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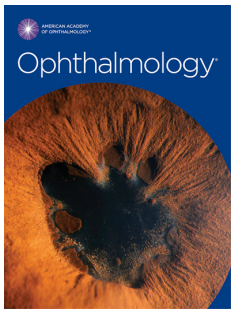

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LiGHT trial: 6-year results of primary selective laser trabeculoplasty versus eye drops for the treatment of glaucoma and ocular hypertension

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Running head: The LiGHT trial 6-year results.

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This article contains additional online-only material. The following should appear online-only: Appendix 1, Appendix 2, Appendix 3, Appendix 4.

Abstract

Purpose: The LiGHT trial has shown selective laser trabeculoplasty (SLT) to be clinically and cost-effective as a primary treatment of open-angle glaucoma (OAG) and ocular hypertension (OHT) at 3 years. This paper reports health-related quality of life (HRQL) and clinical effectiveness of initial treatment with SLT compared to intra-ocular pressure (IOP) lowering eye drops, after 6 years of treatment.

Design: Prospective multicentre randomized controlled trial.

Participants: Treatment-naïve eyes with OAG or OHT, initially treated with SLT or IOP-lowering drops.

Methods: Patients were randomly allocated to initial SLT or eye drops. Eye specific target IOP and monitoring intervals were based on international guidelines. After the initial 3 years of the trial, patients in the SLT arm were permitted a 3rd SLT if necessary; patients in the drops arm were allowed SLT as a treatment switch or escalation. Analysis was by intention to treat. This study is registered at controlled-trials.com (ISRCTN32038223).

Main outcome measures: The primary outcome was HRQL at 6 years; secondary outcomes were clinical effectiveness and safety.

Results: Of the 692 patients completing 3 years in the LiGHT trial, 633 (91.5%) entered the extension and 524 patients completed 6 years in the trial (82.8% of those entering the extension phase, 73% of those initially randomised). At 6 years, there were no significant differences in HRQL for EQ-5D, GUI and GQL-15 (all $p>0.05$). The SLT arm had better GSS scores than the drops arm (83.6 (SD 18.1) vs 81.3 (SD 17.3), respectively). 69.8% of eyes in the SLT arm remained at or below target IOP without the need for medical or surgical treatment. More eyes in the drops arm exhibited disease progression (26.8% vs 19.6%, respectively, $p=0.006$). Trabeculectomy was required in 32 eyes in the drops arm compared to 13 eyes in the SLT arm ($p<0.001$); there were more cataract surgeries in the drops arm (95 compared to 57 eyes, $p=0.03$). There were no serious laser-related adverse events.

Conclusions: SLT is a safe treatment for OAG and OHT, providing better long-term disease control than initial drop therapy, with reduced need for incisional glaucoma and cataract surgery over 6 years.

Selective laser trabeculoplasty (SLT) was endorsed by the United States Food and Drug Administration for the treatment of glaucoma in 2001. SLT has since increasingly been adopted as an alternative to IOP-lowering eye drops, but until recently data on its efficacy as a sole treatment were scarce.[1,2] Recent studies have compared SLT to monotherapy, which does not reflect routine clinical practice where IOP is treated to target. As a result, a Cochrane systematic review called for more research into the efficacy of SLT compared to contemporary medication regimens.[3]

The Laser in Glaucoma and Ocular Hypertension (LiGHT) trial is a multicentre randomized controlled trial comparing initial treatment with SLT to initial treatment with IOP-lowering eye drops for treatment-naive patients with OAG or OHT, assessing health-related quality of life (HRQL), cost-effectiveness, and clinical efficacy after 3 years.[4] In 2019, the LiGHT trial reported that initial treatment of ocular hypertension (OHT) or open-angle glaucoma (OAG) with SLT is more cost-effective than initial treatment with contemporary IOP-lowering eye drops after 3 years, whilst also providing drop freedom to 74.2% of patients, a reduced number of glaucoma surgeries and very low rates of adverse events.[5] Following the publication of our 3-year results, international guidelines on the treatment of glaucoma have been updated; the European Glaucoma Society[6] and the American Academy of Ophthalmology[7] now list SLT as initial treatment for open angle glaucoma and OHT alongside medications and the National Institute for Health and Care Excellence (NICE)[8] recommends SLT is used as a 1st line treatment.

