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Quality of Life in Primary Open-Angle Glaucoma and Cataract: An Analysis of VFQ-25 and OSDI from the iStent *inject*® Pivotal Trial

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Short Title: Quality of life of patients treated with iStent *Inject*®

Abstract

Objective: To assess QOL as measured by patient-reported outcomes (PRO) within the iStent *inject* pivotal trial.

Design: Randomized controlled trial analysis of secondary outcomes.

Methods: The Vision Function Questionnaire (VFQ-25) and Ocular Surface Disease Index (OSDI©) questionnaire were administered at baseline, months 1, 6, 12, and 24. PRO responders were defined as patients reaching improvement based on minimally important differences.

Results: 505 patients were randomized (N = 386 iStent *inject*, N = 119 surgery alone). The iStent *inject* group exhibited a greater percentage of PRO responders across all follow-up visits over 24 months, averaging 58.0% vs. 45.8%; $P < .05$ for VFQ-25 composite scores and 56.7% vs. 48.9%; $P < .05$ for OSDI composite scores. Odds of being a responder in the iStent *inject* group was 60% $(P < .05)$ higher for the VFQ-25 and 32% $(P > .05)$ higher for the ODSI. Driving (49.0% vs. 28.8%; $P < .05$), ocular pain (59.3% vs. 47.2%; $P < .05$) and general vision (71.8% vs. 60.0%; $P < .05$), were the VFQ-25 subscales responsible for differences between treatment

groups. At month 24, 76.5% of VFQ-25 responders and 62.5% of non-responders were medication free regardless of treatment group ($P < .05$).

Conclusions: Exploratory analysis suggests that by reducing medication dependence, implantation with the micro-scale iStent *inject* device with cataract surgery may improve QOL vs. cataract surgery alone over 24 months with improvements influenced by ocular symptoms and vision related activities.

Key Words: iStent *inject*, open angle glaucoma, patient-reported outcomes, PRO, vision-related quality of life, QOL, VFQ-25, OSDI

Introduction

Primary open angle glaucoma (POAG) is characterized by progressive, irreversible and largely asymptomatic vision loss at early stages caused by optic nerve damage. Cataract, a clouding of the lens in the eye, progressively blocks light from entering the eye, causing vision loss and, if not removed, eventually reversible blindness. These conditions often simultaneously progress slowly over extended periods of time and often have a detrimental impact on patients' vision related quality of life (QOL) [1]. Cataract and glaucoma surgeries are commonly performed in combination to achieve two meaningful benefits: (1) clearance of crystalline lens opacity from the visual axis and (2) the reduction of intraocular pressure (IOP) [2]. In treating patients with POAG, however, maintaining and improving patients' QOL remains an unmet need. This is because worsening of a patient's QOL, particularly as it relates to eye comfort and fluctuating vision, is commonly associated with medical treatment using ocular hypotensive medications known to cause ocular surface disease (OSD) [3] and with glaucoma surgical interventions. Several studies have shown the deleterious impact of OSD on QOL among patients with glaucoma [4] [5] [6]. It has been also observed that patients with glaucoma filtering blebs may experience discomfort in the form of burning, foreign body sensation, tearing, pain, or vague discomfort [7] [8] and that those with glaucoma filtering blebs experience significantly more dysesthesia than those without filtering blebs. [9]. Therefore, a range of outcomes including QOL should be considered to assess the quality or success of glaucoma treatment.

Due to the gradual clinical progression of POAG, QOL assessment measures of mild-to-moderate severity patients, who are typically asymptomatic, may not be highly sensitive to glaucomatous changes. Indeed, other randomized clinical trials specifically designed to detect QOL differences among patients with early stage glaucoma have failed to show significant differences among treatment groups. Specifically, the LiGHT (Laser as Initial Treatment of Glaucoma and Ocular Hypertension) study comparing primary selective laser trabeculoplasty (SLT) with eye-drops for initial therapy showed no significant difference using a generic utility measure (EQ-5D) or glaucoma-specific measure (GUI) [10]. In the CIGTS (Collaborative Initial Glaucoma Treatment Study), which aimed to determine whether patients are managed better by initial treatment with IOP-lowering medications or by immediate trabeculectomy, both groups had very similar effects on QOL [11][12]. Another trial, the United Kingdom Glaucoma Treatment Study (UKGTS), showed that vision-related quality of life, assessed by 15-item Glaucoma Quality of Life (GQL-15) and 9-item Glaucoma Activity Limitation (GAL-9), was similar for both groups of patients (i.e., patients receiving a topical prostaglandin analog or placebo eye drops) [13]. Interestingly, the EAGLE study, which compared clear-lens extraction with laser peripheral iridotomy and topical medical treatment as first-line therapy in those with newly diagnosed primary angle closure with raised IOP or primary angle-closure glaucoma, found EQ-5D, VFQ-25, and GUI scores at 36 months significantly favored the clear-lens extraction group [14]. Although this study was conducted in angle closure glaucoma patients, usually a more severe and more symptomatic form of glaucoma than POAG, it demonstrates the impact of lens extraction on QOL.

The pivotal study of cataract surgery plus iStent *inject* for the reduction of IOP in patients with glaucoma and cataracts, which led to the FDA's approval of iStent *inject* in 2018, included patient-reported outcome (PRO) measures in addition to standard efficacy and safety measures. These PRO data were gathered for exploratory analyses and were not intended for the trial endpoints. [15]. While iStent *inject* has been studied extensively and is in widespread use worldwide because of its proven clinical efficacy and safety, changes in QOL within and between treatment groups and the assessment of outcomes from the patients' perspective, such as QOL, are yet to be fully elucidated.

Therefore, the post hoc exploratory analyses presented in this study investigated the comparative QOL changes of cataract surgery plus implantation of the trabecular micro-bypass stent (iStent *inject*) versus cataract surgery alone from patients within the pivotal study of cataract surgery with iStent *inject*.

Methods

Data Source

Details of the pivotal trial of cataract surgery plus iStent *inject* for the reduction of IOP in patients with glaucoma and cataracts are described elsewhere [15]. The study was designed to assess the safety and effectiveness at 2 years postoperative of the second-generation trabecular micro-bypass stent system in patients with mild to moderate primary OAG and cataract at 41 US clinical sites. A targeted total of 500 eyes were randomized in a 3:1 ratio to the treatment group or control group after completion of

uncomplicated cataract surgery. At baseline, month 11, and month 23, patients using ocular hypotensive medication(s) were instructed to undergo medication washout to permit unmedicated DIOP assessment at months 12 and 24, respectively [15]. The primary effectiveness endpoint, a 20% reduction from baseline in diurnal IOP (DIOP) without ocular hypotensive medication at month 24, was met: a greater percentage of patients in the iStent *inject* group achieved a 20% or more reduction in medication-free IOP at 24 months compared with the surgery alone group (75.8% vs. 61.9%, P = 0.005) [15]. The study was conducted with Institutional Review Board approval, and study procedures followed the tenets of the Declaration of Helsinki (2008), including written informed consent of all participating subjects. The study was registered with the National Library of Medicine (clinicaltrials.gov, NCT00323284).

