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ORIGINAL RESEARCH

iStent Trabecular Micro-bypass Stent Implantation Combined with Phacoemulsification for Open-Angle Glaucoma: A 2-Year Post-marketing Surveillance Study in Japan

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ABSTRACT

Introduction: We report 2-year outcomes after implantation of iStent trabecular micro-bypass stent with phacoemulsification, in Japanese patients with mild–moderate open-angle glaucoma (OAG).
Methods: This was a 24-month, prospective, longitudinal, observational, post-marketing study conducted between July 2017 and September 2020. Patients consisted of adults with OAG on antiglaucoma medications who had cataract surgery combined with one iStent implantation. Outcome measures included intraocular pressure (IOP), antiglaucoma medications, treatment success rates (defined as eyes having lower IOP with same or reduced number of medications from baseline, or same IOP with reduced number of medications from baseline, and not requiring secondary glaucoma surgeries postoperatively), and safety. Outcomes were analyzed in the overall cohort and in glaucoma subtypes: primary OAG, normal-tension glaucoma, and exfoliative glaucoma.
Results: Overall, 232 eyes were enrolled. At 24 months, mean ± standard deviation IOP decreased from 17.6 ± 4.0 mmHg preoperatively to 14.3 ± 3.0 mmHg ($p < 0.05$), and mean number of medications reduced from 2.2 ± 1.2 preoperatively to 0.7 ± 1.2 ($p < 0.05$). Similar trends were observed across glaucoma subtypes. In the overall cohort, 96.7%, 95.3%, and 93.7% of patients achieved treatment success at 6, 12, and 24 months, respectively. There were 67.6% medication-free eyes at 24 months compared to 3.2% medication-free eyes preoperatively ($p < 0.0001$). Safety profile was favorable over the 2-year period.
Conclusions: Following iStent implantation with phacoemulsification, clinically relevant and statistically significant reductions in IOP and number of medications were observed in Japanese eyes with OAG over 2 years, with favorable safety profile. These reductions were observed across all glaucoma subtypes.

Keywords: iStent; Japan; Micro-invasive glaucoma surgery; Open-angle glaucoma; Post-marketing surveillance; Trabecular micro-bypass

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Key Summary Points

Why carry out this study?

The iStent trabecular micro-bypass stent system, whether combined with cataract surgery or as a standalone procedure, has an excellent safety profile and has demonstrated sustained long-term efficacy in reducing intraocular pressure (IOP) and medication burden significantly in open-angle glaucoma (OAG).

However, there are relatively limited data evaluating the role of iStent in the Japanese population.

What was learned from the study?

Following iStent implantation with phacoemulsification, clinically relevant and statistically significant reductions in IOP and number of medications were observed in Japanese eyes with OAG over 2 years, with favorable safety profile. These reductions were observed across all glaucoma subtypes.

Outcomes from the current study suggest that one iStent combined with phacoemulsification is a safe and valuable micro-invasive glaucoma surgery treatment modality for Japanese patients with OAG, who are hoping to lower their IOP, reduce their topical medication burden, and avoid the postoperative complications associated with more invasive traditional OAG surgeries.

INTRODUCTION

Glaucoma, a chronic disease of optic neuropathy, has a prevalence of 5.0% in Japan and is the leading cause of blindness and visual impairment in the country [1–3]. Open-angle glaucoma (OAG) is the most common form of glaucoma and affects 2.6% of the Japanese population [4].

Glaucoma is well known to diminish patients' quality of life [5], largely because of vision loss which constrains activities of daily living [6]. In 2007, the economic cost of visual impairment was around USD 72.8 billion in Japan [7]. As glaucoma is the leading cause of visual impairment in Japan, these high overall costs are indicative of the substantial underlying burden of glaucoma.

A previous study in Japan demonstrated that the prevalence of OAG increases exponentially with age, especially above 40 years of age [8]. Japan currently has the highest proportion of elderly citizens of any country in the world, and this is projected to increase further [9]. This suggests that the prevalence and burden of OAG in Japan is likely to increase in the future.

The pathogenesis of OAG is a gradual and irreversible process [10, 11]. OAG is often associated with an elevated intraocular pressure (IOP) which damages the optic nerve, leading to visual impairment [10]. Normal tension glaucoma (NTG), the most common OAG subtype in Japan [12], is associated with a normal range of IOP while causing damage to the optic nerve [13]. The current approach to OAG management is aimed at reducing IOP, which is the most important modifiable risk factor of glaucoma progression [14]. Current treatment options for OAG include antiglaucoma medications and surgical treatment such as trabeculectomy [15]. Limitations with antiglaucoma medications include adverse effects and poor patient compliance [3, 16]. Trabeculectomy, although a highly effective way to reduce IOP, is invasive and poses a high risk of postoperative complications [17]. Micro-invasive glaucoma surgery (MIGS), a relatively novel category of surgical treatments, has a more favorable safety profile compared to trabeculectomy and provides an effective alternative to antiglaucoma medications in reducing IOP [18].

The iStent® trabecular micro-bypass stent system was the first MIGS developed and has been available in Japan for the treatment of mild to moderate OAG combined with cataract surgery since 2016. It is a titanium, L-shaped

stent (1.00 mm by 0.33 mm) that is inserted *ab interno* into the trabecular meshwork to re-establish flow of the aqueous humor into Schlemm's canal. The iStent, whether combined with cataract surgery or as a standalone procedure, is well tolerated and has demonstrated sustained long-term efficacy in reducing IOP and medication burden significantly in OAG [19–26].

To date, there are relatively limited data evaluating the role of iStent trabecular micro-bypass stent system in the Japanese population. The study by Shiba et al. which investigated two iStents as a standalone procedure was limited in size ($n = 10$ eyes) and in scope (only POAG included) [27]. Nitta et al. evaluated one iStent combined with phacoemulsification in patients of all glaucoma subtypes over 2 years, but the study was modestly sized ($n = 73$ eyes) and retrospective [28]. The present study sought to fill these data gaps in the current iStent literature in the Japanese population. It is currently the largest trabecular micro-bypass longitudinal real-world study in Japan, with data through 2 years postoperatively. The study's main objectives were (1) to measure changes in IOP and medication use from preoperative values, and (2) to evaluate the proportion of eyes that achieved success at 6, 12, and 24 months postoperatively, in eyes with OAG implanted with iStent combined with phacoemulsification.

METHODS

Study Design

This was a 24-month, prospective, longitudinal, observational post-marketing surveillance (PMS) study conducted between July 2017 and September 2020 in Japan. Preoperative data were obtained from eyes before they underwent surgical implantation of iStent trabecular micro-bypass stent combined with phacoemulsification. Patients were then followed for a period of 2 years postoperatively. Data obtained preoperatively and postoperatively were included in the analysis. The management of postoperative glaucoma medications was at the discretion of the treating surgeon.