Glaucoma is a long-term condition requiring life-long treatment; average life-expectancy at initial diagnosis of glaucoma is 9–13 years[9] and mean life expectancy after trabeculectomy is 7.5 years.[10] While we previously reported that initial treatment with SLT offers drop-freedom to nearly 75% of LiGHT patients for at least 3 years, longer term IOP control following initial SLT and additional SLT could further prolong drop-freedom and reduce the requirement for intense medical or surgical treatment over patients' lifetime. Such potential may also be invaluable for the management of OAG and OHT internationally, following COVID-19 pandemic-related delays in monitoring and treatment and consequent greater number of glaucoma emergencies and patient anxiety.[11-13]

Following 3 years of treatment and monitoring, the LiGHT trial was extended to a total of 6 years of monitoring. We report HRQL and clinical effectiveness of initial treatment with SLT compared to initial IOP-lowering eye

drops, after 6 years of protocolised treatment to pre-defined eye-specific IOP targets.[4] The cost-effectiveness analysis and data on cross-over outcomes will be presented separately.

Methods

Recruitment

Details of the LiGHT trial design have been described previously.[4,5] Newly diagnosed patients with previously untreated OAG or OHT in one or both eyes, qualifying for treatment according to UK NICE guidelines, were identified at six hospitals across the UK between Oct 10, 2012, and Oct 27, 2014. For patients diagnosed with OAG, mean deviation (MD) visual field (VF) loss was not worse than –12 dB in the better eye or –15 dB in the worse eye and there was corresponding damage to the optic nerve. Patients were aged 18 years or older and were able to read and understand English. Visual acuity was 6/36 or better in the treated eye(s); eyes with no previous intraocular surgery, except uncomplicated phacoemulsification at least 1 year before randomisation, were eligible. Patients were excluded if they had contraindications to SLT (e.g., unable to sit at the slit lamp mounted laser, history of uveitis, inadequate view of trabecular mesh work), an inability to use eye drops, symptomatic cataract, and/or if they were under active treatment for another ophthalmic condition.

Randomisation

Patients were randomised (month 0) using a web-based system (www.sealedenvelope.com) and were randomly assigned to receive either primary therapy with IOP-lowering eye drops or SLT, followed by IOP-lowering eye-drops if required. Stratification factors in the randomisation were diagnosis and treatment centre, with random block sizes (of four, six, or eight). All measurements influencing treatment escalation decisions (VF, optic disc imaging, and IOP) were made by masked observers; clinicians and patients were unmasked to treatment allocation.

Disease definition, deterioration & target IOP

Disease definition and treatment initiation followed the NICE thresholds at the time[14]; this was incorporated into a real-time web-based clinical decision-support software, which was based on optic disc analysis using Heidelberg retina tomography (Heidelberg Engineering, Heidelberg, Germany), auto-mated VF assessment with the Humphrey Field Analyzer Mark II Swedish interactive threshold

algorithm standard 24-2 (Carl Zeiss Meditec, Dublin, CA, USA), and IOP measurements (Goldmann applanation tonometry with daily calibration verification). Disease category and severity were specified at baseline, using predefined objective severity criteria from the Canadian Target IOP Workshop [15] with additional central visual field loss criteria according to Mills et al.[16]

Eye specific target IOP and patient monitoring intervals were based on the Canadian Target IOP Workshop,[15] according to the disease severity stratification (OHT, mild/moderate/severe OAG). The eye-specific target IOP was determined from a single untreated baseline (month 0) IOP measurement: eyes with OHT had a target IOP at least 20% reduced from baseline or less than 25mmHg (whichever was lower), eyes with mild OAG had a target IOP at least 20% reduced from baseline or less than 21mmHg (whichever was lower), eyes with moderate OAG had a target IOP at least 30% reduced from baseline or less than 18mmHg (whichever was lower), and eyes with advanced OAG had a target IOP at least 30% reduced from baseline or less than 18mmHg (whichever was lower).[4,17]

Deterioration of glaucoma, i.e. disease progression, or conversion of OHT to OAG was derived from the decision support software and required verification by a consultant ophthalmologist. Evidence of deterioration was stratified to strong or less strong, based on Glaucoma Progression Analysis (GPA) or Heidelberg retina tomography rim area as previously described.[4] Treatment escalation followed international guidelines of the European Glaucoma Society,[18] the American Academy of Ophthalmology Preferred Practice Patterns [19] and South-East Asia Glaucoma Interest Group.[20] Treatment was escalated when a) IOP was above the target IOP by more than 4 mm Hg at a single visit; b) there was strong evidence of deterioration irrespective of IOP; c) IOP was above the target by less than 4 mm Hg in the presence of evidence of progression.