In this trial, three PRO measures, the Visual Function Questionnaire (VFQ-25), Ocular Surface Disease Index (OSDI©) questionnaire and the Patient Health Questionnaire-9 (PHQ-9) were administered to patients at baseline and months 1, 6, 12, and 24. The VFQ-25 and OSDI were identified as most relevant to the patient experience and so data from these PRO measures were analyzed. Data from the Safety population, defined as all randomized subjects analyzed according to the treatment actually received, were included in the analysis.

Patient Reported Outcomes Measures: VFQ-25 and OSDI

The VFQ-25 is a widely-used vision-related quality of life instrument. It consists of 25 questions that measure the impact of vision-specific symptoms on visual functioning,

disability, and general health and well-being [16]. The patients selected answers from among multiple possible responses to the individual questions, and their responses were then converted to a 0-to-100 score whereby higher scores indicate better functioning. Scores for vision-related questions were averaged to 12 subscale scores, and an overall composite score was calculated by averaging the subscale scores (excluding the general-health-rating subscore) for ocular pain; general vision; near and distance activities; mental health; social functioning; role difficulties; dependency; driving; color vision; and peripheral vision.

The OSDI consists of 12 questions used to measure the severity and effects of ocular surface symptoms related to chronic dry eye diseases and their impact on ability to function [17]. Responses to the individual questions were rated on a scale of 0 to 4 (0 = none of the time, 1 = some of the time, 2 = half of the time, 3 = most of the time, 4 = all the time). An overall composite score was calculated based on the total number of questions answered, and three subscale scores were computed using the questions that comprise the subscale [18]. The composite and subscale scores ranged from 0 to 100, with higher scores indicating greater disability.

Definition of Patient-Reported Outcomes Responders

Following the publication of the FDA's Guidance for Industry Patient-Reported Outcome Measures in 2009 [19], there has been a shift in approach and methodology in studies of patient reported outcomes (PRO). This trend has centered on PRO responders who meet a certain threshold (or a variety of thresholds) for PRO measures, which can be

interpreted as a treatment benefit, and the proportions of such individuals in each trial arm [20]. Ideally this within person threshold of meaningful change, i.e., the amount of within person difference observed in a PRO measure that can be interpreted as a treatment benefit, would be determined using existing literature or anchor-based methods.

Because no specific within-person threshold or minimum important difference, referred to as MID in the rest of the paper, has been established in the mild-to-moderate glaucoma population, a MID was calculated for the scores from each questionnaire using a distributional approach whereby the MID was defined as half the standard deviation (SD) of the baseline scores combined across treatment groups [21]. This approach was based on a literature review by Norman et al. (2003), which showed that the threshold of discrimination for changes in health-related quality of life was approximately half of one SD. Because higher scores on the VFQ-25 reflect better functioning, PRO responders for the VFQ were defined as patients with change from baseline greater than or equal to the MID threshold. For the OSDI, because higher scores reflect greater disability, responders were defined as patients with a change from baseline less than or equal to the MID [21][22]. This PRO responder approach, which is the primary focus of our analysis, differs from a group-level minimum important difference (MID) used to evaluate treatment benefit.

Medication-Free Status at Month 24 by PRO Responders

The pivotal trial data showed 63.2% of iStent *inject* treatment eyes versus 50.0% of control eyes were medication-free at month 24. To assess association between glaucoma-related medications and PRO responders, the treatment groups were pooled and the proportions of medication-free individuals at month 24 were calculated and compared by PRO response. This allowed comparison of the rate of PRO responders who were medication-free versus those who were medicated, regardless of treatment assignment.

Statistical Analysis

For baseline demographic and clinical characteristics, comparisons were made using t-tests for mean age; chi-squared tests were used for age category, gender, race, number of hypotensive medications, and prostaglandin use.

The percentages of VFQ-25 and OSDI PRO responders at the 1-, 6-, 12-, and 24-month follow-up visits were compared between treatment groups using a logistic generalized linear mixed model for repeated measures with stratification by baseline IOP (< 25 mmHg and ≥ 25 mmHg) and an unstructured covariance matrix to estimate the correlation among within-subject repeated measurements. The percentages of responders within each treatment group, the percentage differences between treatment groups, and *P* values for the comparison between treatment groups were reported at each follow-up visit.

A chi-squared test was used to compare the percentage of patients free of medication at month 24 by PRO response.

To identify the factors associated with the likelihood of being a composite score responder for either the VFQ-25 or the ODSI, two mixed effects logistic models were explored: Model 1) which included fixed categorical effects for treatment group (iStent *inject* or surgery alone), baseline IOP (< 25 mmHg or ≥ 25 mmHg), and baseline prostaglandin (PGA) use (yes or no); and Model 2) which included the additional fixed categorical effects for age (≥60 or <60), gender (male or female), and race (black or non-black). The odds ratios and 95% CIs for being a composite responder versus a non-responder were summarized for each of the fixed effects for each model.

Because the analyses performed were post hoc and exploratory in nature, and there was no adjustment for multiplicity, all *P* values resulting from these analyses should be interpreted as descriptive statistics.

Results

Patient Baseline Demographic and Clinical Characteristics.

At 41 US clinical sites, a total of 505 eyes were randomized 3:1 to cataract surgery with iStent *inject* implantation or cataract surgery only. Their baseline demographic and clinical characteristics were well balanced. The mean medicated IOP and unmedicated DIOP were 17.5 mmHg and 24.8 mmHg in the iStent *inject* group and 17.5 mmHg and 24.5 mmHg in the cataract only group. Mean screening visual field mean deviation was -3.4 decibels in both groups. The treatment groups were also reasonably well-balanced by baseline age (iStent *inject* group mean age = 69.0 years old, cataract only group mean age = 70.1), gender (iStent *inject* group 58.1% female, cataract only group 54.2%

female), number of ocular hypotensive medications at screening with 57.9% of the iStent *inject* group and 60.2% of the cataract only group receiving on average 1 medications preoperatively. With regard to the preoperative ocular hypotensive medication class used at screening, 85.0%, 35.1%, 19.6%, 19.1% of the iStent *inject* group and 79.7% 40.7%, 17.8%, 16.1% of the cataract only group were using prostaglandin analogue, beta blockers, alpha agonists, and carbonic anhydrase inhibitors respectively. In the iStent *inject* group, 41.3% of patients had a history of ocular surface disease while 43.2% in the cataract only group did. The baseline characteristics of the Safety population (iStent *inject* group N = 386 and cataract surgery only N = 119) were comparable to those of the Intent-to-Treat population (iStent *inject* group N = 387 and cataract surgery only N =118). Additional details of the baseline trial data are described elsewhere [15].

