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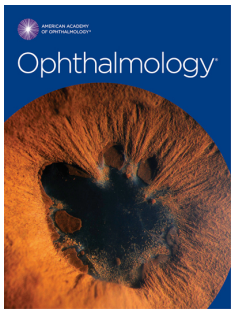

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TITLE

Efficacy of Repeat Selective Laser Trabeculoplasty in Medication-Naïve Open Angle Glaucoma and Ocular Hypertension during the LiGHT Trial

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***A listing of the LiGHT Trial Study Group is provided as an Appendix:** (available at www.aaojournal.org)

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Running head: Efficacy of Repeat SLT in treatment-naïve OAG & OHT patients retreated within 18 months

**This article contains additional online-only material: List of LiGHT Trial Study Group members, Table 5, Table 6, Table 7 and Figure 3 (available at www.aaojournal.org)

ABSTRACT

Purpose: To determine the efficacy of repeat selective laser trabeculoplasty (SLT) in medication-naïve open angle glaucoma (OAG) and ocular hypertensive (OHT) patients requiring repeat treatment for early to medium-term failure during the Laser in Glaucoma and Ocular Hypertension (LiGHT) trial.

Design: Post-hoc analysis of SLT treatment arm of a multicentre prospective randomised-controlled-trial.

Participants: Treatment-naïve OAG or OHT requiring repeat 360-degree SLT within 18 months. Re-treatment was triggered by pre-defined IOP and disease-progression criteria (using objective individualised target IOPs)

Methods: After SLT at baseline, patients were followed for a minimum of 18 months after second ('repeat') SLT. A mixed model analysis was performed with the eye as the unit of analysis, with crossed random-effects to adjust for correlation between fellow eyes and repeated measures within eyes. Kaplan-Meier curves plot the duration of effect.

Outcome Measures: Initial ('early') IOP lowering at 2-months and duration of effect following initial and Repeat SLT.

Results: 115 eyes of 90 patients received Repeat SLT during first 18 months of the trial. Pre-treatment IOP prior to Initial SLT was significantly higher than that prior to pre-retreatment IOP of Repeat SLT (mean difference: 3.4, 95% confidence interval (CI) 2.6 to 4.3, mmHg; p<0.001). Absolute IOP reduction at 2-months was greater following Initial, compared to Repeat, SLT (mean difference: 1.0, 95% CI 0.2 to 1.8, mmHg; p=0.02). Adjusted absolute IOP reduction at 2-months (adjusting for IOP prior to initial or repeat laser) was greater following Repeat SLT (adjusted mean difference: -1.1, 95% CI -1.7 to -0.5, mmHg; p=0.001). 34 eyes were 'early failures' (retreated 2-months after Initial SLT) vs 81 'later failures' (retreatment beyond 2-months following Initial SLT). No significant difference in early absolute IOP reduction at 2-months following Repeat SLT was noted between 'early' vs 'later' failures' (mean difference: 0.3, 95% CI, -1.1 to 1.8,mmHg; p=0.655). Repeat SLT maintained drop-free IOP control in 67% of 115 eyes at 18 months, with no clinically-relevant adverse events.

Conclusion: These exploratory analyses demonstrate Repeat SLT can maintain IOP at or below Target IOP in medication-naive OAG and OHT eyes requiring retreatment with atleast an equivalent duration of effect to initial laser.

INTRODUCTION

Glaucoma is a multifactorial disease characterised by optic nerve damage, resulting in progressive visual field loss. It is a leading cause of blindness worldwide, second only to cataract (1). The mainstay of glaucoma treatment is lowering of intraocular pressure (IOP) to slow or prevent further progression and visual loss (2).

Selective laser trabeculoplasty (SLT) is increasingly becoming an established treatment to lower IOP for open angle glaucoma (OAG) and ocular hypertension (OHT). In a process known as selective photothermolysis, SLT uses a 532nm Q switched, frequency-doubled Nd:YAG laser to deliver a short pulse duration (3 nanoseconds) to pigmented trabecular meshwork (TM) cells, causing less collateral damage compared to argon laser trabeculoplasty (ALT) as a result (3, 4). IOP lowering has been shown to be mediated through an increase of aqueous outflow through the TM (5) but the effect does diminish with time (6).

The efficacy of Repeat SLT when used as a primary treatment in true medication-naïve OAG or OHT patients remains unclear. Repeatability of SLT has previously been studied and considered feasible in suitable patients requiring further IOP reduction (7-14). However, many of these studies are retrospective, limited by small sample sizes and lack pre-defined retreatment criteria. In addition, in all but one of these studies (13), SLT was used as an adjunctive treatment in patients already on topical IOP lowering treatment.

We have previously reported the main results of the Laser in Glaucoma and Ocular Hypertension (LiGHT) trial (15). Primary SLT was found to be more cost-effective than initial medication over three years while health related quality of life (HRQL) at 36 months was equivalent between the two treatment arms. By three years, IOP was still at or below preset targets in 78.2% of eyes with SLT alone, 76.6% of whom had needed only one treatment. The results from the LiGHT trial support other studies in the use of SLT as a primary treatment in newly diagnosed OHT and OAG eyes(16-19).

The purpose of this study was to investigate the effectiveness of Repeat SLT within the context of the LiGHT trial. We assessed whether the IOP lowering efficacy and duration of effect of Repeat SLT were comparable to Initial SLT in completely medication-naïve OAG and OHT eyes. We also investigated whether the timing of Initial SLT failure influenced the efficacy of repeat laser. Whilst 158 eyes out of a total of 611 eyes (25.9%) underwent Repeat SLT during the 36 months duration of the trial, for this post-hoc analysis, we chose the subset of 115 eyes requiring Repeat SLT during the initial 18 months of the LiGHT trial (i.e. ‘early’ to ‘medium-term’ failures) to permit equivalent duration of follow up for initial and Repeat SLT. We hypothesised that Repeat SLT would be effective in restoring IOP control (maintaining IOP ‘at or below’ Target IOP) in eyes previously treated with Initial SLT, but absolute IOP reduction would be less compared to Initial SLT, due to lower pre-treatment IOPs prior to Repeat SLT.

METHODS

The study was conducted in accordance to good clinical practice (GCP) guidelines and adhered to the tenets of the Declaration of Helsinki. Institutional Review Board (IRB)/Ethics Committee approval was obtained. All patients provided written informed consent before participation to the trial. The LiGHT Trial is registered at www.controlled-trials.com (registration number ISRCTN32038223).

This study was a post hoc analysis of the LiGHT trial, the design and baseline characteristics of which have been previously described (20, 21). Inclusion criteria were newly diagnosed, untreated OAG or OHT in one or both eyes, qualifying for treatment according to National Institute for Health and Care Excellence (NICE) guidelines (22), open angles on gonioscopy, and, for OAG, visual field loss with mean deviation (VF MD) not worse than -12 dB in the better eye or -15 dB in the worse eye and corresponding damage to the optic nerve head. Patients were 18 years or older and able to read and understand English, had a visual acuity of 6/36 or better in the treated eye(s) and no prior intraocular surgery, except uncomplicated phacoemulsification at least one year before entering the trial.

