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Randomized Noninferiority Trial of Direct Selective Laser Trabeculoplasty in Open-Angle Glaucoma and Ocular Hypertension

GLAUrious Study

Gus Gazzard, MA(Cantab) FRCOphth,[1,2] Nathan Congdon, MD MPH,[3,4,5] Augusto Azuara-Blanco, PhD,[3] Eytan Z. Blumenthal, MD,[6,7] Ketevan Gomelauri, MD,[8] Monika Zaliniyan, MD,[9] Carlo E. Traverso, MD,[10] Zohar Bracha, MD,[11] Ana Dvalishvili, MD,[12] Yoram Solberg, PhD,[13] Michael Belkin, MA(Cantab) MD,[13,14] Thomas W. Samuelson, MD,[15] on behalf of the GLAUrious Study Group

Purpose: Effective glaucoma treatment is limited by nonadherence to medications and access to selective laser trabeculoplasty (SLT). The GLAUrious study compared automated, gonioscopy-free, noncontact, image-guided direct selective laser trabeculoplasty (DSLT) with conventional SLT in open-angle glaucoma (OAG) and ocular hypertension (OHT) to reduce intraocular pressure (IOP).

Design: Prospective, multicenter, randomized, controlled, evaluator-masked noninferiority trial.

Participants: Participants aged ≥ 40 years with OAG or OHT, on 0–3 hypotensive medications at screening, and washout IOP of 22–35 mmHg at 14 centers.

Methods: After washout, 192 participants randomized 1:1 to DSLT (n = 99) or SLT (n = 93). Intraocular pressure was assessed before treatment and through 12 months after the procedure, with washout IOP at baseline and 6 months.

Main Outcome Measures: Difference between DSLT and SLT in mean IOP change from baseline to 6 months (noninferiority margin, −1.95 mmHg). Exploratory efficacy and safety outcomes were assessed over 12 months.

Results: Of 156 participants (81.3%) without major protocol deviations analyzed at 6 months, the mean ± standard error (SE) washout IOP reduction from baseline was 5.5 ± 0.5 mmHg (−20.6%) after DSLT and 6.2 ± 0.5 mmHg (−23.6%) after SLT. The between-group difference (SLT−DSLT) in mean IOP reduction was −0.7 mmHg (95% confidence interval [CI], −2.2 to 0.8 mmHg; $P = 0.09$ [not significant] for noninferiority). Of 161 participants (83.9%) without major protocol deviations analyzed at 12 months, mean ± SE nonwashout IOP reduction from screening was 3.2 ± 0.4 mmHg (−12.2%) after DSLT and 3.2 ± 0.4 mmHg (−9.4%) after SLT. The between-group difference in mean IOP reduction was 0.01 mmHg (95% CI, −1.1 to 1.1 mmHg; $P < 0.001$ for noninferiority). Safety profiles were similar between groups, although clinically nonsignificant punctate subconjunctival hemorrhage was more frequent in the DSLT group. Ocular AEs generally were mild and resolved without intervention.

Conclusions: The 6-month primary end point did not achieve statistical noninferiority compared with conventional SLT. Nonetheless, DSLT was well tolerated and provided an effective reduction in IOP that was sustained for 12 months. Failure to demonstrate noninferiority does not prove inferiority; DSLT remains an effective option in the early treatment paradigm and can be considered as a first-line treatment when SLT is not readily accessible.

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Glaucoma is a chronic, incurable disease that can lead to progressive optic nerve and visual field damage. Worldwide, glaucoma affects an estimated 76 to 80 million people[1,2] and is the leading cause of irreversible blindness globally.[3] Initially, glaucoma is often an asymptomatic disease, and progression may be prevented or delayed by reducing intraocular pressure (IOP).[4] Therefore, the goal of glaucoma treatment is to maintain visual function through long-term management of IOP, with a minimal impact on patient quality of life. A worldwide need exists for effective

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treatment options for glaucoma that are well tolerated and have convenient methods of administration to maximize treatment accessibility and adherence. Treatment of open-angle glaucoma (OAG), the most prevalent form of glaucoma worldwide,[1,2] commonly is initiated with topical hypotensive medication in the form of eye drops.[3] However, unsatisfactory adherence to daily eye drop regimens is a drawback of this therapeutic approach. In the United States, it is estimated that 20% to 65% of patients with glaucoma do not take medications as prescribed.[5–7] Patients have indicated that common reasons for noncompliance include forgetfulness, medication cost, requirements to use the drops several times daily, difficulty obtaining medications, challenges with self-administration, the asymptomatic nature of the disease, and common side effects, such as ocular surface and dry eye diseases.[5,8]

Long-term clinical studies show that increased nonadherence to topical hypotensive medication is associated significantly with progression of visual field loss.[9] In addition, cost-effective and widely accessible glaucoma therapies are needed where treatment resources and options currently are limited and, hence, where populations have the highest prevalence of blindness resulting from glaucoma.[10,11] Alternative treatment options to daily eye drop medication would be welcomed globally, given the challenge of progressive visual loss resulting from poor adherence.[5,9]

Selective laser trabeculoplasty (SLT) is a long-standing alternative to topical hypotensive medication whereby laser treatment applied to the trabecular meshwork (TM) reduces IOP by increasing aqueous outflow. Selective laser trabeculoplasty has demonstrated similar IOP-lowering effectiveness as hypotensive eye drops in patients with OAG across multiple randomized controlled clinical trials.[12] Models accounting for nonadherence suggest that SLT is less costly than topical hypotensive medication in patients with newly diagnosed OAG.[13] The prospective, multicenter, randomized, controlled Laser in Glaucoma and ocular Hypertension Trial (LiGHT) study concluded that first-line treatment with SLT is more cost-effective than with hypotensive eye drops, with similar health-related quality-of-life and clinical outcomes and lower cost compared with a treatment pathway in which medication is used from the outset.[14] Secondary outcomes from LiGHT showed that SLT provided drop-free disease control for 74% of patients 3 years after treatment, with target IOP achieved at 93% of patient visits[14] and improved visual field preservation versus topical hypotensive medication up to 6 years after treatment.[15,16]

Consequently, SLT now is recommended as a first-line intervention for lowering IOP in OAG[17] by the American Academy of Ophthalmology,[18] the European Glaucoma Society,[19] and the United Kingdom National Institute for Health and Care Excellence.[20] A recent report by the American Academy of Ophthalmology determined that, based on level I evidence, SLT is an effective long-term option for the treatment of OAG that can be used as a first-line intervention, replacement for medication, or additional therapy alongside glaucoma medications.[21]

Direct selective laser trabeculoplasty (DSLT; VOYAGER) is a novel treatment method that eliminates the need for a gonioscopy lens and coupling medium.[22,23] It allows 360° treatment of the TM by delivering up to 120 laser pulses via the overlying limbal tissue.[23,24] Direct SLT is an automated noncontact procedure, and thus can be administered by a broader range of eye care professionals than conventional SLT, according to national regulations.[22] Preliminary studies conducted with earlier versions of the DSLT device suggested similar effectiveness as conventional SLT.[23,24] The GLAUrious trial was conducted to evaluate the safety and effectiveness of DSLT compared with conventional SLT, based on the hypothesis that DSLT may provide a novel, automated treatment option for OAG with comparable IOP-lowering effectiveness to that of SLT and an acceptable safety profile.