Comparison of PRO Responders by iStent *inject* versus Cataract only (Figures 1 and 2)

Overall, compared with the cataract surgery alone group, the iStent *inject* group exhibited a greater percentage of PRO responders during all follow-up visits, averaging 58.0% vs. 45.8% *P* < *.05*) for the VFQ-25 composite scores and 56.7% vs. 48.9% (p < .05) for the OSDI composite scores over 24 months.

Treatment difference favored the iStent *inject* group of 14.1% at month 1, 13.4% at month 6, 11.6 % at month 12 (*P* < *.05*), and 9.0% at month 24 *(P* > *.05).* Over 24 months, the percentage of PRO responders averaged 58.0% in the iStent *inject* group

compared to 45.8% in the cataract surgery only group, a treatment difference of 12.1% (*P < .05*).

When measured by the OSDI composite score, steady PRO improvements were observed within each group at all time intervals, with an average treatment difference favoring the iStent *inject* group of 7.8% over 24 months (*P < .05*).

Although the trial measured the PRO at five time intervals over the course of two years, the majority of patients completed the two questionnaires consistently at each time interval, with completion rates to the questionnaire being similar in each group. (Figure 1 and 2). Completion rates were high and ranged from 91.6% - 99.2% across both instruments and all time points, and as such, there was no need to further investigate the impact of missing data as they were accounted for in the analyses by the mixed models for repeated measures using the correlation among within-patient repeated measures.

Percentage of Responders Among the VFQ-25 and OSDI Subscales (Figure 3 and Table 2)

Differences in PRO response rates at month 24 among the 12 VFQ-25 subscales were most pronounced in the general vision, ocular pain, and driving subscales (*P < .05*). For both groups, the general vision subscale, followed by ocular pain, had the highest proportions of PRO responders. However, the iStent *inject* group had a greater proportion of PRO responders than the cataract only group (71.8% vs. 60.0%; *P < .05* for general vision and 59.3% vs. 47.3%; *P < .05* for ocular pain). The driving subscale

produced the largest difference between the two groups (49.0% vs. 28.8%; *P* < *.05*), a 20.2% treatment difference favoring iStent *inject*.

Similar trends emerged in PRO assessments among the 3 OSDI subscales with the ocular symptom subscale being the greatest driver of PRO response at month 24 (54.5% for the iStent *inject* group vs. 46.5% for the cataract only group; *P* > *.05*). The vision-related function subscale showed a similar treatment difference between the two groups (53.3% for the iStent *inject* group vs 45.9% for the cataract only group; *P* > *.05*).

Medication-Free Status at Month 24 by PRO Responders (Figure 4)

The pivotal trial data showed that at 24 months, 75.8% of the iStent *inject* group versus 61.9% of the cataract only group experienced 20% or greater reduction from baseline in unmedicated DIOP (*P* < *.05*); mean reduction in unmedicated DIOP from baseline was greater in the iStent *inject* group (7.0±4.0 mmHg) than in the cataract only group (5.4±3.7 mmHg; *P* < *0.001*). It is of particular importance to the PRO analysis (given the negative effect of medications on OSD) that in patients who experienced 20% or greater reduction in unmedicated DIOP, 84% of treatment eyes versus 67% of control eyes were not receiving ocular hypotensive medication at 23 months.

Consistent with this finding, those who were VFQ-25 PRO responders were more likely to be medication-free at month 24 than those who were not. More specifically, at month 24, 76.5% of the responders were medication-free while 62.5% of the non-responders were medication-free (*P* < *.05*) regardless of treatment assignment.

Likelihood of Being a Responder: Logistic Mixed Models for Repeated Measures (Table 1)

Analysis of both PRO measures demonstrated that patients in the iStent *inject* group were more likely to be PRO responders than patients in the cataract only group. When measured by VFQ-25, the iStent *inject* group displayed 60% greater odds of being a responder ($P < .05$). When measured by OSDI, the odds for the iStent *inject* group was 32% better than the cataract only group, but its *P* value was > 0.05.

Regarding independent factors associated with being a PRO responder, other than the comparator group, two demographic variables emerged as important explanatory variables associated with being a PRO responder. Specifically, females had 60% and 57% greater odds of being a VFQ PRO responder and OSDI PRO responder, respectively ($P < .05$); and older patients (age ≥60) were 54% and 48% less likely than younger patients to be a VFQ PRO responder and OSDI PRO responder, respectively $P < .05$).

Discussion

The present PRO analysis contributes some of the first data analyzing the effect of a MIGS device on vision related quality of life in patients with glaucoma and concomitant cataract. The rigorous dataset was drawn from the large randomized controlled trial evaluating iStent *inject* implantation with cataract surgery versus cataract surgery alone (i.e., the iStent *inject* pivotal trial). Given that the majority of PRO evaluations in prior

POAG clinical trials have not demonstrated differences between treatments, the results of the current study are notable [10][11][12][13]. Although the iStent *inject* pivotal trial was not specifically designed nor powered for treatment comparisons among PROs, the study found both meaningful and durable PRO improvements in the iStent *inject* group, and a greater PRO response rate in the iStent *inject* group relative to the cataract surgery only group over 24 months. Due to the iStent *inject*'s micro-scale size (the two stents occupy <0.5 mm total space in the trabecular meshwork), tissue-sparing anatomical location, best-in-class safety profile, and streamlined implantation procedure, the PRO benefits demonstrated in this study may not be attained with other glaucoma surgeries that have greater tissue destruction, larger device size, less elegant implantation procedures, and/or more concerning or symptomatic adverse event profiles that may negatively impact QOL. Of note, the overall rate of adverse events from the pivotal was considered comparable between groups [15].

Measured by VFQ-25, the iStent *inject* group had greater odds of being a PRO responder (odds ratio =1.60, $P < .05$) than the cataract only group. The incremental improvements observed in the iStent *inject* group were influenced primarily by the three subscales: driving (49.0% vs. 28.8%; $P < .05$), ocular pain (59.3% vs. 47.2%; $P < .05$) and general vision (71.8% vs. 60%; $P < .05$).