Patients were excluded if there were any relative contra-indications to SLT (history of uveitis, macular oedema, secondary glaucomas), if they were unable to use topical medical therapy, had symptomatic cataract and wanted to undergo cataract surgery, or were having active treatment for another ophthalmic condition. All measurements influencing treatment escalation decisions were performed by masked observers: automated visual field using Humphrey Field Analyzer Mark II Swedish interactive threshold algorithm standard 24-2 programme (Carl Zeiss Meditec, Dublin, CA, USA), Heidelberg Retina Tomography (HRT) disc imaging (Heidelberg Engineering, Heidelberg, Germany) and IOP (Goldmann applanation tonometry with daily calibration). Clinicians and patients were not masked to treatment allocation. Patients were monitored for 3 years in this initial phase of the study.

Glaucoma severity was defined (see Table 1) with pre-set objective severity criteria from the Canadian Target IOP Workshop (23) with additional central VF loss criteria (24). Severity stratification (OHT, mild, moderate or more severe OAG) determined an eye specific 'Treatment Target IOP' and follow-up intervals. Target IOP was objectively defined based on both percentage reduction from untreated IOP and an absolute value and then adjusted during the study according to presence or absence of disease progression.

To minimise bias in escalating treatment, standardised criteria were used according to a protocol following the international guidelines of the European Glaucoma Society, (25) American Academy of Ophthalmology Preferred Practice Pattern (26) and the South-East Asia Glaucoma Interest Group (27). These, alongside NICE thresholds for disease definition (OAG or OHT) (22) were

incorporated into a real-time web-based clinical decision support software, based on optic disc analysis (Heidelberg Retina Tomography, HRT), automated visual fields analysis (Humphrey Visual Field, HVF) and IOP measurements. Objective VF and optic nerve head imaging criteria using the Glaucoma Progression Analysis (GPA) automated change detection and HRT rim area measurements defined 'Strong Evidence' and 'Less Strong Evidence' of deterioration (20).

Treatment escalation was advised when there was:

- IOP above target by more than 4 mmHg at a single visit*, or*
- 'Strong Evidence' of deterioration, irrespective of IOP (i.e. GPA: 'Likely progression' and/or HRT rim area loss >1% per year ($p < 0.001$), *or*
- IOP above target by ≥ 2 <4 mmHg and 'Less Strong Evidence' for progression (i.e. GPA 'Possible progression' and/or HRT rim area >1% per year ($p < 0.01$)

Target IOP was reduced by 20% if deterioration was identified despite the measured IOP being at or below target. If the IOP was above target by less than 4mmHg, but with no evidence for deterioration, then the target IOP was revised to the mean of the previous 3 visits over which deterioration had not occurred. The process for escalating treatment is shown in Figure 1.

Follow-up intervals were initially set at entry to the study according to NICE guidance (22)and subsequently adjusted on the basis of IOP control, glaucoma progression status or adverse reactions. The routine schedule of appointments and assessments for patients has been published previously (21). At follow up, patients underwent visual acuity testing (ETDRS logMAR at a starting distance of 4 m), slit-lamp examination, visual field testing, HRT optic disc imaging, single IOP measurement (Goldmann applanation tonometry) and clinical assessment of the optic discs, maculae and fundi.

Standardisation of SLT delivery was achieved by protocol-defined settings and clinical endpoints. The protocol defined 360-degree TM treatment, delivered by 100 non-overlapping shots (25 per quadrant) of a preset 3 nanoseconds duration and preset 400µm spot size, with the laser energy from 0.3 to 1.9mJ set by the clinician according to observable bubble formation at least 50% of the time. IOP was checked 60 minutes following SLT procedure. One SLT re-treatment was permitted during the study, if/when a treatment escalation was recommended by the decision support software (using criteria for treatment escalation described above) and confirmed by the treating clinician. To allow time for the full effects of laser to occur, the earliest interval at which Repeat SLT was permitted was following the first scheduled visit 2 months post Initial SLT. SLT was not repeated if significant complications of laser treatment had occurred (one patient with IOP spike), if new medical conditions prevented repetition or patients declined re-treatment (usually due to a lack of IOP lowering response following Initial SLT - not protocol

defined). In such cases, treatment escalation with topical medication rather than Repeat SLT was permitted. In eyes that underwent Repeat SLT, if further treatment escalation was later required, then topical medication was the next step.

All eligible study eyes that received 2 SLTs within the first 18 months of the LiGHT trial were included in the analysis, such that eyes had at least as long a duration of follow up after initial and Repeat SLT. For Initial SLT, baseline IOP was the pretreatment IOP measured on the date of the patient's baseline visit. For Repeat SLT, pre-retreatment IOP was the IOP at the clinical visit at which the decision support software recommended a treatment escalation (as confirmed by the treating clinician and when the decision to escalate treatment was made). When eyes received retreatment, IOP values at time points subsequent to Repeat SLT laser were not included as part of Initial SLT values but as the part of "Repeat SLT". Similarly, for eyes started on topical medication following "Repeat SLT", IOP at time points subsequent to initiation of medication were not included as part of "Repeat SLT", since these were a reflection of SLT and medication combined and not SLT efficacy alone.

We present IOP at post-laser time points (2 months, 6 months, 12 months and 18 months). To demonstrate the IOP lowering efficacy of initial and Repeat SLT in this cohort of eyes receiving Repeat SLT due to early/medium-term failure, we focussed primarily on the 2-month timepoint. This was the first scheduled visit following laser, allowing time for the full laser effect to occur, whilst also being free from bias arising from censoring of IOP data due to introduction of additional treatment at later timepoints ('treatment escalations'). Previous analysis of all subjects in the SLT arm has showed 2-month IOP response to be a strong predictor of 3 year outcomes and an indicator of future control (28).

We evaluted whether the treatment response of Initial SLT influenced the efficacy of Repeat SLT in this cohort of early/medium-term SLT failures receiving repeat treatment. We compared IOP lowering between eyes that demonstrated an initial (but insufficient) IOP-lowering response following Initial SLT ('Early Failures': Repeat SLT required following the first scheduled visit at 2 months and performed within 4 weeks) with eyes that demonstrated adequate initial IOP lowering after Initial SLT but in which the treatment effect subsequently diminished triggering Repeat SLT ('Later Failures': Repeat SLT performed beyond 2 months post Initial SLT).