Methods

The GLAUrious trial (ClinicalTrials.gov identifier, NCT03750201) is a multicenter, randomized, controlled, evaluator-masked, non-inferiority trial evaluating the safety and effectiveness of DSLT compared with SLT for IOP reduction in participants with ocular hypertension or OAG, including exfoliative and pigmentary glaucoma. Participants were recruited at 14 ophthalmology centers located in Israel, Italy, Georgia, and the United Kingdom. The study was conducted in accordance with Good Clinical Practice guidelines and ISO 14155, adhered to the tenets of the Declaration of Helsinki and all other related national requirements, and received full regulatory authority and ethics committee approval in each country and site (Clinica Oculistica Università di Genova, Genova, Italy; Queen's University Belfast, Belfast, UK; Moorfields Eye Hospital, London, UK; Rabin Medical Center, Petach-Tiqwa, Israel; Rambam Health Care Campus, Haifa, Israel; Shaarei Zedek Medical Center, Jerusalem, Israel; Soroka Medical Center, Beer-Shava, Israel; Wolfson Medical Center, Holon, Israel; Hadassah Medical Center, Jerusalem, Israel; Assuta Medical Center, Tel Aviv, Israel; Carmel Medical Center, Haifa, Israel; Akhali Mzera Eye Clinic, Tbilisi, Republic of Georgia; Javrishvili Eye Clinic, Oftalmij, Tbilisi, Republic of Georgia; High technology Medical Center University Clinic, Tbilisi, Republic of Georgia) as applicable, before commencement. Full details of the GLAUrious study design have been published previously elsewhere.[22]

Participants

The study population comprised participants $\geq$ 40 years with previously diagnosed OAG, including exfoliative or pigmentary glaucoma, or ocular hypertension and visual acuity of better than 6/60 in both eyes. Eligible participants were receiving between 0 and 3 topical hypotensive medications at screening and demonstrated IOP (measured using Goldmann tonometry) of between 22 and 35 mmHg in the study eye after IOP-lowering medication washout. Additional inclusion criteria in the study eye were 360° visible scleral spur without gonioscopic indention and clear visualization of the perilimbal sclera for 360° using a speculum. Participants with contraindications to SLT, angle-closure glaucoma, congenital or developmental glaucoma, secondary glaucoma (except exfoliative or pigmentary glaucoma), a vertical cup-to-disc ratio of $\geq$ 0.8, or any peripheral anterior synechiae in the study eye were excluded. Participants also were excluded if they were unable to provide reliable visual field test results because of fixation losses, showed false-positive or false-negative responses of $>$ 33%, or had any of the following on Humphrey visual field analysis (Swedish

Interactive Thresholding Algorithm [SITA] standard 24-2 program; Carl Zeiss Meditec AG): visual field mean deviation of less than −12 dB in either eye, ≥ 75% of points depressed below the 5% level or ≥ 50% of points depressed below the 1% level on the pattern deviation plot, ≥ 50% of points (≥ 2) within the central 5° with a sensitivity of ≤ 0 dB or on the decibel plot, or any points within the central 5° of fixation with a sensitivity < 15 dB in both hemifields on the decibel plot. Additional exclusion criteria included other clinically significant disease or amblyopia in either eye, prior incisional glaucoma surgery or SLT in the study eye, visually significant cataract or cataract surgery in the past 6 months, prior corneal refractive surgery, and dense pigmentation or hemorrhage in the perilimbal conjunctiva or anterior sclera. All participants were willing to participate in the 12-month study and provided written informed consent ahead of any study procedures.

Procedures

After screening, participants using topical hypotensive medications underwent a washout period of up to 28 days, determined by medication used (7 days for pilocarpine, 14 days for carbonic anhydrase inhibitors and α-adrenergic agonists, and 28 days for all other medications), with subsequent IOP reassessment. Before randomization, an individual threshold IOP limit was set for each participant, according to the glaucoma severity state, at the discretion of an unmasked investigator. Eligible participants were randomized to receive either DSLT or SLT in 1 eye at a ratio of 1:1. Participants were randomized independently at each site, either after screening (for those not using topical hypotensive medications) or after washout (for those using IOP-lowering medications). Randomization was conducted by the study statistician (Y.S.), with lists generated by a random algorithm stratified according to use of β-blockers in the fellow eye because of known crossover effects[25] and sealed envelopes provided to each site. All treatments were administered by unmasked ophthalmologists with extensive experience in using standard SLT who were trained and certified in the use of DSLT by Belkin Vision Ltd. All follow-up IOP measurements were collected and evaluated by ophthalmologists masked to the participant's treatment. Participants remained unmasked because of the distinct delivery of the two treatments.

Participants randomized to the study group were treated with DSLT using the Eagle device (Belkin Vision Ltd). The study was initiated using an original version of the device; during the trial, an updated version with reduced size and weight and incorporating improved limbus detection and eye tracking algorithms became available and was approved for study use in a protocol amendment. These design changes were made to improve manufacturability and serviceability of the device and not in response to any clinical issues that arose with the original model or any interim analyses of the data regarding safety or effectiveness. Core output laser specifications of the device were unchanged, with the exception of a minor technical improvement by decreasing the laser pulse duration from 6 to 3 nanoseconds.

The Eagle device used a frequency-doubled, Q-switched neodymiyum:yttrium−aluminum−garnet laser with a wavelength of 532 nm delivered in short nanosecond pulses to the TM; 120 deliveries of 3-nanosecond duration and 400-μm spot size were administered automatically at the limbus over 360°. Most participants were treated with a laser energy of 1.6 to 1.8 mJ/shot. Participants randomized to the comparator group underwent conventional SLT, which used a frequency-doubled, Q-switched neodymiyum:yttrium−aluminum−garnet laser with a wavelength of 532 nm delivered manually to the gonioscopically visualized TM; approximately 100 shots of a preset 3-nanosecond duration and 400-μm spot size were administered over 360° through a manually rotated gonioscopy lens. Most participants were treated with a laser energy of 0.7 to 0.9 mJ/shot. For both DSLT and SLT, a portion of the laser energy is lost as it passes through the nontarget tissues to the target TM. In DSLT, it is estimated that 11% of the energy delivered to the anterior limbal surface reaches the TM.[26] For SLT, the corresponding estimated figure is 32%.[26] Applying these rates of transmission to the total energy delivered, it is estimated that, on average, slightly more energy was delivered to the TM in the SLT participants (28.5 mJ) compared with the DSLT participants (21.7 mJ).

In both treatment groups, only 1 eye per participant was treated in the study. If both eyes were found to be eligible for inclusion, the eye with the higher IOP after washout (or more advanced disease in the case of identical IOP, determined by the local investigator based on visual field analysis) was treated, and topical hypotensive medication was (re)initiated in the nonstudy eye at the discretion of the investigator. Before treatment, participants received topical anesthesia, as well as pilocarpine 2% (a single drop administered 45−60 minutes before treatment) and apraclonidine 0.5% or 1% or brimonidine 0.1% or 0.15% (a single drop administered at 45−60 minutes and again 5−10 minutes before treatment) as prophylaxis against laser-induced pressure elevation and subconjunctival hemorrhage after laser treatment. After each procedure, a topical nonsteroidal anti-inflammatory medication was administered 4 times daily for 1 week.

The following assessments were carried out after the procedure on the study eye in both treatment groups: IOP immediately after and 1 to 2 hours after treatment, corrected visual acuity (Early Treatment Diabetic Retinopathy Study vision chart), and slit-lamp examination with grading of anterior chamber cells (0 to +4) and flare (0 to +4). Further follow-up assessments were conducted at 1 and 7 days and at 1, 3, 6, and 12 months after treatment. Participants taking topical hypotensive medications before the 6-month visit were asked to stop taking these medications up to 28 days before the visit so that an unmedicated (washout) IOP could be obtained. Intraocular pressure was assessed at each follow-up visit and was compared with the threshold IOP limit value. Reintroduction of topical hypotensive medication was not permitted during the initial visit 1 month after the procedure unless, in the opinion of the local investigator, an immediate risk to the ocular health of the participant was present. After 1 month, reintroduction of topical hypotensive medication was permitted if a participant's individual threshold IOP limit value was reached or exceeded, starting with a prostaglandin, then β-blocker and other medications at the discretion of the investigator. After implementation of a protocol revision midway through the study, all IOP measurements were obtained at the same time of day ± 2 hours, preferably in the mornings between 8:30 and 10:30 AM local time. Safety was evaluated throughout the study by the recording of all adverse events (AEs) and serious adverse events (SAEs).

Outcomes

The primary trial outcome was the difference between the treatment groups in change in mean washout IOP from pretreatment baseline to 6-month follow-up. Secondary effectiveness end points were the proportion of participants with a ≥ 20% reduction in washout IOP from baseline to 6 months without secondary surgical intervention (SSI; success rate) and change in the number of topical hypotensive medications from screening to 6 months. Exploratory end points included changes in nonwashout IOP, the number of ocular hypotensive medications, and the proportion of participants with a ≥ 20% reduction in nonwashout IOP from screening to 12 months; the mean percentage reduction of IOP at 6 and 12 months; and associations between TM pigmentation or perilimbal findings and the DSLT treatment effect. The primary safety outcome was

rate of ocular AEs in each treatment group at or before 12 months. Additional safety outcomes included rates of nonocular AEs and summaries of all SAEs in each treatment group at or before 12 months. Participants also underwent corrected visual acuity measurement and slit-lamp, pachymetry, visual field, gonioscopy, and fundus ophthalmoscopy examinations.