As described previously, our results relied on the definition used for MID in PRO scores. Estimating the MID of a PRO measure is considered essential to the interpretation of results when assessing within-patient or between-group differences [22]. In a study

population that were newly diagnosed for glaucoma and treated for trabeculectomy or medical therapy, therefore not completely identical to ours, a range of MIDs from 2.3 to 3.8 units for VFQ-25 using a variety of methods reported by Gillespie et al (2013) serves as a most close reference point for our study [23]. Given that the VFQ-25 MID used in our study, derived from the distributional approach of one half the SD of baseline values, was 6.67 (essentially requiring a higher threshold for a meaningful difference), our results could be interpreted as reasonably robust.

In addition to the clinical trial data showing 63.2% of treatment eyes versus 50.0% of control eyes medication-free at 24 months, the PRO findings revealed another notable association: at month 24, 76.5% of the PRO responders were medication-free versus 62.5% of PRO non-responders ($P < .05$) regardless of treatment assignment.

It is widely accepted that cataract surgery alone significantly improves QOL [41][42]. Skalicky et al (2012) found visually significant cataract to be independently associated with QOL. These associations were related to visual acuity as well as other visual influences of cataract (e.g. glare, contrast sensitivity and monocular diplopia) that worsen quality of vision [42]. In the present study, both treatment groups received significant QOL improvements relative to baseline, likely largely attributable to cataract surgery. Incremental benefits in the iStent *inject* group relative to the cataract only group were also demonstrated. Bias associated with cataract surgery is expected to be minimized by the use of randomization. One plausible explanation for the difference in QOL improvement is a reduction in medications or an elimination of dependency on

medications, which are known to promote or worsen OSD and thereby affect QOL. Reducing medications may result in a more stable tear film, allowing for more stable vision and better ocular comfort. Consistent with this possible explanation, Skalicky et al (2012) found that OSD is more common in patients using glaucoma medications and is associated with poorer glaucoma-related QOL [4]. Also, Nordmann et al (2003) highlighted poor treatment satisfaction associated with topical anti-glaucomatous drug side effects and additional visits to the ophthalmologist, all leading to poorer QOL among French patients [5]. In the EAGLE study, the authors point to multiple factors probably contributing to QOL differences between groups, including reduced need for glaucoma medications [14].

The above mentioned possible mechanism of action of iStent *inject* relative to patient QOL improvement is supported by the subscale findings in the study. Specifically, the VFQ-25 driving subscale produced the greatest improvement (20.2%) between the two groups (49.0% vs. 28.8%; $P < .05$), while ocular pain (59.3% vs. 47.2%; $P < .05$) and general vision (71.8% vs. 60%; $P < 0.05$) also contributed to the overall difference between the two groups. In addition, the ocular symptoms subscale of OSDI was the most important factor of OSDI response at month 24 (54.5% for the iStent *inject* group vs. 46.5% for the cataract only group; $P > 0.05$). Improvements in driving, ocular pain, and ocular symptoms could be related to greater eye comfort and less vision fluctuation, rather than to fundamental changes in disease state as measured by IOP, visual acuity, or VF. This suggests that QOL improvements likely go beyond the numeric value of visual acuity, especially given that the majority of eyes in both groups achieved BSCVA

of 20/40 or better at month 24 (98.9% of eyes in the iStent *inject* group and 98.2% of eyes in the cataract only group) [15].

Driving indeed is a key component of maintaining independence of patients with glaucoma. Not surprisingly, driving was the second most important attribute identified among the 13 glaucoma-related outcomes in the FDA-funded patient preference study; this study reported that the outcomes with the largest relative importance weights were "adequate IOP control" and "drive a car during the day" [26]. A number of driving difficulties are commonly reported by glaucoma patients, including problems with glare, night driving and tasks requiring peripheral vision and visual search [24].

In the main study, visual field MD was stable over time (mean change close to zero) from screening to 24 months in both groups suggesting that driving results may not be related to changes in peripheral vision associated with disease progression [15]. The differences in driving subscale scores may also be due to reduction in medications or an elimination of dependency on medications. The severity of OSD symptoms is known to positively correlate to the number of IOP-lowering medications used [27]. Dry eye disease (DED) contributes to ocular discomfort and visual disturbance, such as blurred or foggy vision, fluctuating vision, and problems with glare that may interfere with aspects of quality of life, including activities such as driving [28].

Miljanovic et al (2007) demonstrated that people with DED are significantly more likely than people without DED to report problems with several important tasks of daily living

including daytime driving (OR 2.80, 95 % CI 1.58–4.96), and nighttime driving (OR 2.20, 95 % CI 1.48–3.28) [29]. In Li et al (2012), data collected from the NEI-VFQ and OSDI were analyzed to identify potential differences between the dry eye group and the control group. The dry eye patient group had worse NEI-VFQ scores for several subscales including driving ($P < 0.05$), and higher (worse) OSDI composite and subscale scores (all $P < 0.001$) [30]. Impairment of driving ability due to visual disturbance in patients with dry eye also has been confirmed objectively in a study using a driving simulator by Deschamps et al (2013) [31].

In the iStent *inject* group, 41.3% of patients had a history of ocular surface disease while 43.2% in the cataract only group. Ocular surface disease was reported as an adverse event by 16.1% of those in the iStent *inject* group and 16.8% in the cataract only group. Although it is important to note that no strong correlations have been found among clinical tests and optical examinations, and decline in patient-reported quality of life [32][33][34].

In contrast to previous clinical trials, this study's ability to detect the QOL differences between the two comparator arms may reside in a few key factors. The selected instruments (VFQ-25 and OSDI questionnaires) were sufficiently sensitive to assess a comprehensive set of glaucoma- and eye-comfort-related symptoms and their consequences for vision-related quality of life. In particular, VFQ-25 is widely used in many glaucoma-related studies and therefore useful for comparing results across various studies [12][35][36]. Although power calculations for treatment differences were

not performed for the VFQ-25 and OSDI outcomes, the sample sizes in the trial appear to be sufficiently large for comparisons with the VFQ-25. Of note, there were wider variations around the mean OSDI values in each group. Our study population, in contrast to patients from the LiGHT study, CIGTS, UKGTS patients, were already burdened by the use of glaucoma-related medications over a reasonably long duration prior to study enrollment, which might have been conducive to our study's detecting the QOL differences.

Given that no instruments cover every aspect of patients' experience [37], it is important to note that our study's QOL differentials do not necessarily capture other important dimensions from the patients' perspective such as patient satisfaction or preference, medication adherence and inconvenience, or an even broader set of eye-comfort-related or other ocular symptoms, such as eye-related appearance.

Therefore, in selecting treatment for patients with POAG in combination with cataract, in addition to clinical surrogates such as IOP, visual acuity or visual fields, patients' highest priorities such as ability to drive, eye comfort, vision stability, and possible reduction in blurred vision as well as medication burden should play a central role in electing their suitable treatment [38].