This PMS was conducted as part of the mandatory actions for approval of iStent in Japan and complied with the Japanese ministerial ordinance on Good Post-marketing Study Practice. According to this ordinance, ethical approval of the participating medical institutions and patient consent is not required. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Participants

The inclusion criterion was all eyes implanted with one iStent in conjunction with phacoemulsification.

Outcomes

IOP, number of antiglaucoma medications, visual field mean deviation (VF MD), and central corneal endothelial cell density (ECD) data were collected preoperatively and measured at defined time points postoperatively (day 1 [POD1], week 1 [POW1], month 1 [POM1], month 3 [POM3], month 6 [POM6], month 12 [POM12], and month 24 [POM24]).

The proportion of eyes that achieved treatment success postoperatively was evaluated at POM6, POM12, and POM24. Treatment success was defined by the following: (1) the postoperative IOP was lower than the preoperative IOP and the number of postoperative medications was the same or lower than the preoperative numbers at two consecutive visits after 3 months follow-up, or (2) the number of postoperative medications was lower than the number of preoperative medications and the postoperative IOP was the same as preoperative IOP, and (3) not requiring any laser or surgical glaucoma interventions at any time postoperatively. Treatment failure was defined as the occurrence of any of the following: (1) a lower postoperative IOP compared to preoperative IOP but an increased number of postoperative medications from preoperative value, (2) equal or higher postoperative IOP and number of medications compared to preoperative values, or (3) completion of any laser or

surgical glaucoma intervention at any time postoperatively.

In addition, effectiveness was evaluated by determining the proportion of medication-free eyes at POM24, and the proportion of medication-free eyes that had IOP of $\leq$ 15 mmHg and $\leq$ 18 mmHg at POM24. The IOP thresholds of $\leq$ 15 mmHg and $\leq$ 18 mmHg were selected after taking into consideration the reported outcomes from the trabeculectomy study by Kirwan et al. [29], other MIGS studies [25, 30], and the World Glaucoma Association guidelines for clinical research [31].

Safety outcomes included perioperative or postoperative adverse events, stent malfunctions, and secondary glaucoma procedures (both laser and surgical). These were reported by the physicians and based on their clinical judgement.

Statistical Analysis

IOP, number of antiglaucoma medications, VF MD, and ECD outcomes were presented as mean (standard deviation, SD) or median (interquartile range, IQR). A Shapiro–Wilk *W* test was performed to assess the normality of the IOP data. The test showed that the IOP variable was not normally distributed (except for M24 IOP) and therefore comparison between the preoperative and postoperative outcomes of IOP was determined via a Wilcoxon signed-rank test with a Bonferroni correction. Statistical significance between the preoperative and postoperative outcomes of medications was determined via a Wilcoxon signed-rank test with a Bonferroni correction as count data were utilized. A McNemar test was used for paired proportions. Statistical significance is indicated by a p value of < 0.05 for both Bonferroni adjusted comparisons and paired proportions.

Three-level multilevel mixed models were used to account for repeated measures from the same eye and clustering of eyes by hospital. A multilevel mixed effects linear model was utilized to reconfirm the Wilcoxon signed-rank test results for mean IOP from each postoperative time point compared to the preoperative values in the overall cohort and to explore associations between patient baseline characteristics and changes in IOP while accounting for use of different tonometer or same tonometer per eye over the follow-up period. To explore correlations between patient baseline characteristics and changes in number of medications, a multilevel mixed effects negative binomial model was employed as count data were utilized. Kaplan–Meier survival estimates were utilized to determine the proportion of patients that achieved treatment success postoperatively.

Safety outcomes were presented as the incidence of perioperative or postoperative adverse events, stent malfunctions, or secondary glaucoma surgery among all eyes enrolled.

RESULTS

Patient Disposition and Baseline Characteristics

Overall, 232 eyes were enrolled from 23 sites in Japan between July 2017 and October 2018 and underwent combined phacoemulsification and surgical implantation of iStent. There were 211, 202, and 190 eyes at POM6, POM12, and POM24, respectively. Of the 42 eyes that left the study by POM24, the majority (25/42) were due to non-clinical factors such as not being present at the hospital during the survey period (n = 18) or change in address (n = 7).

Table 1 shows the baseline demographics and preoperative characteristics of the overall cohort. The mean age of patients enrolled was 73.7 years (SD 8.6) and 42.2% of the patients were male. Around half of the patients (49.8%) enrolled in the study had mild glaucoma, as classified according to the staging system reported by Mills et al. [32]. At baseline, the mean IOP was 17.6 mmHg (SD 4.0) and the mean number of antiglaucoma medications was 2.2 (SD 1.2; range 0.0–5.0 medications). Most patients (62.9%) were receiving two or more antiglaucoma medications preoperatively. Among the patients enrolled in the study, 62.5% of patients had POAG, with a mean preoperative IOP of 18.5 mmHg (SD 4.2) and

Table 1 Patients' baseline and preoperative characteristics

Characteristics (n = 232)	Value
Age (years), mean (SD)	73.7 (8.6)
Gender (male), %	42.2
Eye (left), %	47.4
IOP (mmHg)	
Mean (SD)	17.6 (4.0)
Minimum, maximum	10, 40
Number of medications	
Mean (SD)	2.2 (1.2)
Median (IQR)	2.0 (1.0, 3.0)
Minimum, maximum	0, 5
0 medications (%)	3.0
1 medication (%)	34.1
2 medications (%)	25.4
> 2 medications (%)	37.5
Central corneal ECD (cell/mm^2), mean (SD)[a]	2536 (293)
Visual field mean deviation (dB), mean (SD)[b]	− 7.1 (5.4)
Glaucoma severity[a,c]	
Mild (%)	49.8
Moderate (%)	36.8
Advanced (%)	10.5
Severe (%)	2.9
OAG subtype	
POAG, n (%)	145 (62.5)
IOP, mean (SD)	18.5 (4.2)
Medications, mean (SD)	2.2 (1.3)
Median (IQR)	2.0 (1.0, 3.0)
NTG, n (%)	64 (27.6)
IOP, mean (SD)	15.3 (2.6)
Medications, mean (SD)	2.0 (1.0)
Median (IQR)	2.0 (1.0, 3.0)
XFG, n (%)	23 (9.9)
IOP, mean (SD)	18.6 (4.1)
Medications, mean (SD)	2.4 (1.2)
Median (IQR)	2.0 (1.0, 4.0)
Prior glaucoma surgery, n (%)	8 (3.5)
Cyclophotocoagulation, n	1
One selective laser trabeculoplasty, n	5
Two selective laser trabeculoplasties, n	2