Statistical Analysis

The primary trial outcome was the difference between the two treatment groups in mean change in washout IOP between baseline and 6 months. The hypothesis that DSLT is noninferior to SLT for this primary end point was tested using the estimated difference in mean change from baseline IOP between DSLT and SLT (and the associated 2-sided 95% confidence interval [CI]) using the fitted analysis of covariance model, which adjusted for baseline IOP and for the use of β-blocker drops in the fellow eye. Noninferiority would be confirmed if the lower limit of the 95% CI for the difference in the mean change from baseline in washout IOP between the two groups was more than −1.95 mmHg (with 2-sided α value of 0.05). The noninferiority margin of 1.95 mmHg was based on clinical reviews indicating that IOP measurement differences of up to 2 mmHg are likely the result of measurement variability or error and are not clinically significant.[27,28] An anticipated standard deviation (SD) of 3.5 mmHg was chosen for the sample size calculation based on a review of recent SLT literature, which found a similar average SD.[29,30] A 2-sided 95% CI also was calculated for the difference in proportion of participants with a $\geq$ 20% reduction in washout IOP from baseline to 6 months between the two treatment groups, using a prespecified noninferiority margin of 10%. The change in number of medications per eye was compared using a Wilcoxon-Mann-Whitney test using a 2-sided α value of 0.05, using a prespecified noninferiority margin of 1 medication. Hierarchical testing strategy was used to control overall type 1 error at the 5% (2-sided) level. The protocol-designated primary analysis population was the per-protocol population, as is typical with noninferiority and equivalence studies. The results from the intention-to-treat (ITT) population are presented as supportive analysis.

As described in the published GLAUrious study design,[22] 164 participants were needed to complete the trial according to protocol, based on a noninferiority margin of 1.95 mmHg, an anticipated SD of 3.5 mmHg, and 80% power (using a *t* test and 0.025 1-sided α value). Overrecruitment was allowed to compensate for possible protocol deviations and attrition.

Primary and secondary effectiveness analyses included all randomized treated participants for whom 6-month effectiveness data were available and who had no major protocol deviations (Fig 1), as prespecified in the study protocol (6-month per-protocol population). Participants who underwent SSI or had treated-eye ocular SAEs during the first 6-month period or for whom a 6-month washout was considered unsafe were included in the 6-month modified per-protocol (mPP) population and were considered to have experienced treatment failure. For these participants, 6-month IOP was imputed with the baseline IOP measurement for the primary end point analysis. Participants were considered to have experienced treatment failure for the secondary end point of $\geq$ 20% reduction in washout IOP without SSI. For the secondary end point of change in hypotensive medications, participants who underwent SSI or had a treated-eye ocular SAE were assigned the highest number of medications recorded at any time before the SSI or ocular SAE. Participants with missing 6-month data for other reasons were not included in the mPP population.

Exploratory analyses of 12-month outcomes included all randomized and treated participants for whom 12-month effectiveness data were available and who had no major protocol deviations (12-month mPP population). Participants who underwent SSI or experienced treated-eye ocular SAEs during the 12-month study period were included in the 12-month mPP population and were considered to have experienced treatment failure. Similar imputations and treatment failure criteria as used for the 6-month analyses were applied to the 12-month analyses. Both 6-month and 12-month effectiveness analyses also were conducted for the ITT population, which included all enrolled and randomized participants.

Safety analyses included all randomized participants for whom any treatment was initiated (safety population). Adverse events were assessed by investigators who reported the timing of each AE, how it was treated, and the severity, seriousness, and relatedness of the event to the study procedure. Rates of AEs were calculated on a per-person basis. An independent medical monitor was responsible for overseeing safety and evaluating all AEs reported to the sponsor. Other safety outcomes were summarized by visit.

Results

Enrollment was initiated on November 8, 2018, and completed on April 19, 2021. A total of 276 participants were screened for study participation, and 201 participants (72.8%) were randomized (102 participants to DSLT and 99 participants to SLT), constituting the ITT population. After randomization, 9 participants exited the study before treatment (3 from the DSLT group and 6 from the SLT group) because they no longer met the study criteria, were withdrawn by the investigator, or withdrew consent. A total of 192 participants (95.5%) were treated with either DSLT (n = 99) or SLT (n = 93), and these participants constituted the safety analysis population (Fig 1).

Of the 192 participants treated, 156 participants (81.3%) had 6-month effectiveness data available with no major protocol deviations and were included in the 6-month mPP population. Of these, 10 participants (6 from the DSLT group and 4 from the SLT group) were considered to have experienced treatment failure according to mPP population criteria and had 6-month IOP data imputed with the baseline IOP: 3 participants (2 from the DSLT group and 1 from the SLT group) because of SSI and 7 participants (4 from the DSLT group and 3 from the SLT group) for whom 6-month washout was considered unsafe. The proportion of participants excluded from the 6-month mPP population was similar between study groups: 21.6% (22/102) for the DSLT group and 23.2% (23/99) for the SLT group. The main reasons for exclusion were protocol deviations resulting from incomplete washout at baseline or IOP measurements that failed to meet masking criteria.

Baseline demographic (Table 1) and eye (Table 2) characteristics were similar between treatment groups. Mean ± SD screening IOP was 21.6 ± 5.4 mmHg and 20.6 ± 4.5 mmHg (P = 0.26), mean ± SD IOP after pretreatment washout was 26.4 ± 3.6 mmHg and 25.9 ± 3.6 mmHg (P = 0.32), and the mean ± SD number of medications was 1.2 ± 1.0 and 1.1 ± 1.0 (P = 0.79) in the DSLT and SLT groups, respectively.

At 6-month follow-up, the mean ± standard error post-treatment washout IOP reduction from baseline was 5.5 ± 0.5 mmHg in the DSLT group and 6.2 ± 0.5 mmHg in the