Limitations and Strengths

This study was not without limitations. Given that the trial was primarily designed and powered for the key clinical endpoint of IOP reduction, the medication washout protocol prior to and post-surgery might have impeded the ability to capture the true magnitude

of the VFQ-25 or OSDI improvements. Patients preoperatively discontinued glaucoma medications at the time they completed the questionnaires at baseline. This discontinuation of glaucoma medication may have improved the baseline scores, thus minimizing the degree of possible PRO improvement. In clinical practice, however, patients with glaucoma often continue all ocular anti-hypertensives prior to surgery. The wash out at 12 and 24 months could have potentially masked greater differences between groups. For example, if a patient had been taking a glaucoma medication during the study but that medication was subsequently stopped due to wash out protocol, the medication induced symptoms may have abated by the time that the questionnaire was completed, at least at these two time points. The washout, necessary to evaluate IOP, may actually mask QOL differences at these time points. Thus, the true differences are potentially understated in this study. Furthermore, the use of artificial tears (or topical steroid medications) were not assessed in this study. Their use may have diluted the disturbance caused by glaucoma-related medications.

Earlier findings in glaucoma-related PRO studies suggest that PRO measure performance in glaucoma may be driven by the least-affected eye [39][40]. In the absence of such data collected in the trial, our study could not ascertain the impact of the least-affected eye on study outcomes. However, this issue may be rendered moot due to the rigorousness of the study: since the trial randomized and enrolled a large number of patients, had well-balanced treatment groups, and maintained patient masking, it is unlikely that mismatched differentials affecting study outcomes would have existed in the least-affected eye in either group.

The VFQ-25 and OSDI differential results were immediately apparent within 1 month for both groups, generating the QOL gaps between the groups and maintaining those gaps persistently over 2 years. Finally, the results from similar questions and sub-domains between the instruments trended in the same direction, conferring internal congruency and validity, all of these suggesting the relative rigor and robustness of the study findings. However, additional research is needed to conclusively identify the mechanism of action of iStent *inject* relative to patient QOL.

Conclusions

In an exploratory PRO analysis of the VFQ-25 questionnaire, in comparison with subjects undergoing cataract surgery alone, subjects with cataract surgery plus iStent *inject* implantation reported greater vision related quality of life improvement. Maintaining “eye comfort” remains an unmet medical need in glaucoma treatment. These study results suggest that not only does iStent *inject* not compromise “eye comfort,” but that it could potentially improve it.

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References

1. Lamoureux E, Pesudovs K. Vision-specific quality-of-life research: a need to improve the quality. *Am J Ophthalmol*. 2011;151(2):195-7.
2. Berdahl JP. Cataract surgery to lower intraocular pressure. *Middle East Afr J Ophthalmol*. 2009;16(3):119-122.
3. Zhang X, Vadoothker S, Munir WM, Saeedi O. Ocular Surface Disease and Glaucoma Medications: A Clinical Approach. *Eye Contact Lens*. 2019;45(1):11-18.
4. Skalicky SE, Goldberg I, McCluskey P. Ocular surface disease and quality of life in patients with glaucoma. *Am J Ophthalmol* 2012;153:1–9.e2.
5. Nordmann JP, Auzanneau N, Ricard S, et al. Vision related quality of life and topical glaucoma treatment side effects. *Health Qual Life Outcomes* 2003;1:75.
6. Rossi GC, Tinelli C, Pasinetti GM, et al. Dry eye syndrome-related quality of life in glaucoma patients. *Eur. J. Ophthalmol* 2009;19:572-579.
7. Hoskins H, Kass M, editors. Becker-Shaffer's diagnosis and therapy of the glaucomas, 6th edition. CV Mosby Company, 1989:598–600.
8. Sherwood MB, Spaeth G. Complications of glaucoma therapy. Thorofare, NJ: Slack, 1990:283–291.
9. Budenz DL, Hoffman K, Zacchei A. Glaucoma filtering bleb dysesthesia. *Am J Ophthalmol.* 2001 May;131(5):626-30. PubMed PMID: 11336938.
10. Gazzard G, Konstantakopoulou E, Garway-Heath D, et al. Selective laser trabeculoplasty versus eye drops for first-line treatment of ocular hypertension and glaucoma (light): A multicentre randomised controlled trial. *Lancet* 2019;393:1505-1516.
11. Musch DC, Tarver ME, Goren MJ, Janz NK. Development of an 18-Item Measure of Symptom Burden in Patients With Glaucoma From the Collaborative Initial Glaucoma Treatment Study's Symptom and Health Problem Checklist. *JAMA Ophthalmol*. 2017;135(12):1345-1351.
12. Janz NK, Wren PA, Lichter PR, Musch DC, Gillespie BW, Guire KE. Quality of life in newly diagnosed glaucoma patients : The Collaborative Initial Glaucoma Treatment Study. *Ophthalmology*. 2001;108(5):887-898.
13. Jones L, Garway-Heath DF, Azuara-Blanco A, Crabb DP; United Kingdom Glaucoma Treatment Study Investigators. Are Patient Self-Reported Outcome Measures Sensitive Enough to Be Used as End Points in Clinical Trials?: Evidence from the United Kingdom Glaucoma Treatment Study. *Ophthalmology*. 2019;126(5):682-689.
14. Azuara-Blanco A, Burr J, Ramsay C, et al. Effectiveness of early lens extraction for the treatment of primary angle-closure glaucoma (EAGLE): a randomised controlled trial. *Lancet*. 2016;388(10052):1389-1397. doi:10.1016/S0140-6736(16)30956-4
15. Samuelson TW, Sarkisian SR Jr, Lubeck DM, et al. Prospective, Randomized, Controlled Pivotal Trial of an Ab Interno Implanted Trabecular Micro-Bypass in Primary Open-Angle Glaucoma and Cataract: Two-Year Results. *Ophthalmology*. 2019;126(6):811-821. doi:10.1016/j.ophtha.2019.03.006
16. Mangione CM. The National Eye Institute 25-Item Visual Function Questionnaire (VFQ-25). 2000. Available at: https://www.nei.nih.gov/sites/default/files/nei-pdfs/manual_cm2000.pdf. Accessed August 7, 2019.