ECD endothelial cell density, *IOP* intraocular pressure, *IQR* interquartile range, *NTG* normal-tension glaucoma, *OAG* open-angle glaucoma, *POAG* primary open-angle glaucoma, *SD* standard deviation, *XFG* exfoliative glaucoma

[a] n = 226

[b] n = 209

[c] Glaucoma staging system based on Mills et al. [32]

mean number of preoperative antiglaucoma medications of 2.2 (SD 1.3). For patients with NTG, the mean preoperative IOP was 15.3 mmHg (SD 2.6) and mean number of preoperative antiglaucoma medications was 2.0 (SD 1.0). For patients with exfoliative glaucoma (XFG), the mean preoperative IOP was 18.6 mmHg (SD 4.1) and mean number of preoperative antiglaucoma medications was 2.4 (SD 1.2).

Mean IOP over 24-Month Follow-Up

In the overall cohort, mean IOP reduced from 17.6 mmHg (SD 4.0) preoperatively to 14.3 mmHg (SD 3.0) at POM24 (Fig. 1). In eyes with both preoperative and POM24 IOP measurements, the mean IOP decreased by − 3.2 (SD 4.2) from baseline ($p < 0.05$).

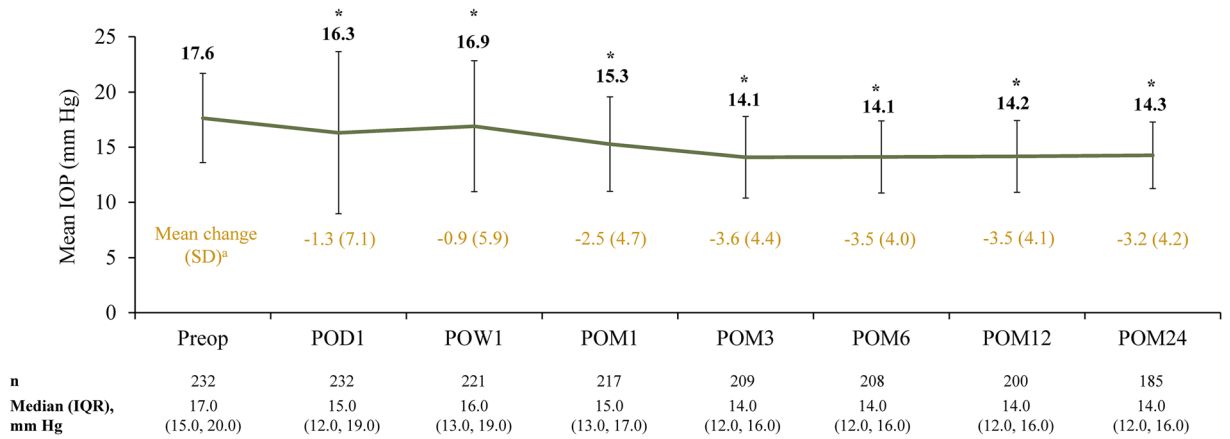

Fig. 1 Mean IOP in preoperative and postoperative periods. *Indicates statistical significance based on a Wilcoxon signed-rank test with a Bonferroni correction ($p < 0.05$); [a]indicates mean change (standard deviation) from baseline. *IOP* intraocular pressure, *IQR* interquartile range, *POD* postoperative day, *POM* postoperative month, *POW* postoperative week, *Preop* preoperative, *SD* standard deviation

Statistically significant reductions in mean IOP from preoperative value were demonstrated by the Wilcoxon signed-rank test, from POD1 to POM24 ($p < 0.05$); this was reconfirmed by multilevel linear mixed effects modeling which estimated reductions from POD1 (− 2.4 mmHg; 95% confidence interval [CI] − 4.5, 0.3) and over POM1 (− 3.3 mmHg; 95% CI − 4.5, − 2.0) to POM24 (− 3.5 mmHg; 95% CI − 4.9, − 2.2), with statistical significance at POD1 and from POM1 onwards in the overall cohort while holding other variables constant (Table 2). Furthermore, the model showed no statistically significant association between changes in IOP and the use of the same or different tonometer for IOP measurement over the follow-up period (Table 2).

The exploration of patient baseline characteristics associated with mean IOP change over time indicated that stratification by preoperative IOP (≤ 15 mmHg, > 15 to 21 mmHg, or > 21 mmHg) and preoperative medication usage (medication-free or on medication) interacted with visit, signifying differences in IOP changes over time relative to the reference group (Table 2). When preoperative IOP > 15 to 21 mmHg was used as the reference group, the mean preoperative IOP was higher in the > 21 mmHg preoperative group by 6.7 mmHg (95% CI 5.3, 8.2) and lower in the ≤ 15 mmHg preoperative group by 3.4 mmHg (95% CI − 4.4, − 2.5), while keeping all other variables constant. At each visit versus baseline, the group with preoperative IOP > 21 mmHg had greater IOP reductions versus the group with preoperative IOP > 15–21 mmHg, while keeping all other variables constant. Those eyes with IOP ≤ 15 mmHg preoperatively had smaller IOP reductions at each visit from POM1 through POM24 versus baseline compared with eyes with preoperative IOP > 15–21 mmHg (Table 2).

At baseline, eyes that were medication-free were estimated to have a mean IOP of 1.6 mmHg (95% CI − 2.6, − 0.5) lower than the mean IOP in eyes on medications. Over the follow-up period from POW1 through POM12 versus baseline, eyes that were originally medication-free were predicted to have greater IOP reductions versus those that were on medications preoperatively, while keeping all other variables constant. There is a significant interaction between medication use and visit: the difference in IOP decreased from POW1 to POM24, with the difference between groups being not statistically significant by POM24. Age group, prior glaucoma surgery, and OAG subtype did not have a statistically significant interaction with visit, indicating that the relationship between the respective subgroups and IOP reduction did not change over time.