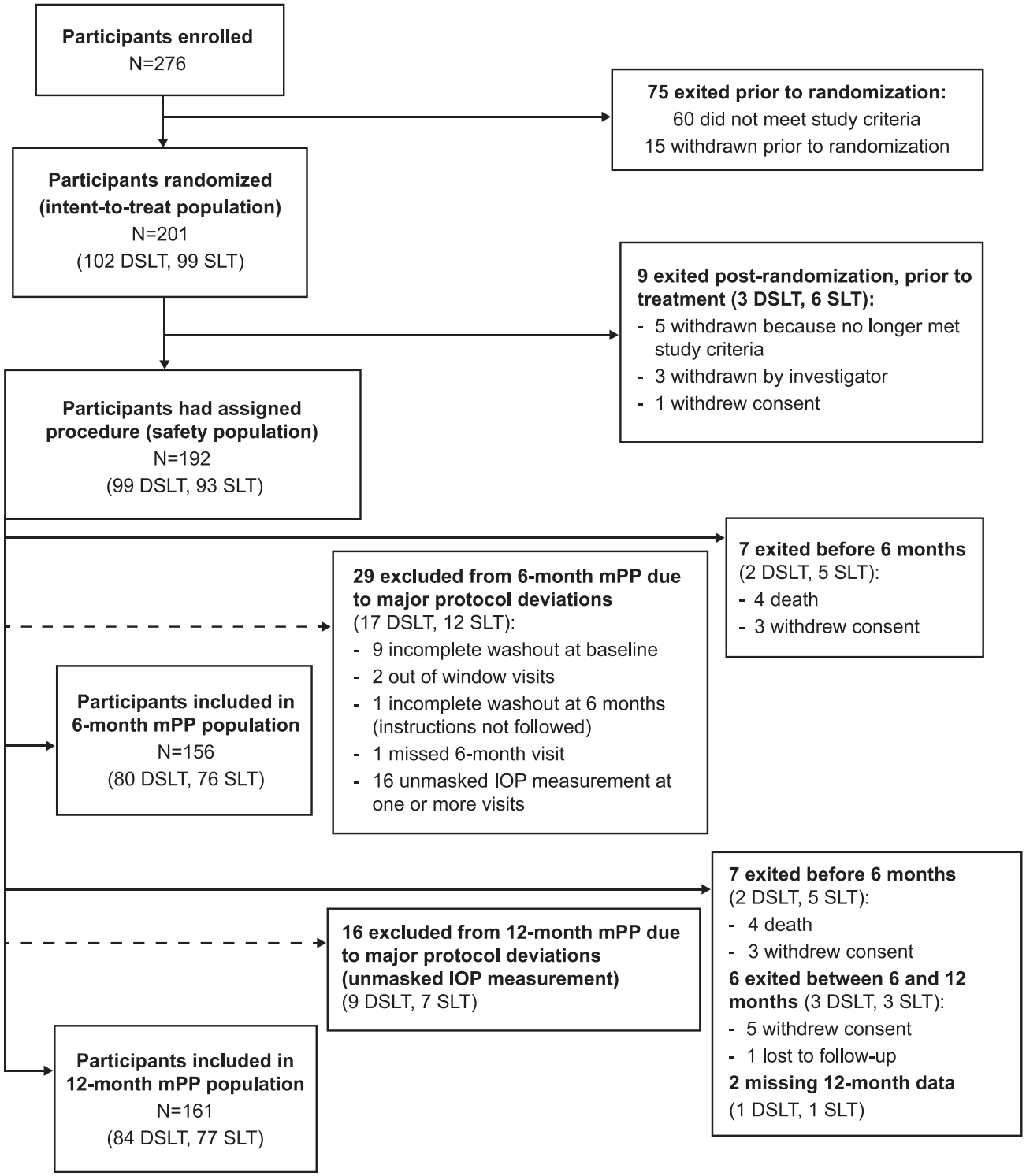

Figure 1. Consolidated Standards of Reporting Trials participant flow diagram. DSLT = direct selective laser trabeculoplasty; IOP = intraocular pressure; mPP = modified per protocol; SLT = selective laser trabeculoplasty.

SLT group, equivalent to mean IOP reductions of 20.6% and 23.6% in the DSLT and SLT groups, respectively (Fig 2). The difference in mean washout IOP reduction between the two groups was −0.7 mmHg (SLT minus DSLT; 95% CI, −2.2 to 0.8 mmHg; P = 0.09 for noninferiority [not significant (NS)]). With the lower limit of the 95% CI < the noninferiority margin of −1.95 mmHg, noninferiority of DSLT to SLT was not established in the primary analysis population for the primary end point of mean washout IOP reduction at 6

Table 1. Baseline Participant Characteristics (Safety Population)

Parameter	Direct Selective Laser Trabeculoplasty (n = 99)	Selective Laser Trabeculoplasty (n = 93)	P Value
Age (yrs)			
Mean ± SD	65.8 ± 8.7	65.4 ± 10.2	0.82
Median	66	66	
Minimum	44	40	
Maximum	82	88	
Sex, no. (%)			
Male	64 (64.6)	54 (58.1)	0.38
Female	35 (35.4)	39 (41.9)	
Race, no. (%)			
Asian	0 (0.0)	1 (1.1)	0.30
Black	2 (2.0)	0 (0.0)	
White	97 (98.0)	91 (97.8)	
Mixed	0 (0.0)	1 (1.1)	

SD = standard deviation.

months. Consistent with the mPP population, the ITT population did not support noninferiority of DSLT to SLT with respect to mean washout IOP reduction at 6 months (DSLT, 4.7 ± 0.5 mmHg; SLT, 5.6 ± 0.5 mmHg; difference in means, −0.9 mmHg; 95% CI, −2.3 to 0.5 mmHg; $P = 0.13$ for noninferiority [NS]).

The proportion of participants (mPP population) with at least 20% reduction in unmedicated (washout) IOP from baseline to 6 months was 56.3% (45/80) for the DSLT group versus 63.2% (48/76) for the SLT group, indicating that most eyes in both groups achieved a successful outcome after treatment. These represent a 6.9% difference in success rates between groups (SLT minus DSLT; 95% CI, −8.5% to 22.0%; $P = 0.35$ for noninferiority [NS]). With the upper limit of the 95% CI more than the noninferiority margin of 10%, noninferiority of DSLT to SLT was not established in the primary analysis population of the proportion of participants with at least 20% reduction in unmedicated IOP at 6 months. Consistent with the mPP population, the ITT population did not support noninferiority of DSLT to SLT with respect to the proportion of participants achieving a ≥ 20% reduction in washout IOP 6 months after treatment (DSLT, 45.1% [46/102]; SLT, 53.5% [53/99]; difference in proportions, 8.4%; 95% CI, −5.4% to 22%; $P = 0.4$ for noninferiority [NS]. The DSLT group had a mean ± SD reduction in ocular hypotensive medications at 6 months from screening of −0.7 ± 1.1 versus −0.8 ± 1.1 in the SLT group. No median difference between the two groups was found (SLT minus DSLT = 0.0; 95% CI, 0.0–0.0; $P < 0.001$ for noninferiority). Although the lower limit of the 95% CI is more than the noninferiority margin of −1, a formal statistical claim to noninferiority of DSLT to SLT cannot be made with respect to the reduction in the number of ocular hypotensive medications from screening to 6 months (Fig 3). The hierarchical testing strategy used to control overall type 1 error at the 2.5% (1-sided) level precludes this formal claim to noninferiority with respect to the reduction in the number of ocular hypotensive medications at 6 months. Similar 6-month results were observed in the ITT population (Table S3, available at www.aaojournal.org).

Overall, 161 participants were included in the 12-month mPP population. Of these, 6 participants (3 in the DSLT group and 3 in the SLT group) were considered to have experienced treatment failure per mPP population criteria and had 12-month IOP data imputed with the screening IOP, 5 participants (3 in the DSLT group and 2 in the SLT group) because of SSI and 1 participant (SLT group) because of a treated-eye ocular SAE. The proportion of participants excluded from the 12-month mPP population was 17.6% (18/102) for the DSLT group and 22.2% (22/99) for the SLT group. The main reasons for exclusion were unmasked IOP measurements, exit from the study, and missing data.

Exploratory analyses of 12-month outcomes showed that mean ± standard error nonwashout IOP reduction from screening was 3.2 ± 0.4 mmHg in both the DSLT and SLT groups, equivalent to mean IOP reductions of 12.2% in the

Table 2. Ocular Characteristics before the Procedure (6-Month Modified Per-Protocol Population)

Parameter	Direct Selective Laser Trabeculoplasty(n = 80)	Selective Laser Trabeculoplasty (n = 76)	P Value
IOP at screening (mmHg)			
Mean ± SD	21.6 ± 5.4	20.6 ± 4.5	0.26
Minimum–maximum	9.0–35.0	11.0–31.5	
Unmedicated IOP at baseline (mmHg)			
Mean ± SD	26.4 ± 3.6	25.9 ± 3.6	0.32
Minimum–maximum	22.0–35.0	22.0–33.5	
Hypotensive drugs at screening, no. (%)			
0	26 (32.5)	24 (31.6)	0.90
1	21 (26.3)	24 (31.6)	
2	25 (31.3)	21 (27.6)	
3	8 (10.0)	7 (9.2)	
Mean ± SD	1.2 ± 1.0	1.1 ± 1.0	0.79
Minimum–maximum	0.0–3.0	0.0–3.0	

IOP = intraocular pressure; SD = standard deviation.