To compare duration of effect between initial and Repeat SLT in this cohort of eyes receiving repeat laser, a Kaplan Meier plot of time to failure was constructed using a clinically relevant definition of success: IOP control (maintaining IOP 'at or below' Target IOP) after SLT without additional IOP lowering medications, further laser procedures or incisional glaucoma surgery (10). The maximum follow up period was 18 months (548 days) such that eyes had an equivalent duration of follow up after initial and Repeat SLT.

STATISTICAL ANALYSIS

The unit of analysis was the eye. All eligible study eyes that received 2 SLTs within the first 18 months of the LiGHT trial were included in the analysis, with appropriate statistical measures taken to account for correlation amongst paired eyes within a patient.

Mean IOP at 2 months (following initial and Repeat SLT) was compared with respective pretreatment IOPs using mixed model analysis with crossed random effects. Random effects were used to adjust for correlation between paired eyes whilst also taking into account repeated measures within eyes. Mixed model analysis with crossed random effects was also used for comparison of absolute IOP reduction and adjusted absolute IOP reduction between initial and Repeat SLT at 2 months, and for comparison of absolute IOP lowering for Repeat SLT in 'early failures' vs 'later failure' eyes.

Statistical comparisons were made at baseline and the 2-month timepoint, but beyond 2 months, eyes were censored if they underwent treatment escalation and so statistical comparison of IOP reduction between initial vs Repeat SLT at further timepoints was not performed.

A sensitivity analysis using one eye chosen at random per patient (for subjects with both eyes in the original analysis) was also performed. A Kaplan Meier plot was also produced using one eye chosen at random (for subjects with both eyes in the original analysis) as a sensitivity analysis to establish whether inclusion of multiple eyes per patient in the original analysis altered the results.

Statistical significance was defined as a 2-sided P value <0.05. Analyses were carried out using Stata15 (StataCorp, 2015. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP).

RESULTS

115 eyes of 90 patients had undergone 2 SLTs by 18 months into the LiGHT trial and were included in this analysis of Repeat SLT. Additionally, 43 eyes had been started on topical medication following Initial SLT (and did not undergo Repeat SLT). 20 of these eyes were started on topical medication following the first scheduled visit at 2 months and were judged by treating clinicians to have had 'no' treatment effect from Initial SLT. A further 23 eyes were started on topical medication *beyond* the first scheduled visit and did not undergo Repeat SLT. The decision to start medication instead of Repeat SLT in these 23 eyes was made jointly by the local treating clinician and patients. At 18 months, 453 eyes were still successfully maintaining IOP control following single, initial baseline SLT and had not required additional treatment.

BACKGROUND CHARACTERISTICS

The demographics of the 90 patients with the study sample of 115 eyes are presented in Table 2. The distribution of glaucoma severities was similar in the sensitivity analysis using one eye randomly selected per patient (see Appendix).

IOP LOWERING EFFICACY OF INITIAL AND REPEAT SLT

Mean IOP values at each post laser time point for initial and Repeat SLT are given in Table 3. Pre-treatment IOP prior to Initial SLT was significantly higher than the pre-retreatment IOP prior to Repeat SLT (mean difference: 3.4mmHg, 95% CI, 2.6 to 4.3mmHg; p<0.001). Comparison of absolute IOP reduction at 2-months between initial and repeat SLT demonstrated a greater reduction following initial SLT which was statistically, and probably clinically, significant (mean difference: 1.0, 95% CI 0.2 to 1.8, mmHg; p=0.02). Adjusting for the corresponding pre-treatment IOP ('adjusted absolute IOP reduction'), the adjusted absolute IOP reduction at 2-months was greater following Repeat SLT (adjusted mean difference: -1.1, 95% CI -1.7 to -0.5, mmHg; p=0.001). Sensitivity analysis using one eye randomly selected per patient also demonstrated similar results (see Appendix). Beyond 2 months, eyes were censored if they underwent treatment escalation and so statistical comparison of IOP reduction between Initial vs Repeat SLT was not performed.

Mean (SD) total power of Initial SLT was 89.1mJ (27.5) and total number of applications was 98.9 (4.6) shots. Mean (SD) total power of Repeat SLT was 100.5mJ (24.9) and total number of applications was 99.5 (4.6) shots. The difference in total power of SLT between Initial vs Repeat SLT was both clinically and statistically significant (mean difference: 11.6mJ, 95% CI 7.7mJ to 15.6mJ; p<0.001). There was no significant difference in the total number of applications (mean difference: 0.6 shots, -0.5 shots to 1.7 shots; p=0.266).

A further sub-analysis of the 115 eyes requiring Repeat SLT within the first 18 months is presented in Table 4. 34 eyes required Repeat SLT at 2 months ('Early Failures') vs 81 eyes required Repeat SLT later ('Later Failures). IOP lowering data at 2 months for 'Early' and 'Later' Failures is presented, alongside for reference, the 2 month IOP lowering data for the 43 eyes started on topical medication following initial SLT and the 453 eyes that were maintaining successful IOP control following initial SLT.

Overall, in both the 'Early Failures' and 'Late Failures' Repeat SLT eyes, there was a greater proportion of eyes with 'moderate' and 'severe' POAG compared to the group of eyes controlled on a single SLT at 18 months. They also had a greater required absolute IOP reduction to achieve 'Target IOP' compared to eyes controlled on a single SLT at 18 months.

Comparison of pre-treatment IOP prior to initial SLT for the 'Early Failures' vs 'Later Failures' who underwent repeat SLT demonstrated a significantly higher pre-treatment IOP in the 'Early Failures' eyes (mean difference: 3.0mmHg, 95% CI, 0.3 to 5.8mmHg; p=0.033). Absolute IOP reduction at 2 months following initial SLT was not statistically or clinically significantly different between 'Early Failures' and 'Later Failures' (mean difference: 0.6 mmHg, 95% CI, -1.4 to 2.6; p=0.551). There was no significant difference in pre-retreatment IOP prior to Repeat SLT between 'Early Failures' vs 'Later Failures' eyes (mean difference: 1.2 mmHg, 95% CI, -0.5 to 3.0 mmHg; p=0.169), with no significant difference in absolute IOP reduction following Repeat SLT at 2 months between 'Early Failures' vs 'Later Failures' (mean difference 0.3mmHg, 95% CI, -1.1 to 1.8mmHg; p=0.655).

For reference, mean absolute IOP reduction at 2 months following Initial SLT (95% CI) in the 20 eyes which then immediately started on topical medication ('no' treatment effect from Initial SLT – as judged by clinician) was 1.3mmHg (-0.2 to 2.7mmHg). Mean absolute IOP reduction (95% CI) at 2 months in the 23 eyes which started on topical medication beyond the first scheduled visit but did not undergo Repeat SLT was 5.1mmHg (3.7 to 6.1mmHg). Mean absolute IOP reduction (95% CI) at 2 months in the 453 eyes successfully maintaining IOP control to 18 months following single Initial SLT was 7.9mmHg (7.6 to 8.2mmHg). The mean IOP at 2 months in eyes following repeat SLT, in both 'Early Failures' and 'Late Failures', was similar to the 2 month IOP in eyes following single SLT and not requiring a repeat treatment.