17. Walt J. Ocular Surface Disease Index (OSDI) Administration and Scoring Manual. Irvine, CA: Allergan, Inc; 2004.
18. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol*. 2000 May;118:615-21.
19. Food and Drugs Administration (FDA). Guidance for Industry Patient- Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. December 2009. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf
20. Wyrwich KW, Norquist JM, Lenderking WR, Acaster S, the Industry Advisory Committee of International Society for Quality of Life Research (ISOQOL). Methods for interpreting change over time in patient-reported outcome measures. *Qual Life Res*. 2013;22(3):475–83
21. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care*. 2003;41:582-92.
22. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials*. 1989;10(4):407-415. doi:10.1016/0197-2456(89)90005-6
23. Gillespie BW, Musch DC, Niziol LM, Janz NK. Estimating minimally important differences for two vision-specific quality of life measures. *Invest Ophthalmol Vis Sci*. 2014;55(7):4206-4212. Published 2014 Jun 6. doi:10.1167/iovs.13-13683
24. Janz NK, Musch DC, Gillespie BW, Wren PA, Niziol LM. Evaluating clinical change and visual function concerns in drivers and nondrivers with glaucoma. *Investigative Ophthalmology & Visual Science*. 2009; 50(4):1718–25. Epub 2008/12/09. doi: iovs.08-2575 [pii] doi: 10.1167/iovs.08-2575 PMID: 19060263.
25. Wood JM, Black AA, Mallon K, Thomas R, Owsley C (2016) Glaucoma and Driving: On-Road Driving Characteristics. *PLOS ONE* 11(7): e0158318
26. Le JT, Mohanty K, Bicket AK, Tarver ME, Eydelman M, Li T. Identifying outcomes that are important to patients with ocular hypertension or primary open-angle glaucoma: a qualitative interview study. *Ophthalmol Glaucoma*. 2019;2(6):374-382. doi:10.1016/j.ogla.2019.07.005
27. Fechtner RD, Godfrey DG, Budenz D, et al. Prevalence of ocular surface complaints in patients with glaucoma using topical intraocular pressure-lowering medications. *Cornea.* 2010;29:618–21.
28. Uchino M, Schaumberg DA. Dry Eye Disease: Impact on Quality of Life and Vision. *Curr Ophthalmol Rep*. 2013;1(2):51-57.
29. Miljanović B, Dana R, Sullivan DA, Schaumberg DA. Impact of dry eye syndrome on vision-related quality of life. *Am J Ophthalmol*. 2007 Mar;143(3):409-15
30. Li M, Gong L, Chapin WJ, Zhu M. Assessment of vision-related quality of life in dry eye patients. *Invest Ophthalmol Vis Sci.* 2012;53(9): 5722–5727.

31. Deschamps N, Ricaud X, Rabut G, Labbe A, Baudouin C, Denoyer A. The impact of dry eye disease on visual performance while driving. *Am J Ophthalmol* 2013; 156(1): 184–189 e3.
32. Schein OD, Tielsch JM, Munoz B, Bandeen-Roche K, West S. Relation between signs and symptoms of dry eye in the elderly. A population-based perspective. *Ophthalmology* 1997; 104(9): 1395–1401.
33. Begley CG, Chalmers RL, Abetz L, et al. The relationship between habitual patient-reported symptoms and clinical signs among patients with dry eye of varying severity. *Invest Ophthalmol Vis Sci*. 2003;44(11):4753-4761. doi:10.1167/iovs.03-0270
34. Nichols KK, Nichols JJ, Mitchell GL. The lack of association between signs and symptoms in patients with dry eye disease. *Cornea* 2004; 23(8): 762–770.
35. Pahlitzsch M, Klamann MK, Pahlitzsch ML, Gonnermann J, Torun N, Bertelmann E. Is there a change in the quality of life comparing the micro-invasive glaucoma surgery (MIGS) and the filtration technique trabeculectomy in glaucoma patients?. *Graefes Arch Clin Exp Ophthalmol*. 2017;255(2):351-357. doi:10.1007/s00417-016-3550-4
36. Niemeyer KM, Gonzales JA, Rathinam SR, et al. Quality-of-Life Outcomes From a Randomized Clinical Trial Comparing Antimetabolites for Intermediate, Posterior, and Panuveitis. *Am J Ophthalmol*. 2017;179:10-17. doi:10.1016/j.ajo.2017.04.003
37. Somner JE, Sii F, Bourne RR, et al. Moving from PROMs to POEMs for glaucoma care: a qualitative scoping exercise. Invest Ophthalmol Vis Sci. 2012;53:5940e5947.
38. Fenwick EK, Man RE, Aung T, Ramulu P, Lamoureux EL. Beyond intraocular pressure: Optimizing patient-reported outcomes in glaucoma. *Prog Retin Eye Res*. 2020;76:100801. doi:10.1016/j.preteyeres.2019.100801
39. Skalicky SE, McAlinden C, Khatib T, et al. Activity limitation in glaucoma: objective assessment by the Cambridge Glaucoma Visual Function Test. *Invest Ophthalmol Vis Sci*. 2016;57:6158e6166.
40. Arora KS, Boland MV, Friedman DS, et al. The relationship between better-eye and integrated visual field mean deviation and visual disability. *Ophthalmology*. 2013;120: 2476e2484.
41. Javed, U., McVeigh, K., Scott, N. W., & Azuara-Blanco, A. (2015). Cataract extraction and patient vision-related quality of life: a cohort study. *Eye (London, England)*, *29*(7), 921–925.
42. Skalicky SE, Martin KR, Fenwick E, Crowston JG, Goldberg I, McCluskey P. Cataract and quality of life in patients with glaucoma. *Clin Exp Ophthalmol*. 2015;43(4):335-341. doi:10.1111/ceo.12454