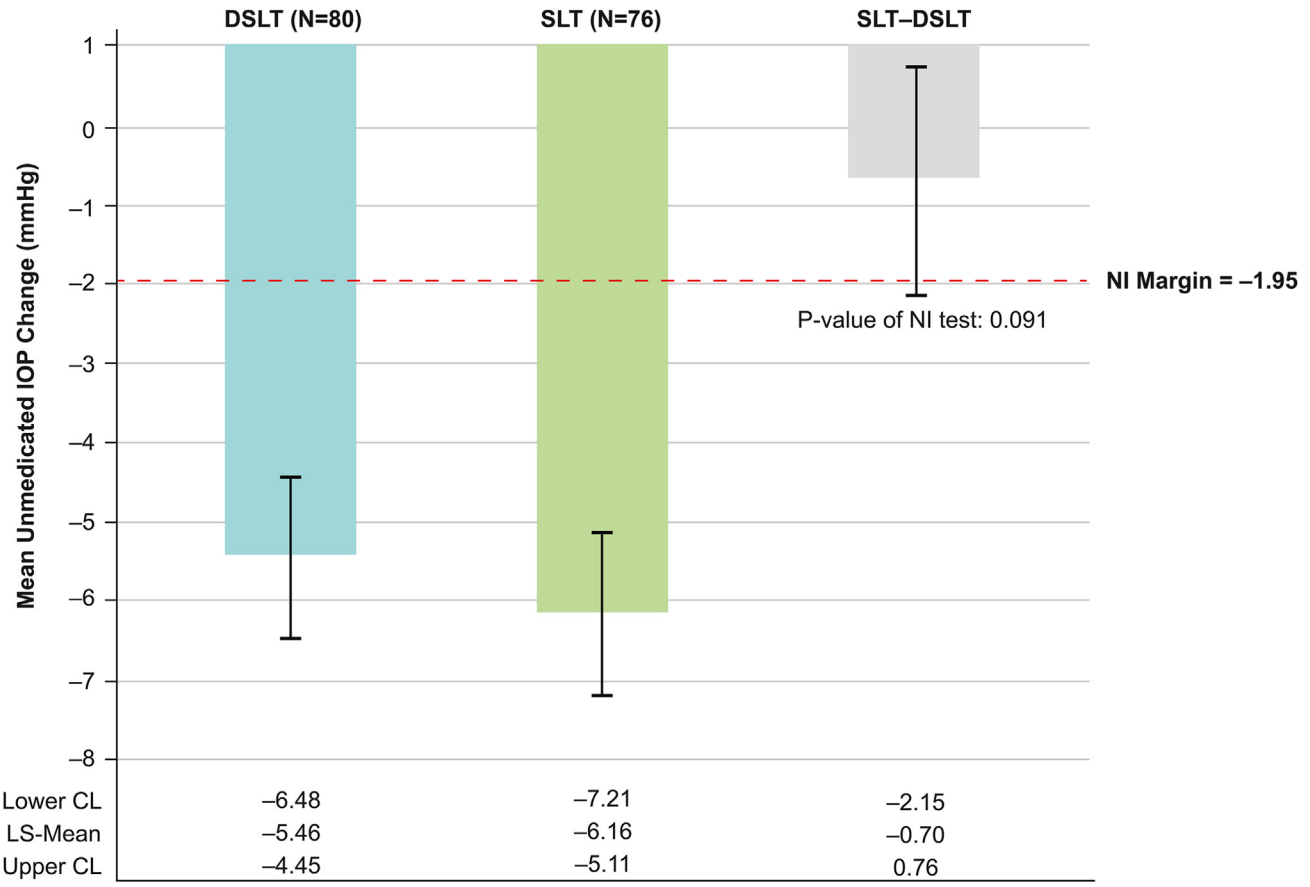

Figure 2. Graph showing the primary effectiveness outcome: 6-month mean intraocular pressure (IOP) change from baseline (6-month modified per-protocol population). CL = confidence limit; DSLT = direct selective laser trabeculoplasty; LS = least squares; NI = noninferiority; SLT = selective laser trabeculoplasty.

DSLT group and 9.4% in the SLT group, respectively (Fig 4). The between-group difference (SLT minus DSLT) in mean nonwashout IOP reduction at 12 months was negligible (0.01 mmHg; 95% CI, −1.09 to 1.10 mmHg; $P < 0.001$ for non-inferiority), suggesting that DSLT was not worse than SLT in terms of IOP reduction at the 12-month follow-up. The results based on the ITT population were similar to those from the mPP population (difference, 0.39 mmHg; 95% CI, −0.63 to 1.42 mmHg; $P < 0.001$ for noninferiority). The proportion of participants (mPP population) with at least 20% reduction in nonwashout IOP with no increase in medication use from baseline at 12 months was 31.0% (26/84) for the DSLT group versus 22.1% (17/77) for the SLT group, with a −8.9% difference in success rates between groups (SLT minus DSLT; 95% CI, −22.3% to 4.9%; $P = 0.003$ for noninferiority). The success rates were similar for the ITT population, with 26.5% (27/102) for the DSLT group versus 19.2% (119/99) for the SLT group, with a −7.3% difference in success rates between groups (SLT minus DSLT; 95% CI, −18.9% to 4.4%; $P = 0.002$ for noninferiority). Both the DSLT and SLT groups showed a reduction in the use of ocular hypotensive medications at the 12-month follow-up, with a mean ± SD change of −0.5 ± 1.3 medications in the DSLT group and −0.5 ± 1.1 medications in the SLT group ($P < 0.001$ for noninferiority). At 12 months, 61.7% of participants treated with DSLT were free of eye drops compared with 59.5% of those treated with SLT (Fig S5, available at www.aaojournal.org), and 70% (19/27) of participants receiving DSLT who entered the study free of medication remained so at 12 months, compared with 73% (16/22) of participants receiving SLT. Similar 12-month results were observed in the ITT population (Table S4, available at www.aaojournal.org).

Figure 6 illustrates the pattern of IOP change over time in a participant undergoing DSLT and the mean IOP at each time point; the SD of the means were consistent with those of participants undergoing SLT. Most patients achieved mean reductions in washout IOP of > 20% from baseline to 6 months in both groups. The SLT group showed slightly lower mean screening and baseline IOPs than the DSLT group, and this trend continued throughout the follow-up period, when the mean IOP for the SLT group at 1, 3, 6, and 12 months was slightly lower than that for the DSLT group. Intraocular pressure measurements at 1, 3, and 12 months were not washed out. Both groups showed a mean IOP of 18 mmHg and a mean use of 0.6 medications at 12 months.

In additional exploratory analyses, no notable differences were found in mean 6-month IOP reduction between DSLT-treated eyes or SLT-treated eyes with and without pigmentation (Table S5, available at www.aaojournal.org) or between