DURATION OF EFFECT

In this analysis, the duration of Repeat SLT effect (and restoration of IOP control) lasted at least as long as after the Initial SLT. For this sample of patients requiring Repeat SLT within 18 months of Initial SLT, using 'no further IOP lowering interventions following Initial SLT' as a definition of success, Kaplan Meier analysis of Initial SLT survival demonstrated a median duration of effect of 189 days (Interquartile range (IQR): 75 – 340 days), see Figure 2. We could not determine overall median duration of effect for Repeat SLT, as 50% of these eyes did not reach the endpoint within the 18 months follow up period, though our results

show that it is at least 18 months. Two eyes in the study sample underwent cataract surgery for visually significant cataract during the study period (following Repeat SLT) and were included in this analysis. If these 2 eyes are excluded from the analysis or treated as Repeat SLT failures, the results and conclusions are unchanged.

Thirty eight of 115 eyes (33%) receiving Repeat SLT within the first 18 months had commenced medical treatment ('Repeat SLT failures') in the 18 months following the Repeat SLT. Approximately 60% of these eyes had a baseline disease severity of either 'moderate' OAG (12 eyes, 31.6%) or 'severe' OAG (11 eyes, 29%), with fewer OHT (1 eye, 2.6%) or 'mild' OAG (14 eyes, 36.8%). In these 38 'Repeat SLT failure' eyes, 20 were 'early failures' and 18 were 'later failures' following Initial SLT.

The remaining 67% of eyes (77 of 115) did not require further intervention in the subsequent 18 months. Approximately 68% of these eyes had a baseline disease severity of either 'OHT' (21 eyes, 27.3%) or 'mild' OAG (32 eyes, 41.6%), with fewer 'moderate' OAG (15 eyes, 19.5%) or 'severe' OAG (9 eyes, 11.7%). Survival estimates taking one randomly-selected eye per patient were similar (see Appendix).

Of the 115 eyes requiring Repeat SLT following Initial SLT, the indication for Repeat SLT in 98.3% (113 eyes) of eyes was due to the IOP not being at target. Of the 2 remaining eyes, 1 eye required Repeat SLT due to IOP not being at target and concurrent visual field progression and the other eye due to visual field progression alone. Of the 38 eyes requiring additional treatment escalation following Repeat SLT (i.e. started on medication), 92.1% (35 eyes) of these eyes were escalated due to the IOP not being at target. Of the 3 remaining eyes, 1 eye required additional treatment due to the IOP not being at target and concurrent visual field progression whilst 2 eyes had visual field progression alone.

SAFETY

We found no evidence of harm caused by SLT during the LiGHT trial (15, 28); no IOP spikes >5mmHg from pre-treatment IOP at 60 minutes post procedure were seen after Repeat SLT. There were no sight threatening adverse events related to initial or Repeat SLT. All laser-related adverse events (e.g. discomfort, headaches, hyperaemia, transient blurred vison) were self-limiting and resolved within 8 weeks following SLT.

DISCUSSION

The aim of this study was to determine and characterise the efficacy of Repeat SLT in eyes requiring retreatment (within 18 months) following Initial SLT. Mean IOP following both Initial and Repeat SLT was clinically and statistically significantly reduced

from the corresponding pre-treatment IOP at 2 months (p<0.001), confirming Repeat SLT to be effective (see Table 3). This supports results from other studies which have suggested effective IOP reduction following Repeat SLT (8-10, 12, 13).

Furthermore, compared to Initial SLT (controlling for difference in pre-treatment IOPs), adjusted absolute IOP reduction was statistically significantly greater following Repeat SLT at the 2 month timepoint than at the same time post-laser following the first treatment. It is possible that this demonstrates an additive effect of Repeat SLT. An alternative explanation is that this may be inflated by superimposed effects of regression to the mean: LiGHT is a pragmatic trial primarily designed to evaluate quality of life and cost-effectiveness and patients were not recalled to define a second baseline IOP prior to Repeat SLT. However, the longer duration of effect for Repeat SLT suggested by fewer failures ('reinterventions') over an equivalent 18 months follow up window supports the idea of a greater, additive IOP lowering after re-treatment. Histological studies have demonstrated that SLT causes minimal TM damage (4, 29) and this also fits with the repeatability of IOP lowering as demonstrated in our results.

Following Initial SLT, there was a trend for mean IOP to increase over time. By the nature of the patient selection for this analysis, this was more rapid than in the LiGHT trial overall (15), since we specifically selected patients requiring retreatment within 18 months. Our trial protocol mandated that more advanced disease had to achieve more stringent targets with greater IOP reductions (minimum 30% reduction vs minimum 20% for mild OAG or OHT eyes) (20) and were thus more likely to need treatment escalation to achieve these lower targets. This is reflected in the greater proportion of 'moderate' OAG or 'severe' OAG (47/115 = 40.9%) eyes in the Repeat SLT study sample compared to those eyes controlled on single SLT at 18 months (44/453 = 9.7%) and the greater IOP reduction required to achieve the target IOP (Table 4), especially in the 'early failure' group.

Similar to other studies (8-10, 13), the pretreatment baseline IOP of Initial SLT was significantly higher than that prior to Repeat SLT (mean difference: 3.4mmHg, 95% confidence interval (CI), 2.6 to 4.3mmHg; p<0.001). This is because Repeat SLT was delivered prior to the full treatment effect of the Initial SLT wearing off, in contrast to the treatment-naïve baseline IOP. This mirrors clinical practice where repeat treatment escalations (medication, laser or surgery) are usually not delayed to allow IOP to return to pre-treatment levels. Higher starting baseline IOP has been found to be a predictor of greater absolute IOP lowering (30) and hence mean absolute IOP reduction was expected to be less for Repeat SLT compared to Initial SLT (e.g. at 2 month timepoint, mean difference 1.0mmHg, 95% CI 0.2 to 1.8mmHg; p<0.001). The greater adjusted absolute IOP reduction after Repeat SLT, controlling for the difference in pre-treatment IOP, suggests that further laser may be additive to the initial treatment. This is also suggested by the cumulative treatment effect measured at 2 months after Repeat SLT being similar to the treatment effect achieved after the Initial SLT in those not requiring re-treatment (see table 4).

Mean (SD) total power of Initial vs Repeat SLT was both clinically and statistically significantly different (mean difference: 11.6mJ, 95% CI 7.7mJ to 15.6mJ; p<0.001) whereas there was no clinically or statistically significant difference in the number of applications (mean difference: 0.6 shots, -0.5 shots to 1.7 shots; p=0.266). The greater total power used for Repeat SLT could be due to several reasons. Firstly, greater energy per shot may have been required during Repeat SLT to generate the 'observable bubble formation at least 50% of the time' as mandated by our SLT treatment protocol. There could also have been treatment bias by the clinicians who may have increased the energy per shot, having recognised that Initial SLT (with a lower total power) had not been as effective as hope, by virtue of the patient receiving Repeat SLT.