Target IOP was reduced by 20% if deterioration was identified despite the measured IOP being at or below the initially set target IOP. IOP was revised upwards if an eye was ≥2mmHg and <4mmHg above Target IOP for 2 consecutive visits, while demonstrating disease stability, assessed by HRT, VF with a minimum of 4 VFs as per EMGT[21] and by a decision support software. In these cases treatment escalation was not attempted, but the target IOP was adjusted to the mean of the last three visits over which deterioration had not occurred.[4] If fewer than 4 VFs had been done additional visits were required to confirm stability before the Target was relaxed.

SLT arm

SLT was delivered according to a pre-defined protocol, at 360° of the trabecular meshwork, with 100 non-overlapping shots (25 per quadrant, energy 0.3-1.4mJ, according to a pre-specified protocol).[4,17] For the first 36 months (3 years) of the trial one additional SLT retreatment was allowed (total 2 SLT treatments) and thereafter the next escalation was medical treatment. After the first 3 years patients were permitted a 3rd SLT treatment; the next escalation was medical treatment. Significant complications of laser treatment (eg, severe uveitis, IOP spike greater than 15 mmHg) or other new medical conditions (e.g. uveitis, angle closure etc) prohibited repetition of SLT.

Eye drops arm

Single drug eye-drops were initially prescribed after randomisation for patients in the drops arm and for patients who remained uncontrolled after SLT. Different or additional eye drops were prescribed in the event of a treatment switch (e.g. adverse reaction) or treatment escalation (e.g. IOP above target). Drug classes for first-line, second-line or third-line treatment were defined as per NICE[14] and the European Glaucoma Society (EGS) guidance[18]; first line: prostaglandin analogues, second line: beta blockers, third or fourth line: topical carbonic anhydrase inhibitors or alpha-agonists. Fixed combination drops were allowed; systemic carbonic anhydrase inhibitors were only permitted as a temporary measure while awaiting surgery and were not considered a treatment escalation for the purposes of the analysis.

Procedures

For the first 36 months (3 years) of the trial, patients initially randomised to receive IOP-lowering eye-drops were not permitted an SLT; failure to control IOP or OAG with eye-drops resulted in surgical treatment (trabeculectomy). After the first 3 years, patients were allowed a cross-over, whereby they could opt to have SLT as a treatment switch i.e., to reduce medication load, or as a treatment escalation i.e., to avoid increasing medication load or delay surgery.

The primary outcome measure was HRQL measured using the EuroQol EQ-5D 5 Levels (EQ-5D) utility scores. Utility scores were calculated from patient reported health states using the EQ-5D descriptive system and value set for England.[22] The secondary outcomes were: glaucoma-specific treatment-related quality of life using the

Glaucoma Utility Index (GUI),[23] patient reported disease and treatment related symptoms, using the Glaucoma Symptom Scale (GSS),[24] patient reported visual function using the Glaucoma Quality of Life-15 (GQL-15), clinical effectiveness and safety of the treatment arms. Adverse events were classified and reported according to local standard operating procedures and good clinical practice guidelines.[25]

Statistical analysis

The statistical analysis plan is described in detail elsewhere.[26] In summary, the primary outcome was analysed using linear regression with terms for randomisation group, baseline EQ-5D, stratification factors (diagnosis and centre), baseline IOP, and number of eyes affected at baseline. The unit of analysis was the patient. If a patient had both eyes in the study, baseline severity and IOP were based on the worse eye, where the worst eye was defined using VF MD at baseline. Several sensitivity analyses were performed to verify the results of this primary analysis (details provided in Appendix 1). In addition, mixed effects models were used to analyse the EQ-5D measurements recorded at all time-points to investigate possible changes in treatment effect over the 72 months (using interaction terms between the randomisation group and time) and to estimate the average treatment effect over the 72-month follow-up period. The secondary outcomes were analysed using similar regression methods to those described above. All analyses were performed on an intention-to-treat (ITT) basis with participants analysed according to the group to which they were randomised. Kaplan-Meier plots were used to summarise disease progression, time to glaucoma surgery and phacoemulsification, and the log-rank test was used to compare these outcomes. Eyes were compared with respect to visits at target and number of clinical visits using mixed effects logistic regression and Poisson regression models respectively. Eyes were also compared with respect to the remaining measurement of pathway effectiveness and visual function variables using the t-test for numerical outcomes and the chi-squared test (or Fisher's exact test when numbers were small) for categorical outcomes. The chi-squared test and Fisher's exact test were also used to compare the number of reported adverse and serious adverse events. All analyses were performed in Stata version 17 [StataCorp, 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC].

