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# Direct selective laser trabeculoplasty in open angle glaucoma study design: a multicentre, randomised, controlled, investigator-masked trial (GLAUrious)

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## ABSTRACT

**Introduction** Laser trabeculoplasty is an effective and widely used treatment for glaucoma. A new laser technology, the Eagle direct selective laser trabeculoplasty (DSLTL) device, may provide automated, fast, simple, safe and effective laser treatment for glaucoma in a broader range of clinical settings. This trial aims to test the hypothesis that translimbal DSLTL is effective and not inferior to selective laser trabeculoplasty (SLT) in reducing intraocular pressure (IOP) in open angle glaucoma (OAG).

**Methods and analysis** This is a multicentre, randomised, controlled, investigator-masked study. The primary efficacy outcome is intergroup difference in mean change from baseline IOP measured at 6 months. Secondary outcomes include mean percentage reduction in IOP at 3, 6 and 12 months; proportion of participants with at least 20% reduction in IOP from baseline at 6 months; change in ocular hypotensive medications at 12 months and evaluation of safety. Participants were aged  $\geq 40$  years with OAG, including exfoliative or pigmentary glaucoma, or ocular hypertension with untreated or washed out IOP 22–35 mm Hg. Treatments: DSLTL: 120 shots, 3 ns, 400  $\mu$ m spot size, energy 1.4–1.8 mJ delivered at the limbus over 2 s. SLT: approximately 100 shots, 3 ns, 400  $\mu$ m spot size administered 360 degrees at the limbus using any gonioscopy lens, energy 0.3–2.6 mJ. A sample size of 164 is sufficient to detect a non-inferiority margin of 1.95 mm Hg for change from baseline IOP.

**Clinical trial registration number** NCT03750201, ISRCTN14033075.

Treatment of glaucoma with topical hypotensive medications depends on patient adherence and may be associated with side effects, inconvenience and financial burden to the patient. As a result, up to 50%–80% of patients fail to adhere to treatment over a 12-month period.<sup>3</sup> This study is addressing the top research priority of the James Lind Alliance: ‘What are the most effective treatments for glaucoma and how can treatment be improved?’<sup>4</sup>

Treatment of glaucoma with laser trabeculoplasty (LTP), such as selective laser trabeculoplasty (SLT), has been available for many years. Treatment with SLT compared with medical treatment offers cost-effective drop-free disease control for 74% of patients at 3 years when used as an initial therapy, as reported in a large randomised controlled trial.<sup>5</sup> The IOP reduction effect is still present in 50% of patients at 5 years, and treatment is repeatable.<sup>6</sup> SLT targets the trabecular meshwork (TM) and is designed to reduce IOP by improving aqueous outflow. The procedure lasts approximately 5–10 min and consists of 50–100 separate laser ‘spots’ delivered through a manually rotated mirrored lens (goniolens) placed on the cornea. Although SLT is considered to be a low-risk procedure, the goniolens requires use of a coupling gel and prolonged contact with the patient’s eye that can result in epithelial damage, blurred vision and discomfort, and carries a small but significant infection risk. Although the effectiveness of SLT as an initial treatment for primary open angle glaucoma (POAG) and ocular hypertension (OHT) has been demonstrated in clinical trials,<sup>5,7</sup> the procedure requires expertise which limits its widespread use.

Recently, Geffen *et al*<sup>8</sup> investigated the safety and efficacy of performing translimbal SLT without the use of a goniolens. In this small study, they were able to show that this technique appeared to be as efficacious as conventional SLT, however, taking less time and possibly causing fewer complications, possibly due to its non-contact methodology and avoidance of transcorneal laser path.

The current protocol uses a new device, the External Automatic Glaucoma Laser (Eagle): a translimbal, direct selective laser trabeculoplasty (DSLTL) system. Non-contact treatment automatically detects and directs laser energy through the

## INTRODUCTION

Glaucoma is a chronic, initially asymptomatic disease that may result in progressive optic nerve damage. An estimated 76 million people suffer from glaucoma worldwide,<sup>1</sup> making it the leading cause of irreversible blindness globally.<sup>2</sup> Although the damage is irreversible, further deterioration (‘progression’) may be prevented or delayed by reducing intraocular pressure (IOP). The goal of glaucoma treatment is to maintain the patient’s visual function with minimal impact on quality of life, and ideally, in the most cost-effective fashion.



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limbus overlying the TM. The entire 360 degrees of the TM is treated simultaneously in about 2 s.