Table 2 Multilevel mixed effects linear model results exploring associations between patient baseline characteristics and changes in IOP

Variable	Unit change (mmHg)	95% CI	*p* value
Constant	18.6	17.7, 19.5	< 0.01*
Visits			
Preop (reference)	–	–	–
POD1	− 2.4	− 4.5, − 0.3	0.02*
POW1	0.7	− 1.6, 3.1	0.56
POM1	− 3.3	− 4.5, − 2.0	< 0.01*
POM3	− 4.0	− 5.2, − 2.8	< 0.01*
POM6	− 3.7	− 5.0, − 2.3	< 0.01*
POM12	− 3.6	− 4.8, − 2.4	< 0.01*
POM24	− 3.5	− 4.9, − 2.2	< 0.01*
Age group	− 0.5	− 1.4, 0.5	0.33
Age group × visit	NS	NS	NS
Prior glaucoma surgery	2.0	− 1.8, 5.8	0.30
Prior glaucoma surgery × visit	NS	NS	NS
OAG subtype			
POAG (reference)	–	–	–
NTG	− 1.0	− 1.7, − 0.2	0.01*
XFG	− 0.7	− 1.7, 0.3	0.17
OAG subtype × visit	NS	NS	NS
Preop IOP (mmHg)			
> 15 to 21 (reference)	–	–	–
≤ 15	− 3.4	− 4.4, − 2.5	< 0.01*
> 21	6.7	5.3, 8.2	< 0.01*
Preop IOP × visit			
> 15 to 21 × visit (reference)	–	–	–
≤ 15 × POD1	− 0.5	− 3.3, 2.4	0.75
≤ 15 × POW1	− 0.3	− 1.6, 1.1	0.72
≤ 15 × POM1	1.9	1.0, 2.8	< 0.01*
≤ 15 × POM3	1.5	0.6, 2.5	< 0.01*
≤ 15 × POM6	1.8	0.8, 2.7	< 0.01*
≤ 15 × POM12	2.3	1.6, 3.0	< 0.01*
≤ 15 × POM24	2.1	1.3, 2.9	< 0.01*
> 21 × POD1	− 3.9	− 7.0, − 0.7	0.02*
> 21 × POW1	− 5.0	− 7.5, − 2.5	< 0.01*
> 21 × POM1	− 4.4	− 7.1, − 1.7	< 0.01*
> 21 × POM3	− 5.5	− 7.6, − 3.3	< 0.01*
> 21 × POM6	− 4.8	− 6.9, − 2.8	< 0.01*
> 21 × POM12	− 4.5	− 6.7, − 2.3	< 0.01*
> 21 × POM24	− 5.8	− 7.8, − 3.8	< 0.01*
Preop medication			
On medication (reference)	–	–	–

Table 2 continued

Variable	Unit change (mmHg)	95% CI	*p* value
No medication	− 1.6	− 2.6, − 0.5	< 0.01*
Preop medication × visit			
On medication × visit (reference)	–	–	–
No medication × POD1	− 2.2	− 5.9, 1.6	0.26
No medication × POW1	− 4.1	− 5.5, − 2.6	< 0.01*
No medication × POM1	− 5.3	− 9.0, − 1.6	< 0.01*
No medication × POM3	− 3.4	− 6.2, − 0.6	0.02*
No medication × POM6	− 2.7	− 4.2, − 1.3	< 0.01*
No medication × POM12	− 2.7	− 4.3, − 1.1	< 0.01*
No medication × POM24	− 1.4	− 2.9, 0.2	0.08
Tonometer			
Same tonometer (reference)	–	–	–
Different tonometer	1.0	− 0.3, 2.2	0.13

× denotes interaction terms added to the regression model to investigate the two-way interactions of specified variables

CI confidence interval, *IOP* intraocular pressure, *NS* not significant, *NTG* normal-tension glaucoma, *OAG* open-angle glaucoma, *POAG* primary open-angle glaucoma, *POD* postoperative day, *POM* postoperative month, *POW* postoperative week, *Preop* preoperative, *XFG* exfoliative glaucoma

*Statistically significant value

Number of Antiglaucoma Medications over 24 Months

Overall, the mean number of medications reduced from 2.2 (SD 1.2; median [IQR] 2.0 [1.0, 3.0]) preoperatively to 0.7 (SD 1.2; median [IQR] 0.0 [0.0, 1.0]) at POM24 (Fig. 2). In eyes with both preoperative and POM24 medication data, the mean POM24 antiglaucoma medications decreased by − 1.5 (SD 1.3) from the preoperative period ($p < 0.05$). Statistically significant reductions in mean antiglaucoma medications were demonstrated by a Wilcoxon signed-rank test with a Bonferroni correction over POD1 to POM24 ($p < 0.05$) from the preoperative period; these were reconfirmed by multilevel negative binomial regression modeling that demonstrated relative reductions in the number of medications over POD1 to POM24 compared to their preoperative values, while keeping all other variables constant (Table 3). In addition, the proportion of eyes that were medication-free increased significantly from 3.2% (6/185) preoperatively to 67.6% (125/185) at POM24 ($p < 0.0001$).

IOP and Antiglaucoma Medications by OAG Subtype

Figure 3 demonstrates the changes in mean IOP and mean number of antiglaucoma medications by each OAG subtype.

For POAG, the mean IOP was reduced from 18.5 mmHg (SD 4.2) preoperatively to 14.6 mmHg (SD 3.2) at POM24 (Fig. 3a). In POAG eyes with IOP data at both preoperative and POM24 visits, the mean change in IOP from the preoperative period to POM24 was − 3.9 (SD 4.7) ($p < 0.05$). Statistically significant reductions in mean IOP from preoperative were demonstrated over POD1 to POM24 ($p < 0.05$). The mean number of medications was reduced from 2.2 (SD 1.3; median [IQR] 2.0 [1.0, 3.0]) preoperatively to 0.9 (SD 1.3; median [IQR] 0.0 [0.0, 2.0]) at POM12, and to 1.0 (SD 1.4; median [IQR] 0.0 [0.0, 2.0]) at POM24 (Fig. 3b). Statistically significant reductions in the mean number of medications were demonstrated over

POD1 to POM24 compared to the preoperative time point ($p < 0.05$).

For NTG, the mean IOP was reduced from 15.3 mmHg (SD 2.6) preoperatively to 13.5 mmHg (SD 2.3) at POM24 (Fig. 3a). In NTG eyes with data at both preoperative and POM24 visits, the mean change in IOP from the preoperative period to POM24 was − 1.6 (SD 2.6) ($p < 0.05$). Statistically significant reductions in mean IOP were demonstrated over POM1 to POM24 compared to the preoperative time point ($p < 0.05$). The mean number of antiglaucoma medications was reduced from 2.0 (SD 1.0; median [IQR] 2.0 [1.0, 3.0]) preoperatively to 0.1 (SD 0.4; median [IQR] 0.0 [0.0, 0.0]) at POM12, and to 0.2 (SD 0.6; median [IQR] 0.0 [0.0, 0.0]) at POM24 (Fig. 3b). Statistically significant reductions in the mean number of medications were demonstrated over POD1 to POM24 compared to the preoperative time point ($p < 0.05$).