The study was conducted in accordance with good clinical practice guidelines (GCP) and adhered to the tenets of the Declaration of Helsinki. Ethical approval was granted by local boards. All patients provided written informed consent before participation. An independent data and safety monitoring committee was appointed by

the independent trial steering committee, to whom adverse events were reported according to standard operating procedures for the duration of the trial. The LiGHT trial is registered at www.controlled-trials.com (ISRCTN32038223) and the protocol can be accessed at https://www.journalslibrary.nihr.ac.uk/programmes/hta/0910440/#/.

Results

Baseline data

Of the 692 patients who completed 3 years of the LiGHT trial, 633 (91.5%) entered the 3-year extension (from 36 to 72 months); 313 patients (547 treated eyes) had initially received SLT and 320 patients (549 eyes) had initially commenced treatment with IOP-lowering eye drops (Figure 1). There were 86 protocol violations or deviations; 30 took place during the first 3 years and 56 during the extension (36 to 72 months), the latter relating to the COVID-19 pandemic. Of the 59 patients not continuing into the extension, 29 came from a single centre that chose not to continue in the study (Appendix 2). A total of 524 patients completed the trial extension (82.8% of those entering the extension phase, 73% of those initially randomised).

Presented results refer to the sample of patients who entered the LiGHT trial extension (36 to 72 months); this sample was representative of the original trial participants and maintained the balance of the allocation groups achieved by randomisation. Baseline (month 0) patient and eye characteristics of the patients who participated in the extension phase were similar between the two groups (Table 1, Appendix 2); 493 patients (77.9%) were diagnosed with OAG in at least 1 eye and 140 patients (22.1%) were diagnosed with OHT. The treatment groups had similar average EQ-5D, GUI and GQL-15 scores at baseline (month 0) (Table 2); the medication group had slightly higher average GSS scores at baseline , similarly to the original trial data.[5] At 36 months (start of the extension) the two groups had average EQ-5D, GUI, GSS and GQL-15 scores that continued to be similar to the scores recorded in the first 3 years of the trial.[5]

Of the 320 patients allocated to medication, 112 (176 eyes, 35% of patients) decided to receive SLT immediately or shortly after the end of the 3-year monitoring period. Of those, 70 patients (115 eyes) had SLT as a treatment switch i.e., to reduce medication load, and 29 patients (35 eyes) had SLT as a treatment escalation due to uncontrolled IOP and/or disease progression. Thirteen patients (26 eyes) had SLT as a treatment escalation in

one eye and as a treatment switch in the other eye. Of the 112 patients who received SLT after 36 months, 94 (83.9%) completed the trial extension to 72 months.

Health-related quality of life

The mean values for the HRQL questionnaires across the 72 months of the trial are shown in in Figure 2. Based on an intention to treat analysis, there was no significant difference in HRQL between the two treatments at 72 months for the EQ-5D, GUI and GQL-15 (Table 3); the eye drops group had an average EQ-5D score of 0.89 (SD 0.14), compared with 0.90 (SD 0.14) in the SLT group (adjusted mean difference [selective laser trabeculoplasty–eye drops] 0·01, 95% CI −0·01 to 0·04, p=0·18). These results were confirmed in sensitivity analyses (results not shown, see Appendix 1). The average GUI score at 72 months in the SLT group was 0.90 (SD 0.14) compared with 0.88 (SD 0.13) for the eye drops group (adjusted mean difference 0·01, 95% CI −0·01 to 0·03). Mean GQL-15 scores were also similar between the two groups (20.80 for the SLT group and 20.57 eye drops, adjusted mean difference −0.13, 95% CI −1.57 to 1·31). For the GSS, the medication group had worse scores at 72 months with a mean score of 81.3 (SD 17.3) compared to 83.6 (SD 18.1) for the SLT group (adjusted mean difference 3.3, 95% CI 0.54 to 6.0), however this was the only timepoint at which a noticeable difference was observed. Repeated measures analysis for the secondary HRQL outcomes (GUI, GSS, GQL-15) showed comparable outcomes between the two groups over the course of the trial (Appendix 3). When excluding the eyes that received SLT after the 36-month time point (n=176), mean scores for all HRQL questionnaires were similar between the two groups (Table 3).