## METHODS

This is a multicentre, randomised, controlled, investigator-masked trial designed to evaluate the relative safety and efficacy of translimbal DSLT compared with conventional SLT for glaucoma.

### Study outcomes

The primary efficacy outcome is the difference between the two treatment groups between the mean (washed out for medicated patients) baseline IOP and the mean (washed out for medicated patients) IOP measured at 6 months. Secondary efficacy outcomes include between-group differences in mean percentage reduction in IOP at 3, 6 and 12 months; the proportion of participants with at least 20% reduction in IOP from baseline at 6 months; and the change in mean number of topical hypotensive medications at 12 months compared with baseline. All treatments will be administered by an unmasked ophthalmologist. All post-randomisation IOP measures will either be collected using a masked technique or by a masked ophthalmologist.

Safety measures include all ocular adverse events (AEs). Quality of life and patient satisfaction will be evaluated with the Glaucoma Quality of Life (GQL-9)<sup>9 10</sup> and a standardised questionnaire.

### Ethics and regulatory approvals

The trial will be conducted according to the World Medical Association Declaration of Helsinki and is in receipt of full regulatory authority and research ethics committee (REC) approval in each country and site. The protocol is prospectively registered on a publicly accessible database (Protocol # 2017\_01, ClinTrials.gov # NCT03750201, ISRCTN14033075). Potential participants will be provided with the REC-approved patient information sheet, and given sufficient time to review and ask questions before providing written informed consent ahead of any study procedures.

### Study population

The study population comprises participants aged over 40 years with OAG, including exfoliative or pigmentary glaucoma, or OHT who are able to give informed consent to participate for 12 months. IOP at randomisation must fall between 22 and 35 mmHg inclusive in either an untreated or washed-out state. Participants must have gonioscopically visible scleral spur for 360 degrees and clear visualisation of the perilimbal sclera for 360 degrees with a vertical cup to disc ratio of less than 0.8. Patients with contraindications to SLT are excluded as are patients with angle closure glaucoma, congenital or developmental glaucoma, secondary glaucoma (except exfoliative or pigmentary glaucoma) or those with the presence of any peripheral anterior synechiae in the study eye. Patients must be able to undertake a reliable visual field test (defined as fixation losses, false positives and false negatives less than 33%). Any of the following visual field findings using the Humphrey visual field (HVF) analyser and Swedish Interactive Thresholding Algorithm (SITA) standard 24-2 programme would exclude a patient: a visual field mean deviation of less than -12 dB, greater than 75% of points depressed below the 5% level and greater than or equal to 50% of points depressed below the 1% level on the pattern deviation plot, at least 50% of points, that is, 2 or more, within the central 5 degrees with a sensitivity of 0 dB on the decibel plot and points within the central 5 degrees of fixation with a sensitivity greater than 15 dB in both hemifields on the decibel

plot. The mean defect in the fellow eye must be greater than -12 dB. Participants must not have any other clinically significant disease in either eye, prior incisional glaucoma surgery in the study eye, any significant cataract or cataract surgery in the last 6 months, prior corneal refractive surgery, prior SLT, significant amblyopia or dense pigmentation or haemorrhage in the perilimbal conjunctiva or anterior sclera. Other exclusions will include pregnancy, participation in another clinical trial other than a substudy of this trial, clinically relevant systemic disease or the anticipated need for other ocular surgery.

### Device description

DSLIT is a treatment modality for POAG, which uses similar laser parameters as SLT and has similar treatment indications. As in SLT, DSLIT employs frequency-doubled, Q-switched Nd:YAG laser with a wavelength of 532 nm. During the procedure, laser energy is delivered to the TM. This increases the permeability of the TM endothelial cells and thereby increases outflow, resulting in reduced IOP. In contrast to SLT, the DSLIT treatment uses the Eagle system to direct the laser energy directly through the limbus to the TM without the need for a delivery device (gonioscopy lens) or any contact with the participant's eye. Laser energy is administered through a full 360 degrees, almost completely automatically by the Eagle system, with only the operator's rough alignment of the eye and approval of the device's automatically acquired target. Laser treatment lasts for about 2 s with 120 laser pulses of preset 3 ns and a preset 400 µm spot size will be used, with the laser energy of 1.4–1.8 mJ delivered to the limbus. For the SLT, approximately 100 shots of a preset 3 ns duration and a preset 400 µm spot size will be used 360 degrees around the limbus, with the laser energy varied from 0.3 to 2.6 mJ by the clinician using any laser gonioscopy lens.