We sought to determine whether 'early' treatment failure compared to 'later' treatment failure of Initial SLT predicted the response to Repeat SLT. Our results show that Early Failures of Initial SLT had higher pre-treatment baseline IOPs and less initial IOP lowering compared to Later Failures of Initial SLT, but that Repeat SLT provided a meaningful additional IOP lowering effect. The greater number of 'moderate' and 'severe' OAG eyes in the Early Failure compared to Later Failure group, also meant that the Early Failure group required greater absolute IOP reductions to achieve target IOP (and similarly compared to those eyes controlled on a single SLT at 18 months) – see Table 4.

In our Kaplan Meier analysis, we used a clinically-relevant and robust definition of success: IOP control (IOP at or below target IOP) maintained after Initial SLT without additional IOP lowering medications, further laser procedures or incisional glaucoma surgery (10). The Kaplan Meier analysis shows that Repeat SLT can have a longer duration of IOP-lowering than the first laser. Thus, even after a waning of effect within 18 months, repeat treatment may work for longer and thus be worthwhile. Other studies have also suggested that Repeat SLT could have a longer duration of clinical benefit than Initial SLT (10, 13). Of the eyes that failed following Repeat SLT, the majority had a baseline disease severity of either 'moderate' OAG (12 eyes, 31.6%) or 'severe' OAG (11 eyes, 29%). This could partly explain the greater proportion of 'early failure' eyes failing Repeat SLT (20/34 = 58.8%) compared to 'later failures' (18/81 = 22.2%) as the increased relative proportion of 'moderate' and 'severe' OAG eyes compared to 'later failures' necessitated a greater absolute IOP reduction to achieve target IOP.

Direct comparison of our results with other studies is difficult due to differences in study design, patient demographics and concurrent use of topical medication at the time of SLT. However, mean absolute IOP reduction in our study for both initial and Repeat SLT was comparable with what has been previously reported (9, 10, 13, 14). Where variations exist, this could be due to higher baseline IOPs (for both Initial and Repeat SLT) in our study, since eyes in our analysis were not on concurrent topical medication at the time of either Initial or Repeat SLT in contrast to other studies (8-10, 12, 14). Differences in SLT treatment protocol such as number of spots and degree of TM treated could also be contributory (13). In our study, we also escalated treatment when patients failed to reach pre-defined indvidualised target IOPs following both Initial and Repeat SLT; thus there

are fewer eyes available for analysis at later time-points due to censoring of IOP data from medication-treated eyes, which means we should be cautious interpreting mean IOP outcomes beyond 2 months.

Certain other cautions should be noted. There is a selection bias in several of the retrospective SLT repeatability studies and also in our study, where eyes included were those having Repeat SLT following an initial response to the first SLT (judged by the treating clinician). During the LiGHT trial, by 18 months, 43 eyes out of original 611 eyes treated with SLT (7.0%) had been started on topical medication following Initial SLT rather than receiving Repeat SLT. Twenty of these eyes were started on topical medication following the first scheduled visit at 2 months and were judged by treating clinicians to have had 'no' treatment effect from Initial SLT. There were also too few eyes (n=15 eyes) that underwent Repeat SLT after 'no' initial response (less than a 10% change in IOP after first SLT) to be able to draw meaningful conclusions about the effects of a Repeat SLT when the first gave no IOP lowering response. This means we cannot comment on the overall efficacy of Repeat SLT entirely irrespective of Initial SLT response from this analysis. Furthermore, our analysis comprises a sample of the original 611 eyes receiving SLT at baseline who then required Repeat SLT *within the first 18 months* of the trial, so that duration of follow-up would be at least as long (18.8%, 115 eyes). It does not include those eyes in the trial that received single SLT and subsequently maintained IOP control until the end of the trial at 36 months. It is therefore important to note that the median duration of survival for Initial SLT presented in this analysis is for eyes that required Repeat SLT *within the first 18 months of the trial* and not for *all* eyes following Initial SLT, or for eyes that had retreatment *beyond* the initial 18 months of the study.

Compared to previous SLT repeatability studies, this study has several strengths. The LiGHT trial was multi-centre and conducted prospectively. Eyes were treated to pre-defined target IOPs based on disease severity with pre-defined treatment escalation criteria and SLT treatment parameters in treatment-naive subjects (20). Limitations include the post-hoc (albeit pre-specified) nature of this analysis. Despite this, we present one of the largest datasets of RCT-collected clinical data on Repeat SLT in treatment-naïve OAG/OHT patients. Whilst the analyses performed are exploratory, they are clinically valuable and add to the body of evidence supporting the use of Repeat SLT in medication-naive eyes that have undergone previous primary SLT.

CONCLUSIONS

Analysis of Repeat SLT responses showed that it is effective at achieving IOP control in OAG and OHT eyes requiring retreatment within 18 months of Initial SLT. Additional SLT maintained drop-free IOP control in 67% of eyes 18 months later. Although in this study, the eyes requiring lower target IOPs would be deemed failures, the laser did contribute significantly to lowering IOPs. Following Repeat SLT, the cumulative effect of initial and Repeat SLT may provide an equivalent and possibly longer duration of clinical benefit than following Initial SLT alone. Repeat SLT is safe, with minimal laser-related side effects seen during the LiGHT trial.

Figure 1: Process for escalating treatment in OAG. * On two consecutive visits. ** As per protocol. ^Until progression confirmed/refuted. VF progression required three follow-up VF assessments. Maximal IOP, IOP above which surgery was offered without progression or 35mmHg for OHT (see text). IOP, intraocular pressure; MMT, maximum medical therapy; OAG, primary open angle glaucoma; VF, visual field –

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Figure 2: Kaplan Meier Plot for 115 eyes: Initial SLT (blue line) vs Repeat SLT (red line)

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APPENDIX 1:

LiGHT TRIAL STUDY GROUP

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APPENDIX 2:

SENSITIVITY ANALYSIS

ONE EYE PER PERSON – RANDOMLY SELECTED

Characteristics	Value
Age (years), mean (SD)	**63.5 (13.1)**
Gender (patients), (%)	
Male	**52 (57.8%)**
Female	**38 (42.2%)**
Ethnicity (patients), (%)	
White European	**63 (70.0%)**
Black	**17 (18.9%)**
Asian	**6 (6.7%)**
Other	**4 (4.4%)**
Disease Severity (eyes), (%)	
OHT	**15 (16.7%)**
'Mild' OAG	**37 (41.1%)**
'Moderate' OAG	**21 (23.3%)**
'Severe' OAG	**17 (18.9%)**
Baseline IOP (mmHg), mean (SD)	**24.9 (6.6)**