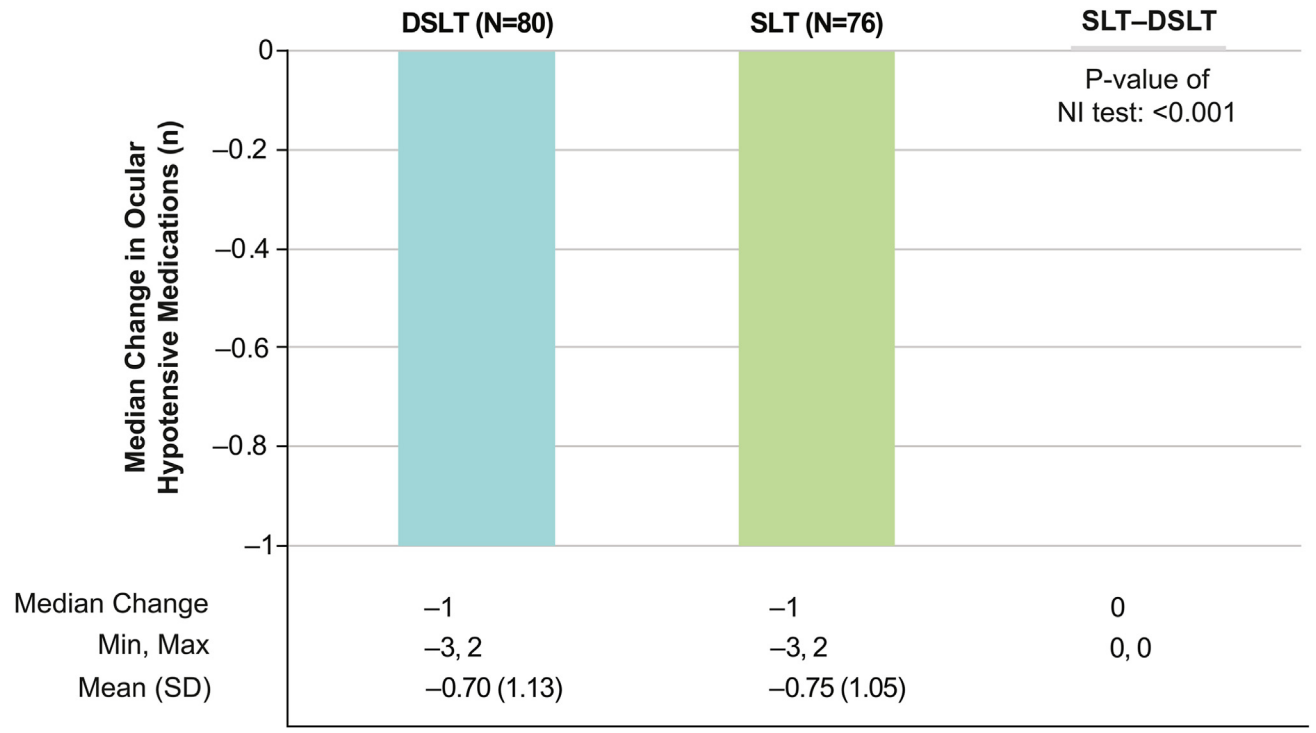

Figure 3. Graph showing the change in number of ocular hypotensive medications used at 6 months from screening (6-month modified per-protocol population). DSLT = direct selective laser trabeculoplasty; Max = maximum; Min = minimum; NI = noninferiority; SD = standard deviation; SLT = selective laser trabeculoplasty.

DSLT-treated eyes with and without perilimbal findings (Table S6, available at www.aaojournal.org). In the DSLT arm, no notable difference was found in 6-month washout IOP change between the original and updated version of the Eagle device ($P = 0.92$); therefore, data were deemed to be equivalent and pooled for the end points evaluated.

Safety

Rates of ocular AEs generally were similar between the two treatment groups, although participants treated with DSLT experienced a higher rate of mild punctate subconjunctival hemorrhage, typically reported immediately after the procedure or on day 1. All cases resolved spontaneously, without treatment and with no sequelae during the follow-up period. Most AEs were minor and resolved within days without intervention; most occurred within the initial 6 months after treatment, with fewer occurring between 6 and 12 months after the procedure (Tables 7 and 8). Ocular surgical interventions were required in 4 participants treated with DSLT (2 participants treated for cataract, 1 participant treated for elevated IOP that required trabeculectomy, and 1 participant treated for retinal tear) and 3 participants treated with SLT (2 participants treated for cataract and 1 participant treated for subluxation of intraocular lens). One unrelated ocular SAE was reported in each group (Supplemental Appendix). Four deaths were reported (1 in the DSLT group and 3 in the SLT group), none of which were related to treatment. Additional safety evaluations did not reveal any evidence of chronic adverse effects subsequent to either the DSLT or the SLT procedure.

Discussion

The objective of the GLAUrious trial was to determine if the effectiveness of DSLT in reducing IOP is noninferior compared with the known effectiveness of SLT. The statistical noninferiority of DSLT compared with SLT was not demonstrated at 6 months for the primary end point, because the lower 95% CI crossed the noninferiority margin. This may be because of a larger than anticipated SD of baseline IOP measurements; the observed SD on change in IOP (5.0 mmHg for DSLT and 4.5 mmHg for SLT) was more than the SD used to calculate the sample size (i.e., 3.5 mmHg). An evaluable sample size of 289 participants at 6 months is required to maintain the same power that corresponds to the observed evaluable sample size of 156 participants (85% increase), given the increased variability (from SD of 3.5 mmHg assumed at design to the observed pooled SD of 4.76 mmHg).

The magnitude of mean reduction in IOP and accompanying reduction in hypotensive medications demonstrated in this trial are consistent with the findings of earlier pilot studies of this DSLT treatment method in patients with OAG.[23,24] Although the primary end point was at 6 months, participants were followed up through 12 months. Importantly, AEs that occurred during the 12-month follow-up were typically mild and resolved without

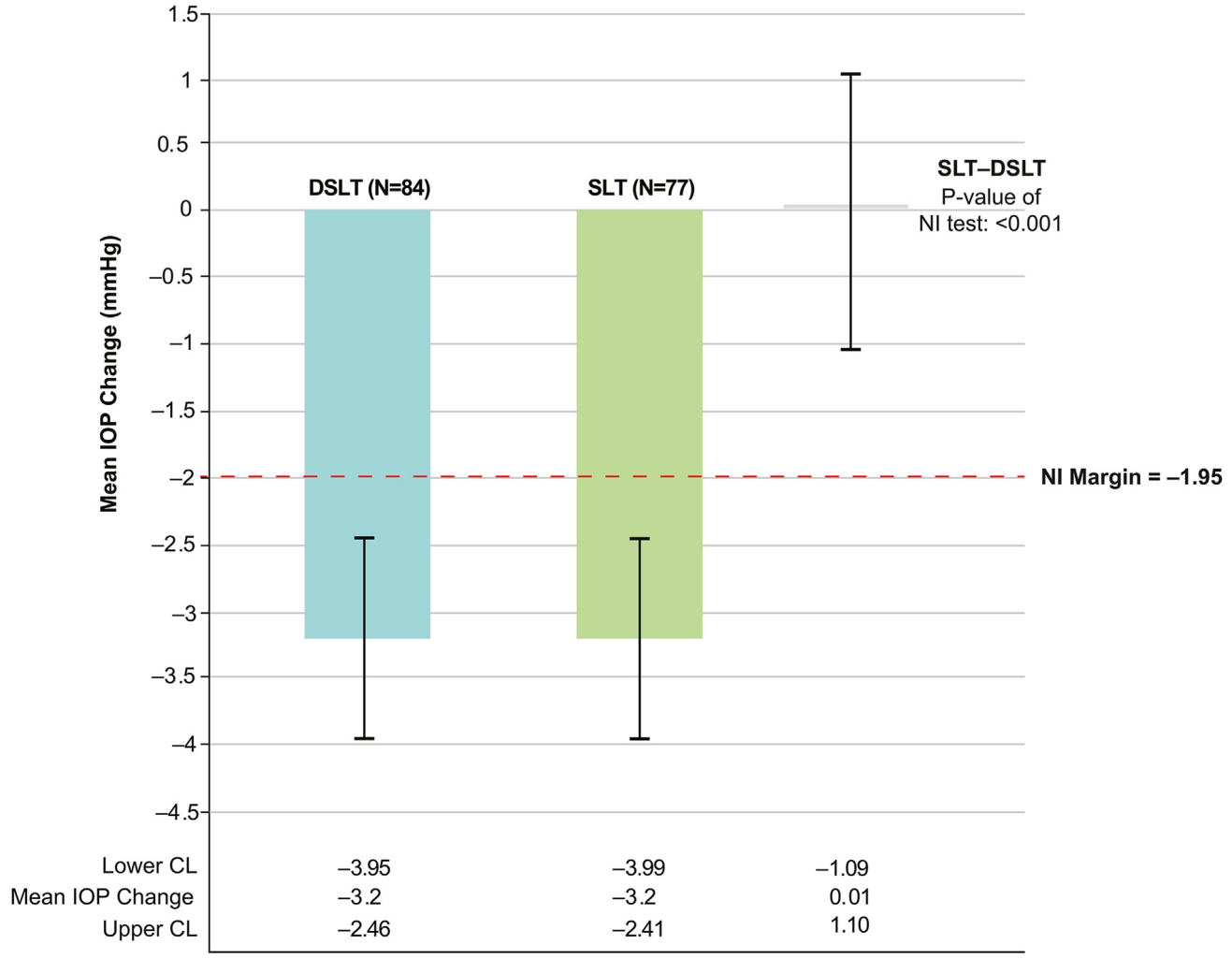

Figure 4. Graph showing the exploratory effectiveness outcome: 12-month mean intraocular pressure (IOP) change from screening (12-month modified per-protocol population). CL = confidence limit; DSLT = direct selective laser trabeculoplasty; NI = noninferiority; SLT = selective laser trabeculoplasty.

intervention. No long-term ocular safety concerns were present in either treatment group. Although 12-month effectiveness end points were exploratory and require cautious interpretation, the mean reduction in nonwashout IOP from screening for DSLT was consistent with that of SLT, and both treatment groups achieved a similar reduction in medication use. Although statistical noninferiority of DSLT to SLT was not demonstrated in the GLAUrious study, with mean percent reduction in washout IOP of 20.6%, 56.3% of participants attaining a 20% reduction in unmedicated IOP at 6 months, and comparable 12-month outcomes between the DSLT and SLT groups, the totality of the evidence supports that DLST provides meaningful IOP-lowering benefit to patients. Furthermore, it could be argued that, given the convenience of the procedure, the benefit of automation and potentially improved accessibility to a broader range of eye care providers, it could have been acceptable to use a slightly more lenient noninferiority margin than the 1.95 mmHg used in the study, which would have made it easier to achieve statistical demonstration of noninferiority. For a chronic disease like glaucoma, the duration of treatment effect is important, so the fact that noninferiority versus SLT was established at 12 months is an important clinical finding supporting the benefit-to-risk profile of DSLT.