Measurements of treatment effectiveness and visual function

At 72 months, 537 patients (267 in drops arm and 270 in SLT arm) and 930 eyes (460 in the drops arm and 470 eyes in the SLT arm) were available for analysis of clinical outcomes (**Error! Reference source not found.**). Overall, 94.2% of eyes initially treated with SLT were at target at 72 months and target IOP was achieved at 92.8% of visits, compared to 94.7% of eyes and 93.2% of visits for eyes initially treated with medication. Fewer eyes initially treated with SLT demonstrated progression from OHT to OAG or deterioration of OAG, compared to eyes initially treated with eye drops (19.6% vs 26.8%, respectively, p=0.006) (Table 4, Figure 3).

Drop free IOP control at 72 months, obtained without incisional surgery, was achieved in 69.8% of eyes initially treated with SLT, compared to 18.0% of eyes initially treated with IOP-lowering eye drops. Of the eyes initially

treated with SLT and being drop and surgery free at 6 years, 90% (295 eyes) needed up to 2 SLT treatments in total. Of the eyes initially treated with eye-drops and being drop free at 72 months, 79.5% (66 eyes) had switched to SLT and 20.5% had either cataract surgery alone or cataract surgery and SLT. At 72 months, 61.2% of eyes initially treated with eye-drops were using 1 or 2 medications, compared to 18.5% of eyes initially treated with SLT.

Target IOP was revised in 85 eyes initially treated with SLT and in 89 eyes initially treated with IOP-lowering eye drops. Target IOP was revised downwards on 50 occasions in eyes initially treated with SLT and on 65 occasions in eyes initially treated with IOP-lowering eye drops and upward on 40 and 31 occasions, respectively. Eyes initially treated with SLT needed fewer trabeculectomies (13 eyes, 2.4%) compared to eyes initially treated with eye drops (32 eyes, 5.8%) (Table 4, Figure 4, $p<0.001$) and fewer phacoemulsifications (57 compared to 95, respectively, $p=0.03$) (Table 4, Figure 5). Of the 32 eyes that needed a trabeculectomy during trial's 6-year duration, 11 eyes initially treated with drops had a trabeculectomy during the first 3 years of the trial; none of the eyes initially treated with SLT required a trabeculectomy during the initial 3 years of the trial. During the extension of the trial, i.e. from 3 to 6 years, minimally invasive glaucoma surgery (MIGS) was performed in 11 eyes of 6 patients initially treated with IOP-lowering eye drops (all were angle procedures; no MIGS was performed in eyes initially randomised to SLT). This may have resulted in fewer trabeculectomy surgeries in the drops arm, but is not expected to have affected the reported statistical and clinical differences in incisional glaucoma surgery between the treatment arms.

Eyes initially treated with SLT had higher IOP at 72 months compared to eyes initially treated with IOP-lowering eye drops (16.3mmHg vs 15.4mmHg, respectively, $p<0.001$); however, VF MD loss and visual acuity at 72 months were similar between the two groups (-4.0dB vs -3.9dB, and 0.1 vs 0.1, respectively, both $p>0.05$) (Table 4, Appendix 4). Patients initially treated with SLT needed a total of 5175 visits over 72 months and patients initially treated with eye-drops needed 4970 visits. Excluding the 2-week post-laser visits resulted in 4678 visits for the SLT group compared to 4852 for the eye-drops group.

