in pseudophakic patients. Ophthalmology 1995;102:70–5.

12. Khaw PT, Doyle JW, Sherwood MB, et al. Effects of intraoperative 5-fluorouracil or mitomycin C on glaucoma filtration surgery in the rabbit. Ophthalmology 1993;100:367–72.
13. Crowston JG, Akbar AN, Constable PH, et al. Antimetabolite-induced apoptosis in Tenon's capsule fibroblasts. Invest Ophthalmol Vis Sci 1998;39:449–54.
14. Stamper RL, McMenemy MG, Lieberman MF. Hypotonus maculopathy after trabeculectomy with subconjunctival 5-fluorouracil. Am J Ophthalmol 1992;114:544–53.
15. Parrish R, Minckler D. "Late endophthalmitis"—filtering surgery time bomb? [editorial]. Ophthalmology 1996;103:1167–8.
16. Jampel HD, Pasquale LR, Dibernardo C. Hypotony maculopathy following trabeculectomy with mitomycin C. Arch Ophthalmol 1992;110:1049–50.
17. Jampel HD, Roche N, Stark WJ. Transforming growth factor-beta in human aqueous humor. Curr Eye Res 1990;9:963–9.
18. Cordeiro MF, Reichel MB, Gay JA, et al. Transforming growth factor-beta1, -beta2 and -beta3 in vivo: effects on normal and mitomycin-C modulated conjunctival scarring. Invest Ophthalmol Vis Sci 1999;40:1975–82.
19. Cordeiro MF, Gay JA, Khaw PT. Human anti-transforming growth factor-beta2 antibody: a new glaucoma anti-scarring agent. Invest Ophthalmol Vis Sci 1999;40:2225–34.
20. Connor TB, Roberts AB, Sporn MB, et al. Correlation of fibrosis and transforming growth factor-beta type 2 levels in the eye. J Clin Invest 1989;83:1661–6.
21. Cousins SW, McCabe MM, Danielpour D. Identification of transforming growth factor-beta as an immunosuppressive factor in aqueous humor. Invest Ophthalmol Vis Sci 1991;32:2201–11.
22. Pasquale LR, Dorman-Pease ME, Lutty GA, et al. Immunolocalization of TGF-beta1, TGF-beta2, and TGF-beta3 in the anterior segment of the human eye. Invest Ophthalmol Vis Sci 1993;34:23–30.
23. Pfeffer BA, Flanders KC, Guerin CJ, et al. Transforming growth factor beta2 is the predominant isoform in the neural retina, retinal pigment epithelium choroid and vitreous of the monkey eye. Exp Eye Res 1994;59:323–33.
24. Lutty GA, Merges C, Threlkeld AB, et al. Heterogeneity in localization of isoforms of TGF-beta in human retina, vitreous and choroid. Invest Ophthalmol Vis Sci 1993;34:477–87.
25. Tripathi RC, Li J, Chan WF. Aqueous humor in glaucomatous eyes contains an increased level of TGFβ2. Exp Eye Res 1994;59:723–7.
26. Picht G, Welge-Luessen U, Grehn F. Transforming growth factor beta2 levels in the aqueous humor in different types of glaucoma and the relation to filtering bleb development. Graefes Arch Clin Exp Ophthalmol 2001;239:199–207.
27. Thompson JE, Vaughan TJ, Williams AJ, et al. A fully human antibody neutralising biologically active human TGF-beta2 for use in therapy. J Immunol Methods 1999;227:17–29.
28. Mead AL, Wong TT, Cordiero MF, et al. Evaluation of anti-TGF-beta2 antibody as a new postoperative anti-scarring agent in glaucoma surgery. Invest Ophthalmol Vis Sci 2003;44:3394–401.
29. Siriwardena D, Khaw PT, King AJ, et al. Human antitransforming growth factor β2 monoclonal antibody: a new modulator of wound healing in trabeculectomy. A randomized placebo controlled clinical study. Ophthalmology 2002;109:427–31.
30. WuDunn D, Cantor LB, Palanca-Capistrano AM, et al. A prospective randomized trial comparing intraoperative 5-fluorouracil vs mitomycin C in primary trabeculectomy. Am J Ophthalmol 2002:134:521–8.
31. Akarsu C, Onol M, Hasanreisoglu B. Postoperative 5-fluorouracil versus intraoperative mitomycin C in high-risk glaucoma filtering surgery: extended follow up. Clin Experiment Ophthalmol 2003;31:199–205.
32. Morris DA, Peracha MO, Shin DH, et al. Risk factors for early filtration failure requiring suture release after primary glaucoma triple procedure with adjunctive mitomycin. Arch Ophthalmol 1999;117:1149–54.
33. Fagerli M, Lofors KT, Elsas T. Needling revision of failed filtering blebs after trabeculectomy: a retrospective study. Acta Ophthalmol Scand 2003;81:577–82.
34. Broadway DC, Bloom PA, Bunce C. Needle revision of failing and failed trabeculectomy blebs with adjunctive 5-fluorouracil. Survival analysis. Ophthalmology 2004;111:665–73.
35. Jacobs S, Gillis A, Van Malderen L. Needling-revision of failed filtering blebs. Bull Soc Belge Ophtalmol 2005;(297):59-64.
36. Banitt M, Juzych MS, Chopra V, et al. The effect of the timing of scleral flap suture release on the safety and long-term success of phacotrabeculectomy. Am J Ophthalmol 2006;141:742–4.
37. Edmunds B, Bunce CV, Thompson JR, et al. Factors associated with success in first-time trabeculectomy for patients at low risk of failure with chronic open-angle glaucoma. Ophthalmology 2004;111:97–103.
38. Garrett Q, Khaw PT, Blalock TD, et al. Involvement of CTGF in TGF-beta1-stimulation of myofibroblast differentiation and collagen matrix contraction in the presence of mechanical stress. Invest Ophthalmol Vis Sci 2004;45:1109–16.
39. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med 1999;340:253–9.
40. Johnsen AK, Schiff MH, Mease PJ, et al. Comparison of 2 doses of etanercept (50 vs 100 mg) in active rheumatoid arthritis: a randomized double blind study. J Rheumatol 2006;33:659–64.