The findings of the GLAUrious study have potentially important implications for health care systems worldwide. In 2020, the global number of people with glaucoma was estimated to be 76 million, and approximately 4 million experienced moderate to severe visual impairment or blindness as a result of glaucoma.[1,31] Early reduction of IOP has been associated with sustained IOP control and less frequent glaucoma progression than delayed treatment over a 6-year follow-up period.[4] Therefore, access to early effective treatment is a paramount public health concern. However, nonadherence has been shown to limit the long-term effectiveness of topical hypotensive medication,[9] whereas widespread use of SLT is limited by lack of access to the procedure. Conventional SLT requires delivery of the laser treatment via a gonioscopy lens with

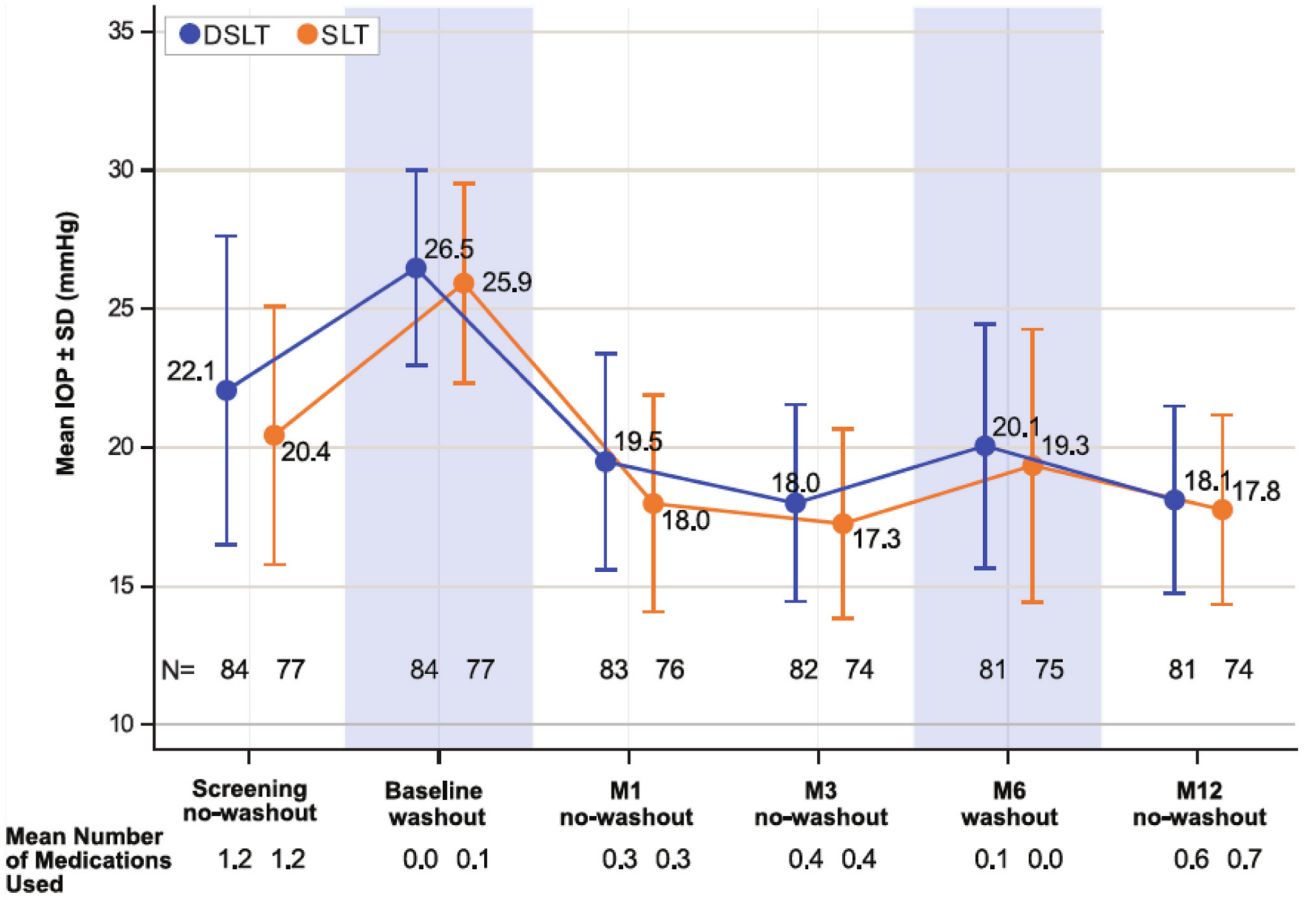

Figure 6. Graph showing the descriptive mean observed intraocular pressure (IOP) measurements over the 12-month study duration (12-month modified per-protocol population). Yellow highlighted sections indicate visits at which washout IOP was measured. DSLT = direct selective laser trabeculoplasty; M = month; SD = standard deviation; SLT = selective laser trabeculoplasty.

a coupling medium placed on the cornea, with manual administration of 50 to 100 laser shots,[17] which limits it to a relatively small number of specialists. Therefore, the gap is widening between supply and the increasing demand for effective and efficient glaucoma care.[32,33]

A significant increase in future glaucoma workload is expected as a result of rising numbers of people affected by glaucoma as the global population ages.[1–3] Such an increase may be exacerbated further by rising demand for SLT procedures because of recent guideline changes recommending use of SLT as a first-line therapy.[18–20] In England alone, demand for SLT procedures is expected to increase more than three-fold over the next 5 years, and experts suggest that currently an appropriately trained workforce to deliver SLT is lacking. As a result, most glaucoma services currently do not offer routine SLT as a first-line treatment.[34] In addition, the rationale for the use of low-energy SLT repeated annually as maintenance therapy for mild to moderate OAG is being investigated in the COAST (Clarifying the Optimal Application of Selective laser therapy Treatment) study, funded by the National Institutes of Health in the United States.[35] If proven to be advantageous, the associated increase in demand for laser trabeculoplasty treatment would be achievable only with greater access to treatment than is available currently.

Automation of laser trabeculoplasty could help to relieve this increasing burden of care by expanding the pool of performing practitioners beyond conventional SLT providers. The DSLT procedure is automated, with the operating physician confirming target points and eye-tracking functions,[23] and has the potential for broader use than conventional SLT. Direct SLT also may provide a desirable alternative for patients who struggle with adherence to daily eye drop medications or have common side effects[24,36] and for those who experience the financial burden of daily glaucoma medication or do not have access to a glaucoma specialist.[5] The potential of DSLT as a widely accessible and convenient treatment for glaucoma may be especially beneficial in underserved regions where treatment resources and options currently are limited.[10,11] Accessibility is crucial to relieving the burden of glaucoma,[10,11,13] and DSLT is a treatment method that has the potential to change glaucoma management significantly by expanding access to treatment across the world, especially in resource-limited settings.