The trial has started using the prototype device, which was used in the first human study.<sup>9</sup> During this trial, the Eagle system became available. The Eagle system has the same functionality as the prototype, but with increased usability, namely, the device is now a smaller and lighter table top unit.

### Enrolment, randomisation and data acquisition

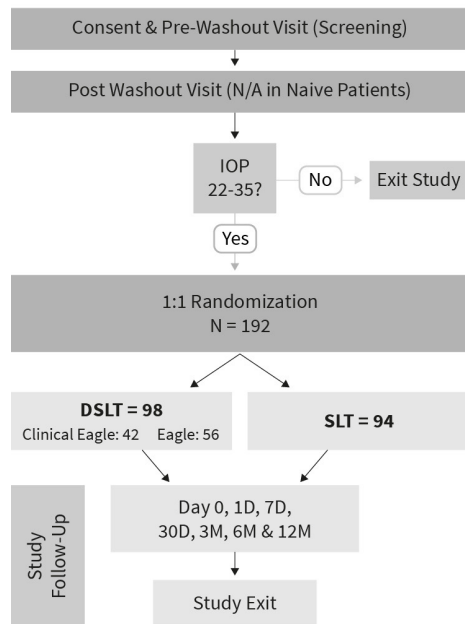
Randomisation will be per site, with lists generated as a 1:1 random algorithm by the study statistician (two sequences according to whether or not the participant is receiving beta-blockers) and sealed envelopes provided to site. All treatments will be administered by unmasked ophthalmologists, although masked investigators will collect post randomisation IOP and study assessments. It is not possible to mask participants due to the varying nature of the two treatments. [Figure 1](#) summarises the study design and patient flow.

After providing written informed consent, potential participants will be screened to ensure eligibility.

At this visit, the following examinations will be performed on both eyes:

- ▶ Goldmann applanation tonometry.
- ▶ Corrected visual acuity (CVA) using the ETDRS alphabet chart on a backlit light box.
- ▶ Slit-lamp examination of the anterior segment.
- ▶ Gonioscopy.
- ▶ Fundus examination.
- ▶ HVF examination using the 24-2 SITA standard programme.
- ▶ Recording of current ocular hypotensive medications and systemic medications (type and dosage).

If a participant is currently using topical ocular medications, IOP will be reassessed in a post-washout visit after a washout



**Figure 1** Flowchart depicting the enrolment and progression of participants through the trial. DSLT, direct selective laser trabeculoplasty; IOP, intraocular pressure; SLT, selective laser trabeculoplasty.

period of length determined by the type of medication(s) being used (up to 28 days).

During the washout period, additional visits can be conducted at the discretion of the investigator, to ensure continued safety, particularly for patients considered at risk for an unacceptably high IOP spike during washout.

If during one of these visits it is found that the participant's IOP increases to an unsafe level (at the investigators' discretion), ocular hypotensive medication will be reintroduced and they will be followed for safety until any AEs are resolved or stabilised, and then exited from the study.

Following washout, the eligibility of patients is confirmed and the threshold IOP value is determined by the investigators' clinical judgement. Participants will then be randomised 1:1 to SLT or DSLT. If both eyes are washed out and found to be eligible for inclusion, the principal investigator will enrol the eye with the highest post-washout IOP. If both eyes have the same IOP, the eye with the more advanced disease will be chosen. Standard glaucoma treatment will be (re)initiated in the non-study eye at the discretion of the investigator.

### Study interventions

As a prophylaxis against laser-induced IOP elevation, apraclonidine or brimonidine drops will be administered (45–60 min and 10 min before treatment) as well as a drop of pilocarpine (60 min before treatment).

Following treatment, the following assessments will be made on the study eye only:

- ▶ IOP immediately following treatment.
- ▶ IOP 1–2 hours after treatment (additional care at the discretion of the investigator).
- ▶ CVA using ETDRS.
- ▶ Slit-lamp examination with grading of anterior chamber cells (0 to +4) and flare (0 to +4).

Patients will be asked to provide feedback following treatment to assess satisfaction, pain and willingness to undergo the treatment again (graded using a Likert scale).

Following the treatment, participants will be instructed to use topical non-steroidal anti-inflammatory medications in the treated eye for 1 week at the discretion of the investigator.

Scheduled follow-up and assessment visits are planned at 1 day, 1 week, and 1, 3, 6 and 12 months following treatment. Patients receiving glaucoma medications will be asked to stop these 28 days before the 6-month visit.

Gonioscopic examination will be repeated at the 6-month follow-up visit to detect any changes to the anterior chamber angle after the laser treatment.