For XFG, the mean IOP was reduced from 18.6 mmHg (SD 4.1) preoperatively to 14.4 mmHg (SD 3.3) at POM24 (Fig. 3a). In XFG eyes with data at both preoperative and POM24 visits, the mean change in IOP from baseline to POM24 was − 3.8 (SD 4.0) ($p < 0.05$). Statistically significant reductions in mean IOP were demonstrated over POM1 to POM24 compared to the preoperative time point ($p < 0.05$). The mean number of antiglaucoma medications reduced from 2.4 (SD 1.2; median [IQR] 2.0 [1.0, 4.0]) preoperatively to 0.6 (SD 1.2; median [IQR] 0.0 [0.0, 0.0]) at POM12, and to 0.7 (SD 1.0; median [IQR] 0.0 [0.0, 1.0]) at POM24 (Fig. 3b). Statistically significant reductions in mean number of medications were demonstrated over POD1 to POM24 compared to the preoperative time point ($p < 0.05$).

In the multilevel mixed effects linear modeling for mean IOP, the OAG subtype and visit interaction was not statistically significant while keeping all other variables constant (Table 2). However, multilevel negative binomial regression modeling examining the association between patient baseline characteristics and medication changes showed that OAG subtype and visit interaction was statistically significant (Table 3). With POAG as the reference group, NTG eyes were predicted to have additional medication reductions from baseline at every time point, keeping all other variables constant. The interactions between XFG and time and POAG and time were not statistically significant, suggesting the changes in medication were similar over time in these two subgroups.

Treatment Success

On the basis of Kaplan–Meier survival analysis, 96.8%, 95.3%, and 93.7% of eyes achieved

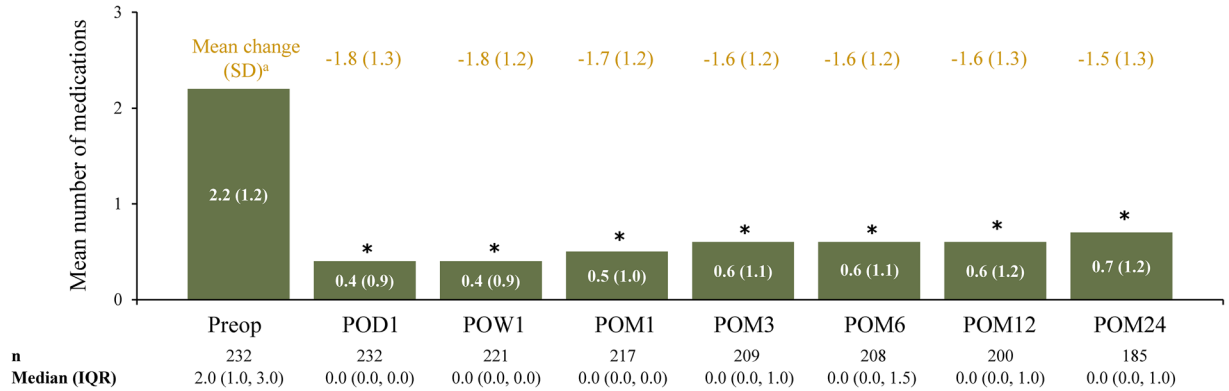

Fig. 2 Mean number of antiglaucoma medications in preoperative and postoperative periods. *Indicates statistical significance based on a Wilcoxon signed-rank test with a Bonferroni correction ($p < 0.05$); [a]indicates mean change (standard deviation) from baseline. *IOP* intraocular pressure, *IQR* interquartile range, *POD* postoperative day, *POM* postoperative month, *POW* postoperative week, *Preop* preoperative, *SD* standard deviation

Table 3 Multilevel mixed effects negative binomial model results exploring associations between patient baseline characteristics and medication changes

Variable	Relative risk	95% CI	*p* value
Constant	1.9	1.4, 2.8	< 0.01*
Visits			
Preop (reference)	–	–	–
POD1	0.2	0.1, 0.4	< 0.01*
POW1	0.3	0.1, 0.6	< 0.01*
POM1	0.3	0.1, 0.8	0.02*
POM3	0.4	0.2, 0.9	0.03*
POM6	0.3	0.1, 1.0	0.05*
POM12	0.4	0.2, 1.0	0.04*
POM24	0.4	0.2, 1.0	0.05*
Age			
< 65 years old (reference)	–	–	–
≥ 65 years old	0.8	0.7, 1.0	0.01*
Age × visit	NS	NS	NS
OAG subtype			
POAG (reference)	–	–	–
NTG	1.5	1.0, 2.1	0.06
XFG	1.2	0.8, 2.0	0.37
OAG subtype × visit			
POAG × visit (reference)	–	–	–
NTG × POD1	0.2	0.1, 0.9	0.04*
NTG × POW1	0.3	0.1, 0.6	< 0.01*
NTG × POM1	0.4	0.1, 0.9	0.03*
NTG × POM3	0.3	0.1, 0.7	< 0.01*
NTG × POM6	0.3	0.1, 0.9	0.03*
NTG × POM12	0.1	0.0, 0.6	0.01*
NTG × POM24	0.2	0.1, 0.7	< 0.01*
XFG × POD1	0.6	0.2, 1.3	0.18
XFG × POW1	0.6	0.1, 2.5	0.49
XFG × POM1	0.9	0.5, 1.6	0.73
XFG × POM3	0.9	0.5, 1.7	0.76
XFG × POM6	0.9	0.5, 1.8	0.82
XFG × POM12	0.8	0.3, 1.7	0.48
XFG × POM24	0.7	0.4, 1.3	0.25
Preop IOP (mmHg)			
> 15 to 21 (reference)	–	–	–
≤ 15	0.9	0.7, 1.3	0.7
> 21	0.9	0.7, 1.2	0.5
Preop IOP × visit	NS	NS	NS

CI confidence interval, *IOP* intraocular pressure, *NS* not significant, *NTG* normal-tension glaucoma, *OAG* open-angle glaucoma, *POAG* primary open-angle glaucoma, *POD* postoperative day, *POM* postoperative month, *POW* postoperative week, *Preop* preoperative, *XFG* exfoliative glaucoma

*Statistically significant value

treatment success at POM6, POM12, and POM24 time points, respectively (Supplementary Fig. 1). Seven eyes failed as both postoperative IOP and number of medications were greater than or equal to their preoperative values; four eyes failed from having lower IOP but with greater number of medications than preoperative values; and two eyes failed from having any laser or invasive glaucoma surgery. NTG eyes and eyes that were medication-free at baseline were all successful. As a result of the 100% success rate, it was not possible to include these subgroups in the Cox proportional hazards regression model and their effect was only investigated in Kaplan–Meier analyses. Patient characteristics such as age group (≤ 65 and > 65 years old), preoperative IOP group, and OAG subtype (i.e., XFG, POAG) were not associated with treatment success in the entire cohort.