Table 7. Study Eye Adverse Events at or before the 6-Month Follow-up (Safety Population)

Ocular Events	Direct Selective Laser Trabeculoplasty (n = 99)	Selective Laser Trabeculoplasty (n = 93)
Serious adverse events	0	**1 (1.1)**
Subluxation of intraocular lens	0	1 (1.1)
Nonserious adverse events	34 (34.3)	20 (21.5)
Punctate subconjunctival hemorrhage	20 (20.2)	1 (1.1)
Foreign body sensation	3 (3.0)	3 (3.2)
Cataract progression	3 (3.0)	1 (1.1)
Superficial punctate keratitis	2 (2.0)	4 (4.3)
Elevated IOP (> 10-mmHg increase from baseline)	2 (2.0)	2 (2.2)
Conjunctivitis	2 (2.0)	0
Anterior chamber inflammation (mild to moderate)	1 (1.0)	3 (3.2)
Transient blurred vision	1 (1.0)	2 (2.2)
Corneal erosion	1 (1.0)	1 (1.1)
Eye discharge	1 (1.0)	1 (1.1)
Eye discomfort	1 (1.0)	1 (1.1)
Eye pain	1 (1.0)	1 (1.1)
Hordeolum externum	1 (1.0)	1 (1.1)
Blepharitis	1 (1.0)	0
Eye itchiness	1 (1.0)	0
Periodical hyperlacrimation	1 (1.0)	0
Retinal tear	1 (1.0)	0
Subconjunctival hemorrhage (moderate)	1 (1.0)	0
Cystoid macular edema	0	1 (1.1)
Elevated IOP (≤ 10-mmHg increase from baseline)	0	1 (1.1)
Eye burning sensation	0	1 (1.1)
Floater	0	1 (1.1)
Periorbital pain	0	1 (1.1)
Any adverse events	44 reports from 34 participants (34.3%)	27 reports from 20 participants (21.5%)
Any adverse events (excluding punctate subconjunctival hemorrhage)	24 reports from 19 participants (19.2%)	26 reports from 19 participants (20.4%)

IOP = intraocular pressure.
Data are presented as no. (%).

Study Limitations

As discussed in "Procedures" above, the study was initiated with the original version of the DSLT device and introduced an updated version into the ongoing trial. These design changes did not impact the treatment procedure; the image-processing algorithms and laser performance specifications remained unchanged, with the exception of a minor decrease in the laser pulse duration (from 6 ns to 3 ns). Forty-three participants receiving DSLT were treated with the original Eagle device, and 56 participants were treated with the updated one. As described in "Results," of the 192 participants treated, only 156 participants (81.3%) had 6-month effectiveness data available with no major protocol

Table 8. Study Eye Adverse Events Beyond the 6-Month Follow-up (Safety Population)

Ocular Events	Direct Selective Laser Trabeculoplasty (n = 99)	Selective Laser Trabeculoplasty (n = 93)
Serious adverse events	1 (1.0)	0
Acute optic neuropathy	1 (1.0)	0
Nonserious adverse events	6 (6.1)	7 (7.5)
Cataract progression	3 (3.0)	4 (4.3)
Conjunctivitis	1 (1.0)	0
Diabetic retinopathy	1 (1.0)	0
Elevated IOP	1 (1.0)	0
Foreign body sensation	1 (1.0)	0
Cataract	0	1 (1.1)
Cataract surgery	0	1 (1.1)
Guttata	0	1 (1.1)
Any adverse events	8 reports from 7 participants (7.1%)	7 reports from 7 participants (7.5%)

IOP = intraocular pressure.
Data are presented as no. (%).

violations deviations and were included in the 6-month mPP population. The clinical trial site locations were limited to 4 regions in Europe that enrolled 98% White patients, which does not reflect the overall population with glaucoma. The medication washout requirement enabled a direct assessment of the device alone on IOP not confounded by medication use but simultaneously limited the population to patients with mild and moderate severity of disease who could tolerate the washout procedure safely.

In conclusion, the GLAUrious study failed to demonstrate that DSLT was noninferior to SLT. However, DSLT did provide effective IOP reduction for 12 months in patients with OAG or ocular hypertension. Aside from punctate subconjunctival hemorrhage, the safety profile was similar between DSLT and SLT. Delivered via an automated, noncontact, and well-tolerated treatment method, DSLT may provide a convenient and widely accessible alternative to conventional SLT across a broad range of clinical settings. Given the high global prevalence of glaucoma and the increased recognition of SLT as the initial treatment for the disease, DSLT's efficiency and comparable efficacy warrants first-line consideration in glaucoma's worldwide treatment armamentarium.

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Footnotes and Disclosures

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[1] NIHR Moorfields Biomedical Research Centre, Moorfields Eye Hospital, London, United Kingdom.

[2] Institute of Ophthalmology, University College London, London, United Kingdom.

[3] Centre for Public Health, Queen's University Belfast, Belfast, United Kingdom.

[4] Zhongshan Ophthalmic Center, Sun Yat-Sen University, Guangzhou, China.

[5] Orbis International, New York, New York.

[6] Department of Ophthalmology, Rambam Health Care Campus, Haifa, Israel.

[7] Ruth and Bruce Rappaport Faculty of Medicine, Technion Israel Institute of Technology, Haifa, Israel.

[8] Javrishvili Eye Clinic Oftalmij, Tbilisi, Georgia.

[9] Akhali Mzera Eye Clinic, Tbilisi, Georgia.

[10] Clinica Oculistica, Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili, University of Genova, Policlinico Ospedale San Martino IRCCS, Genova, Italy.

[11] Shaare Zedek Medical Center, Jerusalem, Israel.

[12] New Vision University, Tbilisi, Georgia.

[13] BELKIN Vision Ltd., Yavne, Israel.

[14] Goldschleger Eye Research Institute, Tel Aviv University, Sheba Medical Centre, Tel Hashomer, Israel.

[15] Minnesota Eye Consultants and University of Minnesota, Minneapolis, Minnesota.

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Y.S.: Employee and Equity owner — Belkin Vision Ltd.

M.B.: Employee, Financial support, Safety Advisory Board, Patents, and Equity owner (as the founder) — Belkin Vision Ltd.

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HUMAN SUBJECTS: Human subjects were included in this study. The study was conducted in accordance with Good Clinical Practice guidelines, adhered to the tenets of the Declaration of Helsinki, ISO 14155, and all other related national requirements, and received full regulatory authority and Ethics Committee approval in each country and site (Clinica Oculistica Università di Genova, Genova, Italy; Queen's University Belfast, Belfast, UK; Moorfields Eye Hospital, London, UK; Rabin Medical Center, Petach-Tiqwa, Israel; Rambam Health Care Campus, Haifa, Israel; Shaarei Zedek Medical Center, Jerusalem, Israel; Soroka Medical Center, Beer-Shava, Israel; Wolfson Medical Center, Holon, Israel; Hadassah Medical Center, Jerusalem, Israel; Assuta Medical Center, Tel Aviv, Israel; Carmel Medical

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Author Contributions:

Conception and design: Congdon, Azuara-Blanco, Solberg, Belkin, Samuelson

Analysis and interpretation: Gazzard, Azuara-Blanco, Blumenthal, Traverso, Solberg, Belkin, Samuelson

Data collection: Gazzard, Congdon, Azuara-Blanco, Blumenthal, Gomelauri, Zaliniyan, Traverso, Bracha, Dvalishvili, Solberg, Belkin, Samuelson

Obtained funding: N/A

Overall responsibility: Gazzard, Congdon, Azuara-Blanco, Blumenthal, Gomelauri, Zaliniyan, Traverso, Bracha, Solberg, Belkin, Samuelson

Abbreviations and Acronyms:
AE = adverse event; **CI** = confidence interval; **COAST** = Clarifying the Optimal Application of Selective Laser Trabeculoplasty Therapy; **DSLT** = direct selective laser trabeculoplasty; **IOP** = intraocular pressure; **ITT** = intention-to-treat; **LiGHT** = Laser in Glaucoma and ocular Hypertension Trial; **mPP** = modified per protocol; **NS** = not significant; **OAG** = open-angle glaucoma; **SLT** = selective laser trabeculoplasty; **SAE** = serious adverse event; **SD** = standard deviation; **SSI** = secondary surgical intervention; **TM** = trabecular meshwork.

Keywords:
Direct selective laser trabeculoplasty, Intraocular pressure, Ocular hypertension, Open-angle glaucoma, Selective laser trabeculoplasty.

Correspondence:
Gus Gazzard, FRCOphth, UCL Institute of Ophthalmology and NIHR Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust, City Road, London, EC1V 2PD, United Kingdom. E-mail: g.gazzard@nhs.net; a.gazzard@ucl.ac.uk.

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