At each visit, the IOP will be assessed and compared with the threshold IOP limit value, if this value is reached, topical hypotensive medications will be initiated, starting with prostaglandin, then beta-blocker and other medications according to standard of care.

Patients will be asked to repeat the GQL-9 questionnaire at the 6-month visit and they will assess their willingness to repeat the treatment and whether they would recommend the treatment to a friend with glaucoma.

Treatment modification will be allowed for safety reasons if IOP becomes uncontrolled after treatment. There will be no reintroduction of medication for at least 1 month after treatment unless, in the opinion of the investigator, there is immediate risk to the health of the participant.

If cataract surgery, trabeculectomy or any other glaucoma surgery is required during the study follow-up period, the participant will undergo such treatment as deemed necessary (at the discretion of the investigator) and will be considered a treatment failure. She/he will continue to be followed up in the study glaucoma clinics thereafter.

Safety will be evaluated throughout the study consisting of recording of all AEs. An independent medical monitor will be responsible for overseeing safety and for evaluating all AEs reported to the sponsor. AEs and serious AEs are defined according to the International Conference on Harmonization E6 (R2) and International Organization for Standardization 14155:2011(E) definition.

### Statistical analyses and sample size calculation

A total of 164 patients will be required to reject a non-inferiority null hypothesis that DSLT change-from-baseline IOP is more than 1.95 mmHg worse (less) than the SLT change-from-baseline IOP. The primary hypothesis will be tested at 6 months post-treatment using the estimated difference in change-from-baseline IOP between study groups (DSLT and SLT) with 80% power and the associated 95% two-sided CI, a fitted analysis of covariance (ANCOVA) model will adjust for baseline IOP and for the use of beta-blocker drops in the fellow eye.

The sample size calculation was based on a non-inferiority margin of 1.95 mmHg and an anticipated SD of 3.5.<sup>10</sup> The non-inferiority margin of 1.95 mmHg was chosen based on clinical judgement as IOP measurement differences of up to 2 mmHg are considered to be non-clinically significant.<sup>11 12</sup> Other literature reports a predefined non-inferiority margin of 1–2.5 mmHg.<sup>13</sup>

The mean percentage reduction in IOP from baseline will be summarised by treatment group at 3, 6 and 12 months after enrolment. The proportion of participants with at least 20% reduction in IOP from baseline will be summarised at 6 months with associated 95% CI. The mean number of medications will be calculated for each group before treatment and at 12 months, and compared between groups. The GQL-9 questionnaire results will be summarised in appropriate tables by treatment group.

AEs will be coded and presented according to relatedness, severity and seriousness. Rates of AEs (on a per person basis) will be

calculated, and 95% CIs for the rates, and for the difference between treatment groups, will be produced using score-based methods.

## CONCLUSION

Laser trabeculoplasty is an approved treatment available to patients with OAG that can be used with or without ocular hypotensive medication to reduce IOP. The safety and effectiveness of SLT has been well demonstrated in prior studies.<sup>13–16</sup> Due to its IOP-lowering effect, SLT may result in a decrease or elimination of ocular hypotensive medications. SLT may cause inflammatory reactions, including cystoid macular oedema and, more commonly, anterior chamber inflammation.<sup>17–19</sup> The inflammation is usually mild to moderate in its severity and transient, with reductions in intensity seen within 24 hours post-treatment, and resolution in most eyes within 5 days.<sup>20</sup>

Another risk associated with SLT is the occurrence of post-operative IOP elevation. This usually occurs in the immediate postoperative phase (1–2 hours) and careful patient selection and prophylactic treatment can greatly reduce their occurrence.<sup>21</sup>

DSLTL is performed without physically touching the cornea, and preliminary studies have shown that it is a more rapid and simpler technique when compared with SLT.<sup>8</sup> Further, it has been suggested that it could be more easily administered in patients in whom contact techniques prove problematic or where anatomical obstacles exist, such as narrow iridocorneal angles or prominent facial bones.<sup>8</sup> The same study demonstrated similar IOP-lowering effect in both DSLTL and SLT, and suggested that DSLTL resulted in less corneal injury, inflammation and post-operative discomfort when compared with standard SLT.

Benefits of DSLTL may include a faster and simpler treatment, less postoperative inflammation and less subjective discomfort. In addition, the procedure does not require use of a gonioscope and therefore has the potential to increase the accessibility of glaucoma care throughout the world. This study will determine the efficacy and safety of the new Eagle system.

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