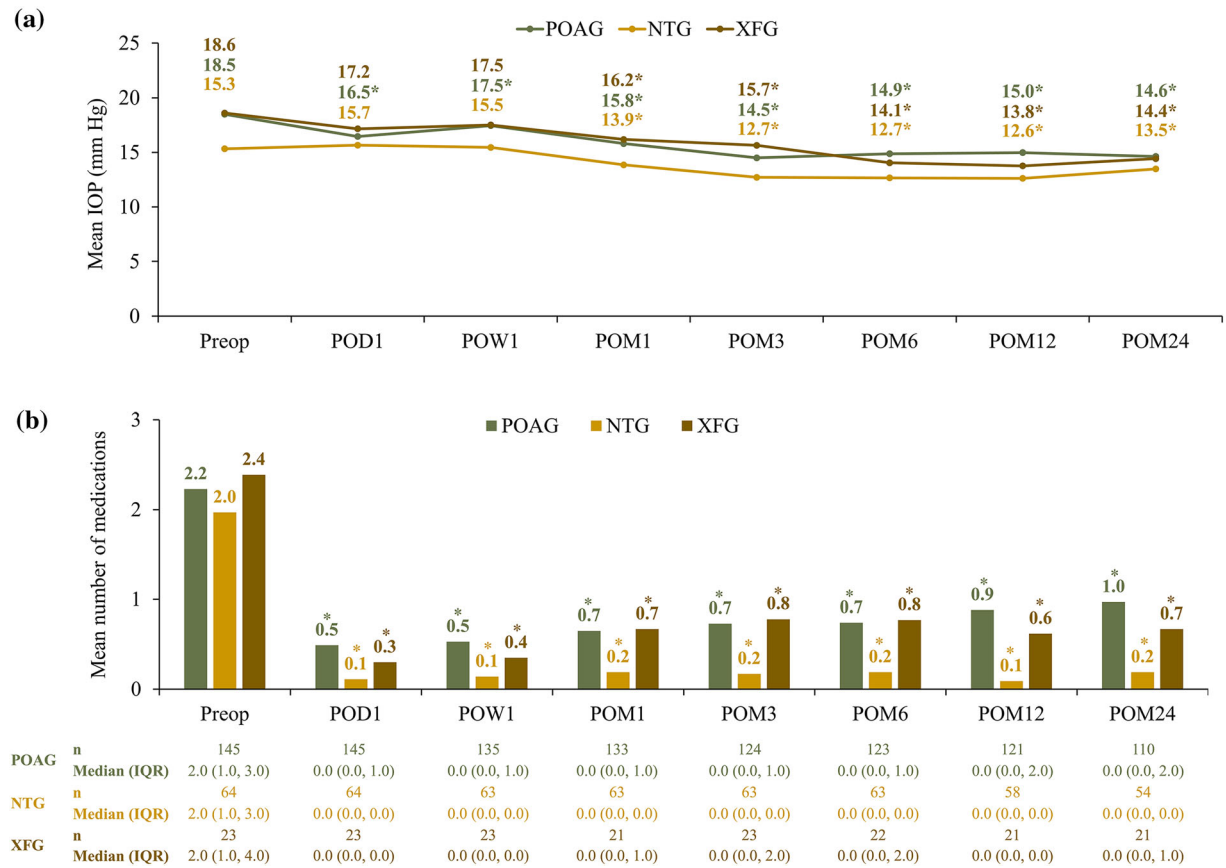

Fig. 3 **a** Mean IOP and **b** mean number of medications in preoperative and postoperative periods by OAG subtype. *Indicates statistical significance based on a Wilcoxon signed-rank test with a Bonferroni correction for IOP and for medication ($p < 0.05$). *IOP* intraocular pressure, *IQR* interquartile range, *NTG* normal-tension glaucoma, *POAG* primary open-angle glaucoma, *POD* postoperative day, *POM* postoperative month, *POW* postoperative week, *Preop* preoperative, *XFG* exfoliative glaucoma

Among eyes with POAG, 95.3%, 92.9%, and 90.3% achieved treatment success at POM6, POM12, and POM24, respectively (Fig. 4). All eyes with NTG (100.0%) and 95.7% of eyes with XFG achieved treatment success at POM6, POM12, and POM24 (Fig. 4). The Kaplan–Meier survival curve for NTG eyes was statistically significantly different from those for POAG eyes based on the log-rank test ($p = 0.0096$).

In eyes that were measured with the same type of tonometer preoperatively and at POM24, the proportion of eyes that had IOP ≤ 18 mmHg and were medication-free increased significantly from 2.3% (4/173) preoperatively to 64.2% (111/173) at POM24 ($p < 0.0001$), and the proportion of eyes that had IOP ≤ 15 mmHg and were medication-free increased significantly from 1.2% (2/173) preoperatively to 50.9% (88/173) at POM24 ($p < 0.0001$).

Safety

Adverse events were reported in a total of 11 out of 232 eyes (4.7%), with the most common adverse event being elevated IOP (7/232 or 3.0%) (Table 4). Six eyes with elevated IOP eventually had secondary glaucoma surgery. A total of 13 out of 232 eyes (5.6%) experienced stent malfunctions, with stent occlusion being the most common (8/232 or 3.4%). Five eyes