Table 5: Baseline characteristics of study sample

APPENDIX 3:

SENSITIVITY ANALYSIS

ONE EYE PER PERSON – RANDOMLY SELECTED

	Number of eyes (n)	Initial SLT Mean IOP (SD) (mmHg)	Initial SLT Mean absolute IOP reduction from pre-treatment IOP (mmHg; 95% CI)	Initial SLT Mean % IOP reduction from pre-treatment IOP (SD)	Number of eyes (n)	Repeat SLT Mean IOP (SD) (mmHg)	Repeat SLT Mean absolute IOP reduction from pre-retreatment IOP (mmHg; 95% CI)	Repeat SLT Mean % IOP reduction from pre-retreatment IOP (SD)	Initial vs. Repeat SLT Mean difference in absolute IOP reduction from pre-treatment IOP (mmHg; 95% CI)	Initial vs. Repeat SLT *Adjusted* mean difference in absolute IOP reduction from pre-treatment IOP (mmHg; 95% CI)
Pre-treatment	**90**	**24.9** ** **(6.6)**			**90**	**21.1** ** **(4.1)**				
2 months	**78**[a,b]	**19.2 (3.9)**	**5.4* (4.5 to 6.4)**	**20.0 (13.5)**	**80**[c,d]	**16.5 (3.3)**	**4.3* (3.6 to 5.0)**	**19.8 (12.8)**	**1.5 (0.4 to 2.6)**	**-0.9 (-1.7 to -0.2)**
6 months	46[a,b]	19.0 (3.9)	4.9* (3.7 to 6.2)	19.0 (14.0)	68[c,d]	17.1 (3.3)	4.3 (3.4 to 5.1)	18.9 (13.6)	0.7 (-0.8 to 2.2)	-0.8 (-1.8 to 0.2)
12 months	21[a,b]	20.8 (4.6)	3.6* (1.8 to 5.4)	13.5 (13.6)	58[c,d]	17.5 (3.6)	3.9 (2.9 to 4.8)	16.8 (16.0)	-1.1 (-4.0 to 1.7)	-1.7 (-3.3 to -0.1)
18 months	0[b]	-	-	-	47[c,d]	16.8 (3.7)	3.9 (2.9 to 4.9)	17.7 (15.2)	-	-

Table 6: Summary of Mean IOP for Initial SLT and Repeat SLT.

a: IOP data missing: 9 eyes at 2 months, 2 eyes at 6 months, 1 eye at 12 months for Initial SLT.
b: IOP data censored (no longer at target, treatment escalated): 3 eyes at 2 months, 42 eyes at 6 months, 68 eyes at 12 months, 90 eyes for Initial SLT.

c: IOP data missing: 9 eyes at 2 months, 5 eyes at 6 months, 6 eyes at 12 months, 12 eyes at 18 months for Repeat SLT.
d: IOP data censored (no longer at target, treatment escalated): 1 eye at 2 months, 17 eyes at 6 months, 26 eyes at 12 months, 31 eyes at 18 months for Repeat SLT.

**Significant reduction in mean absolute IOP reduction from pre-treatment IOP at 2 months for Initial and Repeat SLT (p<0.001) calculated using t-test*
*** Significant difference in pre-treatment IOP between Initial and Repeat SLT (mean difference: 3.9, 95% CI 2.8 to 4.9; p<0.001) using t-test*

APPENDIX 4:

SENSITIVITY ANALYSIS

	Number of eyes (n)	'Early Failure' Repeat SLT Mean IOP (SD) (mmHg)	'Early Failure' Repeat SLT Mean (SD) absolute IOP reduction (mmHg)	'Early Failure' Repeat SLT % IOP reduction (SD)	Number of eyes (n)	'Later Failure' Repeat SLT Mean IOP (SD) (mmHg)	'Later Failure' Repeat SLT Mean (SD) absolute IOP reduction (mmHg)	'Later Failure' Repeat SLT % IOP reduction (SD)	'Early Failure' vs. 'Later Failure' Mean difference in absolute IOP reduction (mmHg; 95% CI)
Pre-treatment	**29**	**21.8 (3.6)**			**61**	**20.7 (4.2)**			
2 months	**25**	**17.5 (3.0)**	**4.1 (3.7)**	**17.7 (13.9)**	**55**	**16.0 (3.3)**	**4.4 (3.1)**	**20.7 (12.3)**	**-0.4 (-1.9 to 1.2)**

Table 7: Summary of Repeat SLT IOP reduction at 2 months for 'Early Failures' vs 'Late Failures'

No significant difference in pre-treatment IOP between 'Early Failures' vs 'Late Failures' for Repeat SLT (p=0.223) – (mixed model analysis)
**No significant reduction in mean absolute IOP reduction at 2 months (p=0.645) – (mixed model anaylsis)*

APPENDIX 5:

SENSITIVITY ANALYSIS

ONE EYE PER PERSON – RANDOMLY SELECTED

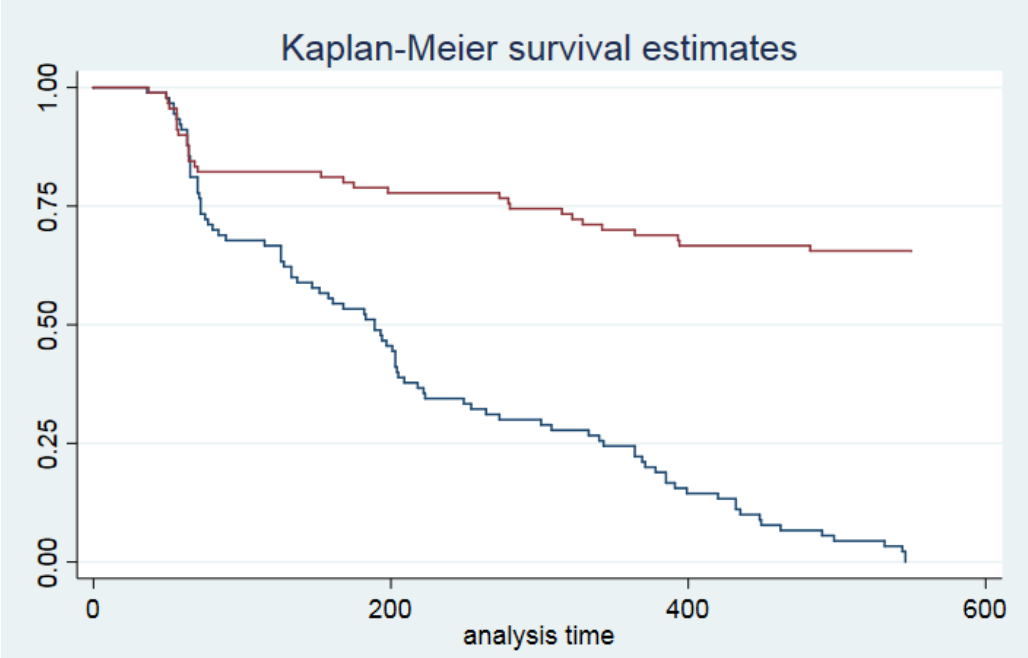


Figure 3: Kaplan Meier Plot for 90 eyes: Initial SLT (blue line) vs. Repeat SLT (red line)