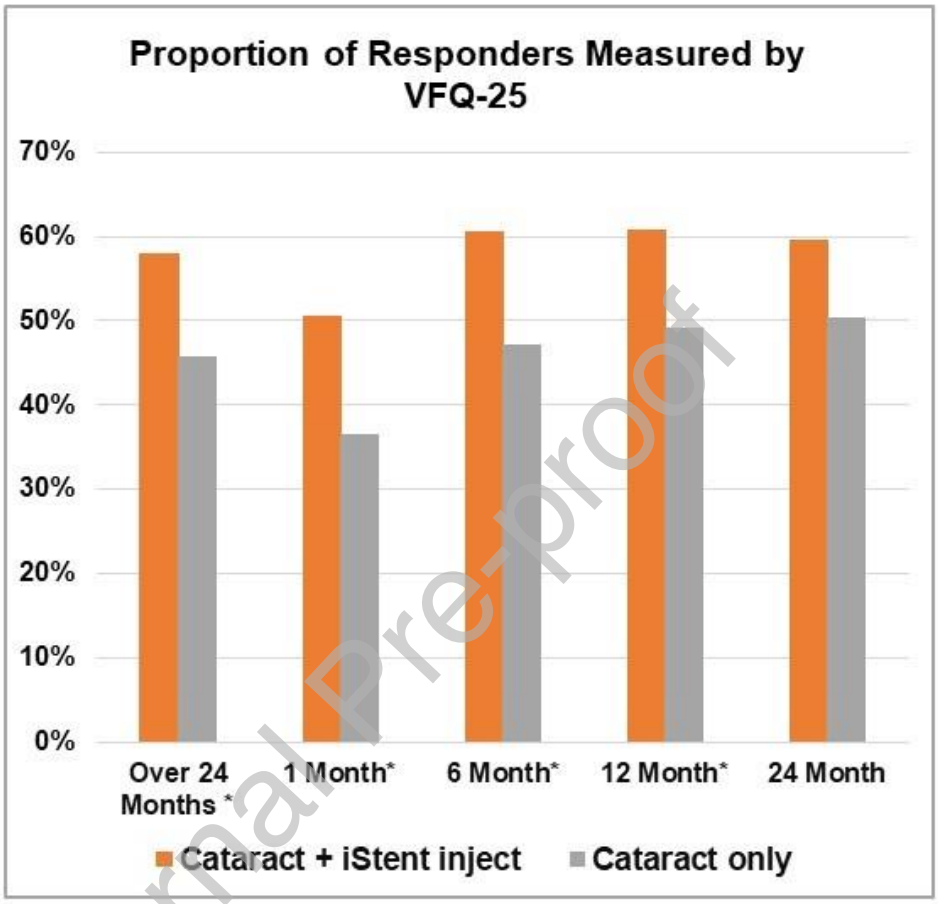

Figure 1. Proportion of PRO Responders Measured by VFQ-25. Footnote: *P < .05;
N=1,490 for Cataract Surgery with iStent *inject*, N=460 for Cataract only over 24 months;
N=382 for Cataract Surgery with iStent *inject*, N=118 for Cataract only at 1 month;
N=376 for Cataract Surgery with iStent *inject*, N=118 for Cataract only at 6 month;
N=368 for Cataract Surgery with iStent *inject*, N=115 for Cataract only at 12 month;
N=364 for Cataract Surgery with iStent *inject*, N=109 for Cataract only at 24 month

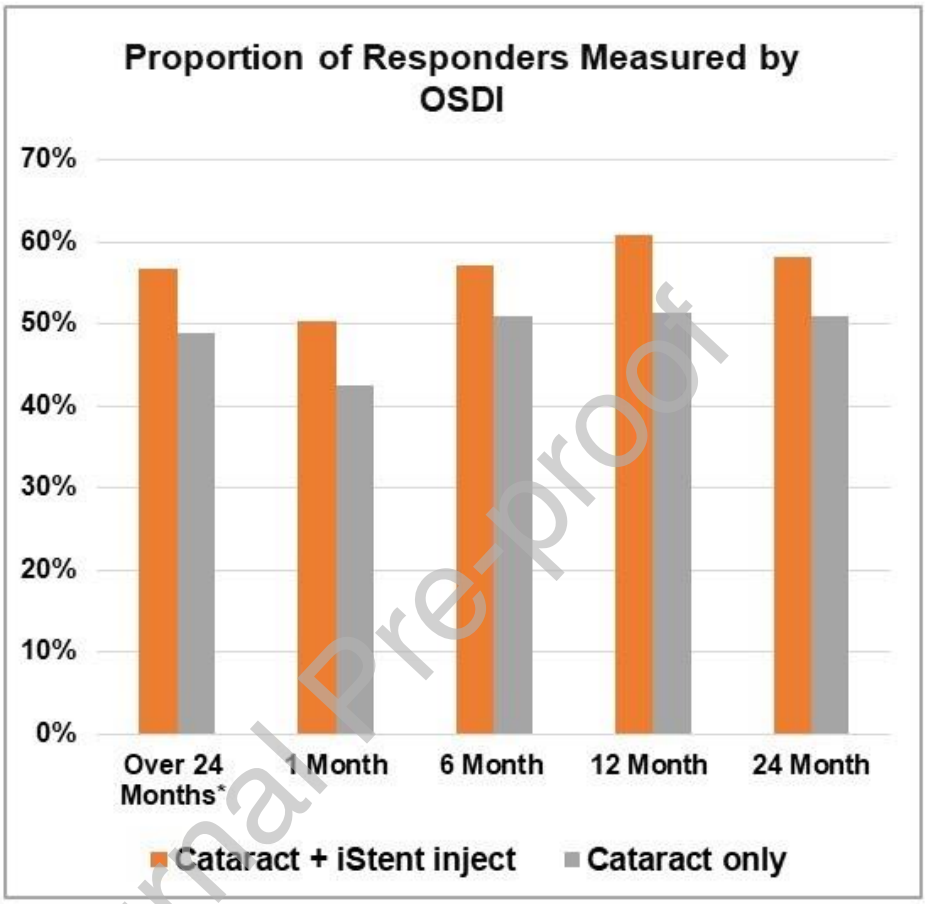

Figure 2. Proportion of PRO Responders Measured by OSDI. Footnote: *****P < .05;
N=1,486 for Cataract Surgery with iStent *inject*, N=459 for Cataract only over 24 months
N=382 for Cataract Surgery with iStent *inject*, N=117 for Cataract only at 1 month;
N=376 for Cataract Surgery with iStent *inject*, N=118 for Cataract only at 6 month;
N=367 for Cataract Surgery with iStent *inject*, N=115 for Cataract only at 12 month;
N=361 for Cataract Surgery with iStent *inject*, N=109 for Cataract only at 24 month

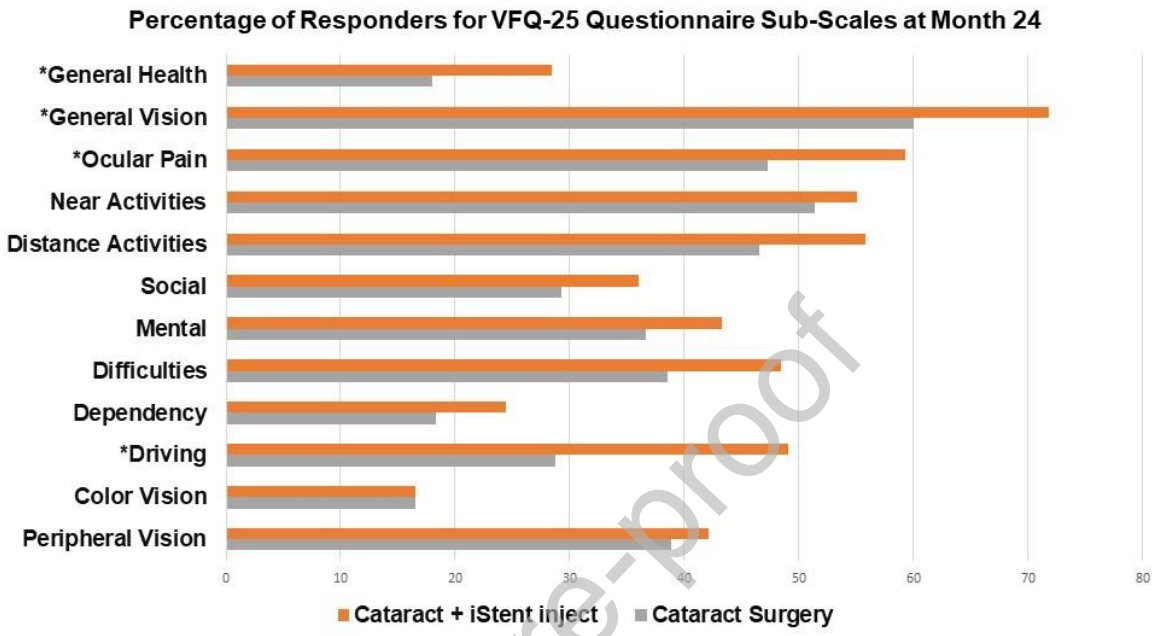

Figure 3. Percentage of PRO Responders for VFQ-25 Questionnaire Sub-Scales at Month 24. Footnote: **P < .05.*