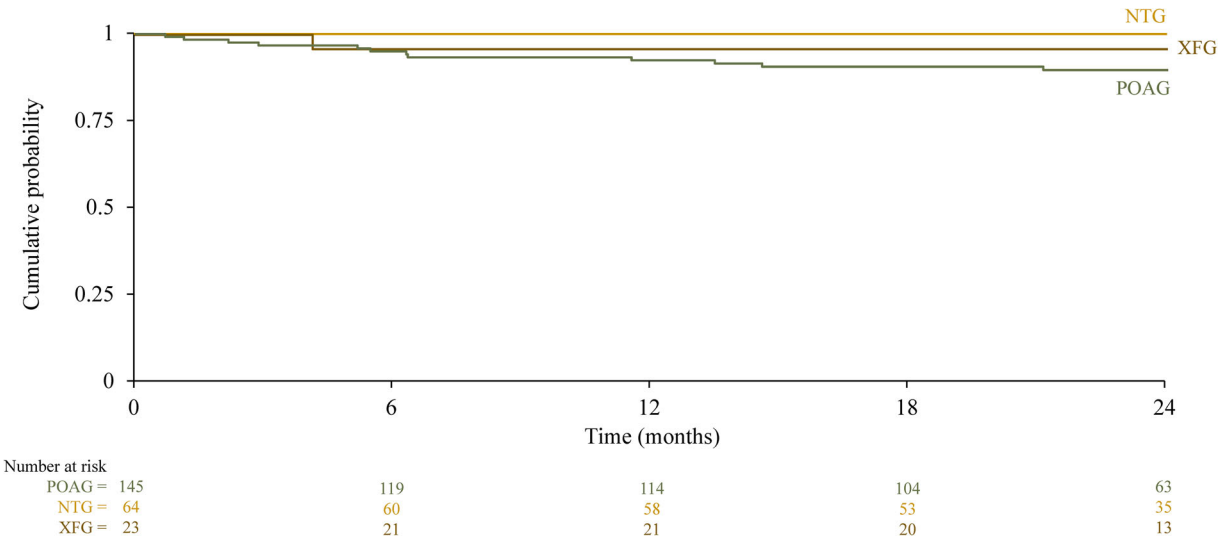

Fig. 4 Kaplan–Meier % success by OAG subtype. Note: treatment success was defined by the following: (1) postoperative IOP was lower than preoperative IOP and the number of postoperative medications was the same or lower than the preoperative values at two consecutive visits after 3 months follow-up, or (2) number of postoperative medications used was lower than the number of preoperative medications used and postoperative IOP was the same as preoperative IOP, and (3) not requiring any laser or surgical glaucoma interventions at any time postoperatively. Failure was defined as the occurrence of any of the following: (1) a lower postoperative IOP compared to preoperative IOP, but increased number of postoperative medications used from preoperative values, (2) equal or higher postoperative IOP and number of medications compared to preoperative values, or (3) completion of any laser or surgical glaucoma intervention at any time postoperatively. *NTG* normal-tension glaucoma, *POAG* primary open-angle glaucoma, *XFG* exfoliative glaucoma

with stent occlusions were resolved with YAG laser while one eye had selective laser trabeculoplasty. In the stent malposition category, three eyes had stents in close contact with the iris with no occlusion and two eyes were malpositioned. A total of six eyes (6/232 or 2.6%) required secondary glaucoma procedures (Table 4).

The average VF MD improved from − 6.6 dB preoperatively to − 6.1 dB at POM24 ($p = 0.0423$). Mean central corneal ECD was 2536 cells/mm^2 (SD 293) at the preoperative visit, 2482 cells/mm^2 (SD 326) at POM6, 2516 cells/mm^2 (SD 328) at POM12, and 2477 cells/mm^2 (SD 382) at POM24. In the 71 eyes with both baseline and POM24 mean central ECD data, 6 eyes (8.5%) had mean central corneal ECD reductions of > 30%.

DISCUSSION

To date, this was the largest prospective real-world longitudinal study of iStent trabecular micro-bypass with phacoemulsification in Japan. Given the limited number of real-world published data on trabecular micro-bypass in Japanese populations, the present study supplies valuable evidence of the effectiveness and safety profile of iStent in conjunction with cataract surgery in Japan. The results showed a significant reduction in mean IOP and mean number of antiglaucoma medications after one iStent implantation combined with phacoemulsification at the end of 2 years, in the overall cohort as well as across OAG subgroups (POAG, NTG, and XFG). In the overall cohort, between 93.7% and 96.8% of eyes achieved treatment success at study visits through POM24. The safety profile remained highly

Table 4 Safety

Event	*n* (%)
Adverse events	11 (4.7)
Elevated IOP	7 (3.0)
PAS formation	3 (1.3)
Uveitis	3 (1.3)
Macular edema	1 (0.4)
Capsule rupture	1 (0.4)
IOL dislocation	1 (0.4)
Secondary cataract	1 (0.4)
Vitreous loss	1 (0.4)
Stent malfunctions	13 (5.6)
Stent occlusion	8 (3.4)
Stent malposition	5 (2.2)
Secondary glaucoma surgery	6 (2.6)
Ahmed valve implantation	1 (0.4)
iStent removal and Express implantation	1 (0.4)
SLT, iStent removal, and Tanito Microhook	1 (0.4)
SLT, iStent removal, and trabeculectomy	1 (0.4)
Trabeculectomy	2 (0.9)

Incidence is number of eyes with adverse events or stent malfunctions or additional glaucoma surgery over total number of eyes. Summary of adverse events represents all adverse events regardless of whether it is stent-related

IOL intraocular lens, *IOP* intraocular pressure, *PAS* peripheral anterior synechiae, *SLT* selective laser trabeculoplasty

favorable, with only two eyes (< 1%) needing filtering surgery during follow-up.

This post-marketing surveillance study in Japanese eyes is consistent with extensive international evidence demonstrating efficacy of iStent in conjunction with phacoemulsification in reducing IOP. The study demonstrated a significant IOP reduction of 19.1% at POM24 after iStent implantation with phacoemulsification. This was similar to the results of the 2-year retrospective study ($n = 73$) by Nitta et al. in Japan, which reported a statistically significant IOP reduction of 18.0% at POM24 [28]. In comparison to studies in other countries with iStent combined with cataract surgery, the IOP reduction in the present study was less marked than the reduction reported in a German study (38.8%) in which patients had higher baseline IOP (mean 23.7 mmHg) [22]. This latter comparison aligns with our finding that eyes with higher preoperative IOP (> 21 mmHg) were estimated to have greater IOP reductions compared to eyes with preoperative IOP > 15–21 mmHg.

In addition to lowering IOP, the current study demonstrated a statistically significant reduction in the mean number of antiglaucoma medications by 67.4%. This equated to the elimination of approximately 1.5 mean number of medications at POM24 after iStent implantation with phacoemulsification from the patients' preoperative regimens (from 2.2 mean medications preoperatively to 0.7 mean medications at POM24). The trend in medication reduction is in line with data from Nitta et al. in Japan which revealed a statistically significant reduction in mean number of antiglaucoma medications by 81.1% at POM24 (from 2.0 mean medications preoperatively to 0.4 mean medications at POM24) [28]. In the aforementioned Spanish study, the mean number of antiglaucoma medications was reduced by 63.8% at POM24 (from 1.3 mean medications preoperatively to 0.5 mean medications at POM24) [33]; and in the German study, the mean number of medications was reduced by 90.0% at POM24 (from 2.0 mean medications preoperatively to 0.2 mean medications at POM24) [22]. Although antiglaucoma medications are standard first-line treatment for OAG [34], they are associated with various issues such as adverse ocular and systemic effects, and poor patient compliance [16, 35]. The present study's demonstration of reduced number of medications after iStent implantation with phacoemulsification supports the role of combination iStent treatment in the management of OAG and alleviating medication burden.