Severity	Definition of Severity for Treatment Target IOP				
	Optic Nerve		**VF MD**		**Central (10^o) Scotoma on VF**
OHT	Healthy		Any		No GON related VFL
Mild OAG	GON	**+**	> -6dB	**+**	None
Moderate OAG	GON	**+**	< -6dB to > -12dB	**or**	At least 1 central 5º point <15dB but none <0dB and only 1 hemifield with central point <15dB
'Severe' OAG	GON	**+**	< -12dB	**or**	Any central 5º point with sensitivity <0dB Both hemifields contain point(s) <15dB within 5º of fixation

Table 1: Severity criteria for setting Treatment Target IOP from the "Canadian Target IOP Workshop" (with central field criteria defined according to Mills). VF MD: Visual field mean deviation GON: Glaucoma optic neuropathy

Characteristics	Value
Age (years), mean (SD)	**63.5 (13.1)**
Gender (patients), (%)	
Male	**52 (57.8%)**
Female	**38 (42.2%)**
Ethnicity (patients), (%)	
White European	**63 (70.0%)**
Black	**17 (18.9%)**
Asian	**6 (6.7%)**
Other	**4 (4.4%)**
Disease Severity (eyes), (%)	
OHT	**22 (19.1%)**
'Mild' OAG	**46 (40.0%)**
'Moderate' OAG	**27 (23.5%)**
'Severe' OAG	**20 (17.4%)**
Baseline IOP (mmHg), mean (SD)	**24.5 (6.6)**

Table 2: Baseline characteristics of study sample

	Initial SLT				Repeat SLT				Initial vs Repeat SLT	
	Number of eyes (n)	**Mean IOP (SD) (mmHg)**	**Mean absolute IOP reduction from pre-treatment IOP (mmHg; 95% CI)**	**Mean % IOP reduction from pre-treatment IOP (95% CI)**	**Number of eyes (n)**	**Mean IOP (SD) (mmHg)**	**Mean absolute IOP reduction from pre-retreatment IOP (mmHg; 95% CI)**	**Mean % IOP reduction from pre-retreatment IOP (95% CI)**	**Mean difference in absolute IOP reduction from pre-treatment IOP (mmHg; 95% CI)**	***Adjusted**** **mean difference in absolute IOP reduction from pre-treatment IOP (mmHg; 95% CI)**
Pre-treatment	**115**	**24.5** (6.6)**			**115**	**21.0** (4.2)**				
2 months	**97**[a,b]**	**19.1 (3.9)**	**5.3* (4.5 to 6.0)**	**21.6 (18.4 to 24.5)**	**104**[c,d]**	**16.3 (3.3)**	**4.6* (4.0 to 5.2)**	**21.9 (19.0 to 24.8)**	**1.0 (0.2 to 1.8)**	**-1.1 (-1.7 to -0.5)**
6 months	58[a,b]	18.8 (4.1)	4.5 (3.6 to 5.4)	18.4 (14.7 to 22.0)	88[c,d]	17.0 (3.4)	4.0 (3.4 to 4.6)	19.0 (16.2 to 21.9)	0.3 (-0.8 to 1.3)	-1.1 (-1.9 to -0.2)
12 months	26[a,b]	21.0 (4.9)	2.4 (1.2 to 3.7)	9.8 (4.9 to 15.1)	76[c,d]	17.2 (4.0)	3.8 (3.1 to 4.5)	18.1 (14.8 to 21.4)	-1.0 (-2.7 to 0.7)	-2.4 (-3.9 to -0.9)
18 months	0[b]	-	-	-	62[c,d]	16.7 (3.8)	3.8 (3.1 to 4.5)	18.1 (14.8 to 21.4)	-	-

Table 3: Summary of Mean IOP for Initial SLT and Repeat SLT.

a: IOP data missing: 15 eyes at 2 months, 2 eyes at 6 months, 1 eye at 12 months for Initial SLT.
b: IOP data censored (no longer at target, treatment escalated): 3 eyes at 2 months, 55 eyes at 6 months, 88 eyes at 12 months, 115 eyes at 18 months for Initial SLT.

c: IOP data missing: 9 eyes at 2 months, 6 eyes at 6 months, 8 eyes at 12 months, 15 eyes at 18 months for Repeat SLT.
d: IOP data censored (no longer at target, treatment escalated: 2 eyes at 2 months, 21 eyes at 6 months, 31 eyes at 12 months, 38 eyes at 18 months for Repeat SLT.

**Significant reduction in mean absolute IOP reduction from respective pre-treatment IOP at 2-month time point for initial and Repeat SLT (p<0.001)*