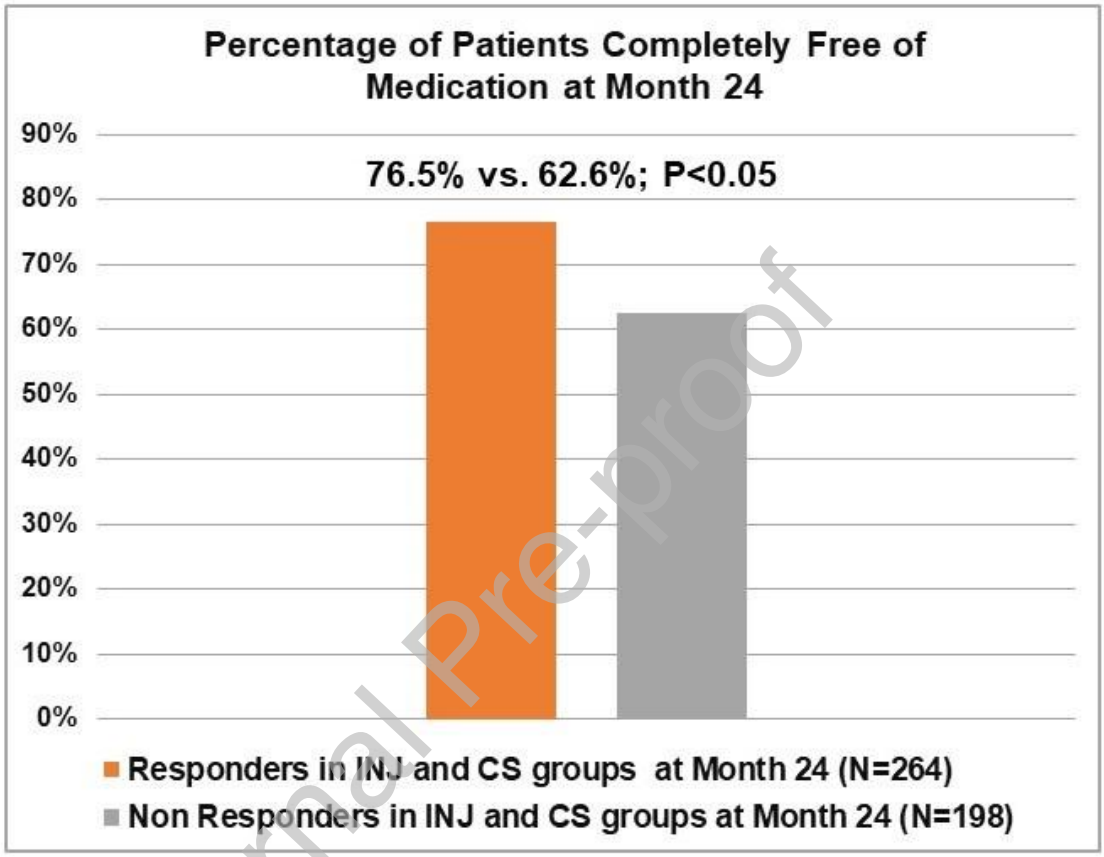

Figure 4. Percentage of Patients Completely Free of Medication at Month 24 by PRO Responders Regardless of Treatment

Table 1: Factors Associated with Likelihood of Being a Responder: Logistic Generalized Linear Models for Repeated Measures

	VFQ-25		OSDI	
	Model 1	**Model 2**	**Model 1**	**Model 2**
iStent *inject vs* Cataract Surgery	1.64* (1.12, 2.39)	1.60* (1.09, 2.33)	1.35 (0.92, 1.97)	1.32 (0.90, 1.94)
IOP (IOP < 25 mmHg)	0.93 (0.64, 1.35)	0.96 (0.65, 1.40)	0.92 (0.63, 1.35)	0.95 (0.65, 1.40)
Prostaglandin use at screening (reference group= no)	0.93 (0.61, 1.42)	0.88 (0.58, 1.35)	1.17 (0.77, 1.78)	1.13 (0.74, 1.72)
Age (reference group <60)	----	0.46* (0.27, 0.77)	----	0.52* (0.31, 0.87)
Gender (reference group =male)	----	1.60* (1.16, 2.20)	----	1.57* (1.14, 2.17)
Race (reference group= black)	----	0.84 (0.56, 1.26)	----	0.86 (0.57, 1.29)

**P < .05* vs. reference group. Factors associated with PRO improvement were assessed using a mixed effects ANCOVA model for repeated measures; factors associated with the likelihood of being a responder were assessed using a logistic generalized linear mixed model for repeated measures.

Table 2.
Percentage of PRO Responders for VFQ-25 Questionnaire Sub-Scales at Month 24

Percentage of Responders for VFQ-25 Questionnaire Sub-Scales at Month 24	iStent *inject*	Cataract Surgery	Difference (iStent-Surgery)	P-value
General Health	28.43	18.03	10.40	0.0404
General Vision	71.78	59.99	11.79	0.0250
Ocular Pain	59.29	47.25	12.05	0.0330
Near Activities	55.09	51.41	3.68	0.5114
Distance Activities	55.78	46.58	9.20	0.0997
Vision Specific Social Functioning	36.04	29.25	6.79	0.2025
Vison Specific Mental Health	43.25	36.66	6.59	0.2322
Vision Specific Role Difficulties	48.46	38.51	9.96	0.0750
Vision Specific Dependency	24.43	18.35	6.07	0.1898
Driving	49.01	28.79	20.22	0.0008
Color Vision	16.53	16.53	0.00	0.9997
Peripheral Vision	42.15	38.80	3.35	0.5393

*The percentages of responders and P-values at month 24 were derived from the model least squares means of a logistic generalized linear mixed model for repeated measures.