Reductions in mean IOP and mean number of medications were also observed across all OAG subtypes (POAG, NTG, and XFG). The mean preoperative and postoperative IOP in NTG eyes was the lowest of the glaucoma

subtypes. Despite the well-known difficulty of further reducing an IOP that is already relatively low in NTG eyes [36], the mean IOP reduction in NTG eyes was significant (from 15.3 mmHg preoperatively to 13.5 mmHg at POM24, $p < 0.05$). Meanwhile, mean number of medications in NTG eyes also decreased significantly from the preoperative period to POM24 (from 2.0 mean medications preoperatively to 0.2 mean medications at POM24, $p < 0.05$). Similar to our study, Nitta et al. also reported meaningful reductions of mean IOP and number of antiglaucoma medications at POM24 across all OAG subtypes, with NTG eyes having the lowest IOP and medication burden of all the subtypes at POM24 [28]. Given the challenge of reducing a low IOP when managing NTG [36], the results of these studies support the use of iStent in the NTG subtype. Such findings are particularly useful for the Japanese population, given that NTG is the most common OAG subtype in Japan [12].

Treatment success was defined by the following in the current study: (1) the postoperative IOP was lower than the preoperative IOP and the number of postoperative medications was the same or lower than the preoperative values at two consecutive visits after 3 months follow-up, or (2) the number of postoperative medications was lower than the number of preoperative medications and the postoperative IOP was the same as preoperative IOP, and (3) not requiring any laser or surgical glaucoma interventions at any time postoperatively. At POM24 after iStent implantation with phacoemulsification, 93.7% of patients in this study achieved treatment success. The Spanish study, in which 72.4% of patients achieved treatment success (defined as $\geq$ 20% reduction in postoperative IOP from preoperative IOP) at POM24 [33]. The current study also reported that 67.6% of eyes became medication-free at POM24 compared to 3.2% preoperatively. Nitta et al. reported medication freedom in 77.0% of eyes at POM24 compared to 0.0% preoperatively [28], and Neuhann et al. reported medication freedom in 82.0% of eyes at POM24 compared to 5.0% preoperatively [22]. Given the adverse effects, ocular toxicity, high economic burden, and reduced vision-related quality of life were associated with long-term antiglaucoma medications [35, 37–40], achieving medication-free status would be advantageous for both patients and health care providers (HCPs).

In addition to assessing the percentage of medication-free eyes, evaluating the proportion of eyes that achieved IOP of $\leq$ 15 mmHg and $\leq$ 18 mmHg also provides an indication of treatment success. This study reported that 50.9% of medication-free eyes had IOP $\leq$ 15 mmHg at POM24 compared to 1.2% preoperatively ($p < 0.0001$), while 64.2% of medication-free eyes had IOP $\leq$ 18 mmHg at POM24 compared to 2.3% preoperatively ($p < 0.0001$). In eyes that were either on medication or medication-free, Nitta et al. showed that 81.0% of eyes had IOP $\leq$ 15 mmHg at POM24 compared to 42.0% preoperatively, and 87.0% of eyes had IOP $\leq$ 18 mmHg in POM24 compared to 75.0% preoperatively [28]. Neuhann et al. reported that 70.0% of eyes had IOP $\leq$ 15 mmHg at POM24 compared to 2.0% preoperatively, and 95.0% of eyes had IOP $\leq$ 18 mmHg at POM24 compared to 14.0% preoperatively [22]. These findings collectively demonstrate that a large proportion of patients achieve the desired target IOP after iStent implantation in conjunction with cataract surgery.

In this surveillance study, 8.5% of eyes with mean central ECD data at baseline and POM24 exhibited ECD reductions of > 30%. Without a control group, it is difficult to identify the cause; however, on the basis of the iStent *inject*, the second-generation iStent technology, combined cataract surgery randomized clinical trial, the percentage of eyes with endothelial cell loss > 30% at POM24 was 10.4% in the treatment group and 9.5% in the cataract surgery only group [41]. Hence, one can consider that the ECD reduction of > 30% in this study is within reasonable ranges for standard ophthalmic procedures. The safety profile in this study was consistent with other iStent implantation and cataract surgery studies [22, 28, 33, 41]. The iStent device and *ab interno* trabecular microbypass approach were designed to allow safer surgical placement compared to larger and more invasive glaucoma surgeries (such as

trabeculectomy or tube shunt implantation) which have a higher risk of postoperative complications [41]. Consistent with the intended purpose of iStent's design to allow safer surgical placement, the present study showed very low rates of adverse events, and an absence of complications associated with traditional bleb-forming glaucoma surgeries such as endophthalmitis, hypotony, bleb infections, bleb leaks, and subconjunctival fibrosis [42–45].

The main study limitation was the lack of a control group of patients receiving phacoemulsification alone and long-term follow-up, which would determine whether iStent is effective in controlling visual field impairment. However, the characteristics of the patients included in this 2-year study, including preoperative medication burden and surgical history, and postoperative care were reflective of routine clinical practice in Japan. This enhances the applicability of the study, enabling ophthalmologists to incorporate its findings when considering surgical treatment options for their patients with OAG.

While this study investigated iStent, the second-generation iStent *inject* [41] and its enhanced iStent *inject* W [46] have since been commercially released and consist of two micro stents preloaded into a single-use injector. The stents have the same mechanism of action as iStent but create two bypasses through the trabecular meshwork and comprise a central outlet and four side flow outlets to provide multidirectional flow in Schlemm's canal. Retrospective studies have shown better IOP reductions with iStent *inject* vs. iStent combined with cataract surgery while maintaining the similar beneficial safety profile of iStent [47–49].

CONCLUSION

This prospective 2-year post-marketing surveillance study of iStent implantation, the largest study conducted in Japan to date, demonstrated the clinical benefit and safety of the iStent trabecular micro-bypass stent system with phacoemulsification. The results of this study align with existing studies on the use of iStent, which have consistently shown significant reductions in IOP and antiglaucoma medications, alongside an excellent safety profile. Outcomes from the current study suggest that one iStent combined with phacoemulsification is a safe and valuable MIGS treatment modality for Japanese patients with OAG, who are hoping to lower their IOP, reduce their topical medication burden, and avoid the postoperative complications associated with more invasive traditional OAG surgeries.

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Compliance with Ethics Guidelines. This PMS was conducted as part of the mandatory actions for approval of iStent in Japan and complied with the Japanese ministerial ordinance on Good Post-marketing Study Practice. According to this ordinance, ethical approval of the participating medical institutions and patient consent is not required. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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