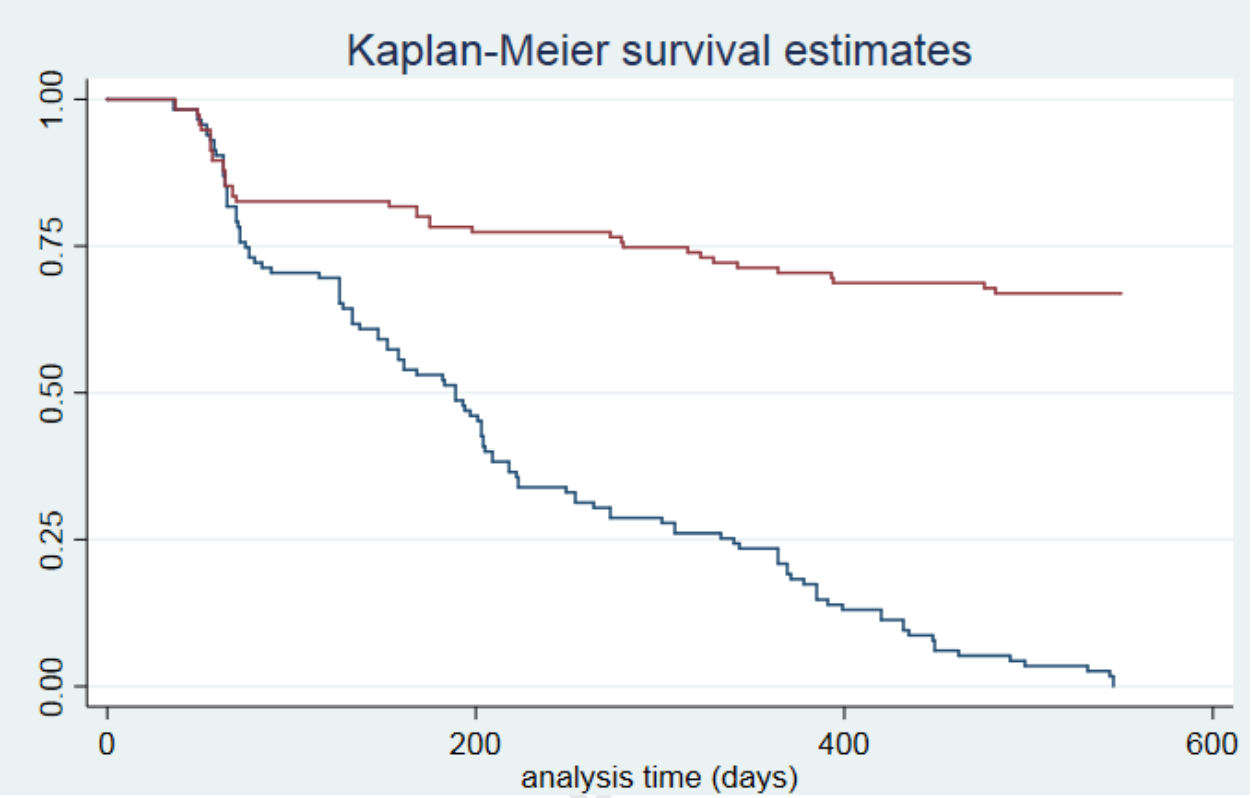
*** Significant difference in pre-treatment IOP between initial and Repeat SLT (mean difference: 3.4, 95% CI 2.6 to 4.3, mmHg; p<0.001)*

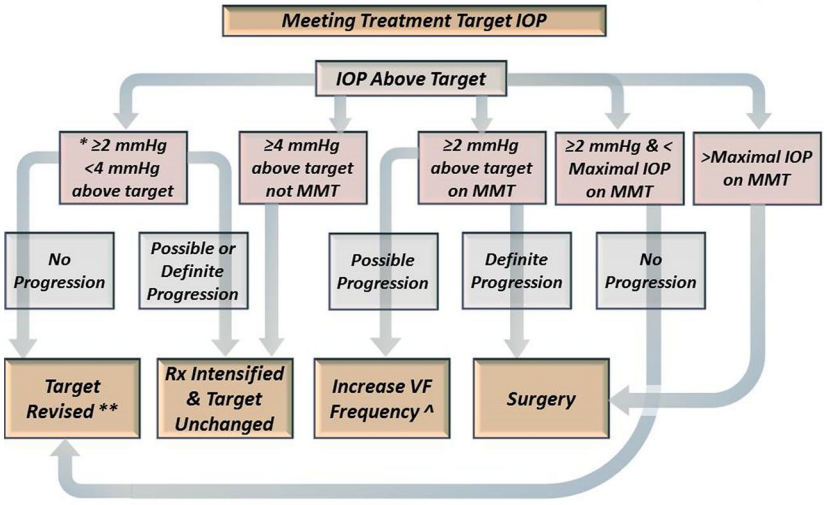
**** Adjusted analysis of absolute IOP reduction from pre-treatment IOP (adjusting for corresponding pre-treatment IOP)*

	'Early failures' who underwent Repeat SLT	'Later failures' who underwent Repeat SLT	'Early failures' started on topical medication without Repeat SLT	'Later failures' started on topical medication without Repeat SLT	Single SLT treatment still successful at 18 months, no additional treatment
Disease Severity: Eyes (n) / (%)					
OHT	3 (8.8)	19 (23.5)	4 (20.0)	1 (4.4)	168 (37.1)
'Mild' OAG	15 (44.1)	31 (38.3)	10 (50.0)	12 (52.2)	241 (53.2)
'Moderate' OAG	8 (23.5)	19 (23.5)	5 (25.0)	4 (17.4)	31 (6.8)
'Severe' OAG	8 (23.5)	12 (14.8)	1 (5.0)	6 (26.1)	13 (2.9)
Mean IOP reduction required to achieve Target IOP (mmHg; 95% CI)	9.7 (7.7 to 11.6)	6.5 (5.8 to 7.2)	5.4 (4.6 to 6.1)	6.1 (4.9 to 7.4)	5.7 (5.5 to 5.9)
Eyes (n)	34	81	20	23	453
Mean pre-treatment IOP prior to Initial SLT (SD) (mmHg)	26.1* (7.8)	23.8* (5.9)	22.6 (4.4)	22.1 (4.6)	24.7 (4.8)
Eyes (n)	34	81	20	23	453
Mean IOP at 2 months post initial SLT (SD) (mmHg)	21.6 (3.9)	17.8 (3.4)	21.1 (4.0)	16.8 (2.9)	16.7 (2.3)
Eyes (n)	32	65	20	21	414
Mean absolute IOP reduction at 2 months after initial SLT (mmHg; 95% CI)	4.4* (2.6 to 6.2)	5.7* (4.9 to 6.5)	1.3 (-0.2 to 2.7)	5.1 (3.7 to 6.4)	7.9 (7.6 to 8.2)
Eyes (n)	32	65	20	21	414
Mean pre-retreatment IOP prior to repeat SLT (SD) (mmHg)	21.6* (3.7)	20.7* (4.3)	-	-	-
Eyes (n)	34	81			
Mean IOP at 2 months post repeat SLT (SD) (mmHg)	17.5 (3.0)	15.9 (3.4)	-	-	-
Eyes (n)	29	75			
Mean absolute IOP reduction at 2 months after repeat SLT (mmHg; 95% CI)	4.1* (2.8 to 5.4)	4.8* (4.1 to 5.4)	-	-	-
Eyes (n)	29	75			
Mean IOP at 2 months after LAST SLT (mmHg; 95% CI)	17.5 (3.0)	15.9 (3.4)	21.1 (4.0)	16.8 (2.9)	16.7 (2.3)
Eyes (n)	29	75	20	21	414
Mean total absolute IOP reduction at 2 months from pre-treatment IOP after LAST SLT (mmHg; 95% CI)	9.1 (6.4 to 11.8)	7.7 (6.6 to 8.8)	1.3 (-0.2 to 2.7)	5.1 (3.7 to 6.4)	7.9 (7.6 to 8.2)
Eyes (n)	29	75	20	21	414

Table 4: Early IOP lowering of Eyes following Initial SLT and Repeat SLT

**Difference between 'Early failures' vs 'Later failures' who underwent repeat SLT calculated using mixed model analysis with cross random effects and presented in main manuscript results*





Post-hoc analysis of treatment-naïve OAG or OHT eyes requiring repeat 360-degree SLT within 18 months from the LiGHT trial