Appendix

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*Indicates investigator who performed surgery during the study.

Table 3. Concurrent Eye Disorders for All Participants

Eye Disorders*	CAT-152 (n = 167), n (%)	Placebo (n = 171), n (%)	Total (n = 338), n (%)
Amblyopia	1 (0.60)	3 (1.8)	4 (1.2)
Astigmatism	4 (2.4)	3 (1.8)	7 (2.1)
Blepharitis	4 (2.4)	8 (4.7)	12 (3.6)
Cataract	7 (4.2)	4 (2.3)	11 (3.3)
Cataract, nuclear	3 (1.8)	0 (0)	3 (0.89)
Conjunctivitis	2 (1.2)	0 (0)	2 (0.59)
Conjunctivitis, allergic	1 (0.60)	2 (1.2)	3 (0.89)
Eyelid trichiasis	2 (1.2)	0 (0)	2 (0.59)
Hypermetropia	5 (3.0)	6 (3.5)	11 (3.3)
Keratitis	3 (1.8)	0 (0)	3 (0.89)
Lenticular opacities	4 (2.4)	1 (0.58)	5 (1.5)
Macular degeneration	0 (0)	3 (1.8)	3 (0.89)
Myopia	9 (5.4)	7 (4.1)	16 (4.7)
Ocular hypertension	2 (1.2)	1 (0.58)	3 (0.89)
Presbyopia	4 (2.4)	2 (1.2)	6 (1.8)
Retinal pigment epitheliopathy	1 (0.60)	1 (0.58)	2 (0.59)
Vitreous detachment	2 (1.2)	0 (0)	2 (0.59)
Total*	50 (30)	43 (25)	93 (28)

PEXG = pseudoexfoliative glaucoma; PG = pigmentary glaucoma.
*Only disorders affecting more than 1 subject shown; total includes unlisted disorders.

Table 6. Intraocular Pressure in the Study Eye with or without Medication in Those with either Primary Open-Angle Glaucoma or Chronic Angle-Closure Glaucoma

	CAT-152 (n = 135)				Placebo (n = 139)			
	Baseline	*Month 3*	*Month 6*	*Month 12*	*Baseline*	*Month 3*	*Month 6*	*Month 12*
	IOP (mmHg)							
n	135	135	135	132	139	139	138	134
No. (%) with medication*	131 (97)	10 (7.4)	9 (6.7)	17 (13)	132 (95)	5 (3.6)	8 (5.8)	15 (11)
Mean†	22.2	12.4	13.2	14.7	21.6	12.7	12.9	13.3
SD	6.0	3.8	4.2	4.9	5.5	4.7	4.7	4.0
Median	22.0	12.0	13.0	14.5	21.0	12.0	13.0	13.0
Range	11–45	4–25	5–29	4–35	10–42	3–37	4–34	2–26
	Percentage change from baseline for IOP							
No.	135	135	135	132	139	139	138	134
Mean		−40.5	−36.4	−29.7		−38.3	−37.4	−34.8
SD		23.7	26.7	29.1		25.5	24.2	25.4
Median		−43.8	−39.6	−35.1		−43.9	−39.3	−34.6
Range		−86 to 58	−87 to 108	−81 to 109		−89 to 56	−83 to 47	−89 to 53

IOP = intraocular pressure; SD = standard deviation.
*No. (%) of patients on antiglaucoma medication on the day that IOP was measured.
†Each patient contributed a mean of 2 measurements recorded at each time point. Intraocular pressure measurements recorded after repeat surgery or after a postsurgery intervention were excluded.

Table 7. Types of Ocular Adverse Events Affecting at Least 1% of Patients in Either Treatment Group

	CAT-152 (n = 166)		Placebo (n = 172)	
Event	No. of Patients	%	No. of Patients	%
Cataract	24	14.46	23	13.37
Eye pain	21	12.65	12	6.98
Conjunctival hemorrhage	19	11.45	7	4.07
Nonfunctioning bleb	13	7.83	10	5.81
Conjunctivitis	12	7.23	0	0
Hypotony	12	7.23	19	11.05
Visual acuity reduced	10	6.02	13	7.56
Choroidal detachment	9	5.42	5	2.91
Conjunctival injection	7	4.22	2	1.16
Blepharitis	6	3.61	2	1.16
Corneal epithelial defect	5	3.01	7	4.07
Conjunctival edema	3	1.81	3	1.74
Dry eye syndrome	3	1.81	5	2.91
Hyphema	3	1.81	5	2.91
Iris adhesions	3	1.81	4	2.33
Keratitis	3	1.81	3	1.74
Lacrimation increased	3	1.81	3	1.74
Maculopathy	3	1.81	2	1.16
Meibomianitis	3	1.81	2	1.16
Wound leak	3	1.81	4	2.33
Bleb leak	2	1.2	7	4.07
Cataract extraction	2	1.2	0	0
Chalazion	2	1.2	0	0
Dellen	2	1.2	0	0
Eye irritation	2	1.2	4	2.33
Iridocele	2	1.2	1	0.58
Tenon's cyst	2	1.2	0	0
Vitreous detachment	2	1.2	1	0.58
Anterior uveitis	1	0.6	3	1.74
Eyelid ptosis	1	0.6	2	1.16
Corneal infiltrates	0	0	2	1.16
Cystic bleb	0	0	2	1.16