Safety

There were no sight-threatening complications of SLT and no clinically identifiable corneal changes throughout the trial (Table 5). A total of 274 transient SLT-related adverse events were reported, including 10 incidents of

a rise in IOP (1.0% of all SLT treatments, with only one eye requiring treatment). More ocular adverse events were reported in the group initially treated with IOP-lowering eye drops (1470 ocular adverse events were reported by 271 patients) compared to the group initially treated with SLT (897 ocular adverse events by 224 patients) (Table 5**)**. Serious adverse events were similar overall between the two groups (180 events in 110 patients initially treated with eye-drops; 209 events in 107 patients initially treated with SLT), with pulmonary and cardiac events being balanced between the two groups (Table 5).

Discussion

In 2019, the LiGHT trial reported that initial treatment with SLT provided newly diagnosed OHT and OAG eyes with predominantly drop free IOP control (78.2% of eyes after 3 years) and a reduced need for glaucoma and cataract surgery, compared to initial treatment with IOP-lowering eye drops[5]. Data from this 3-year trial also indicated that eyes initially treated with SLT may demonstrate less frequent progression to more advanced stages of glaucoma and a further VF analysis indicated that more eyes initially treated with topical medical therapy undergo rapid VF progression compared to eyes initially treated with SLT.[27]

The LiGHT trial was extended to a total of 6 years to provide longer-term, pragmatic treatment outcome data. Patients within five UK settings, initially treated with IOP-lowering eye drops were permitted to have SLT to reduce medication load, avoid increasing medication load or delay surgery. Patients initially treated with SLT were allowed a 3rd and final SLT, before escalating to IOP-lowering eye drops. Data after 6 years of treatment indicate statistically significant lower rates of disease progression and reduced need for glaucoma and cataract surgery for eyes initially treated with SLT. Drop free IOP control and safety of SLT as a 1st line treatment for OHT and OAG are confirmed after 6 years of careful, protocolised monitoring and treatment.

SLT allowed successful drop free IOP control in nearly 70% of the eyes after 6 years of treatment. This is only slightly reduced form 78% of eyes not needing topical therapy at 3 years and an important outcome for long-term glaucoma and OHT management; of the initial SLT eyes which were drop free, 90% had only one or two SLT treatments. IOP-lowering eye drops come with, sometimes significant, adverse effects, affecting trabeculectomy outcomes, increasing expenditure for healthcare systems and/or patients,[28,29] and often leading to non-adherence.[30] Drop-freedom was achieved in nearly a fifth of eyes initially treated with eye drops, predominantly by switching to SLT (79.5%) alone or after undergoing SLT and/or cataract surgery (20.5%).

The LiGHT trial reports 70% of eyes being drop free following 6 years of treatment, whereby IOP had to be reduced by a minimum of 20% from pre-treatment IOP (and at least by 30% for moderate and severe OAG) and below 25mmHg for OHT, below 21mmHg for mild OAG, below 18mmHg for moderate OAG and below 15mmHg for severe OAG.[4,15] Absolute IOP reduction has been reported elsewhere[31]; reporting absolute IOP reduction at 6 years has limited usefulness since no washout was preformed and a proportion of eyes were on IOP-lowering topical medical treatment. Success rates for SLT have been published using various definitions.[1,32] A large US-based retrospective study has clearly indicated that reported success rates are heavily influenced by disease severity and co-morbidities of the included populations, concluding that SLT can be an effective means of prolonging medication-free IOP-control,[33] but lower SLT success rates have been reported for less carefully selected eyes already on medication[34].

LiGHT used eye-specific target IOPs, which could be revised in the absence of evident deterioration[4]; this has been suggested to potentially drive the reported outcomes.[35] The European Glaucoma Society Guidelines recommend clinicians consider upward revision of target pressure in stable patients, when the initial target has not been reached.[36] In LiGHT, Target IOP was reassessed using decision support software and applied to both treatment arms, according to pre-set criteria,[37] when VF and disc imaging analysis provided evidence of disease stability accounting for inter-visit IOP measurement variation.[38] A risk-dependent upper limit was set, at which surgery might be offered even in the absence of progressive glaucomatous optic neuropathy. Here we report the number of upward and downward IOP revisions, which are comparable between the two treatment arms and are, therefore, unlikely to affect the reported outcomes.

The LiGHT trial has carefully and objectively monitored patients in a pragmatic manner across 5 NHS centres, retaining more than 80% of participants after 6 years of treatment. Data reported by the LiGHT trial are an accurate representation of realistic and complete glaucoma management for newly-diagnosed, previously untreated eyes with OHT/OAG; these data have supported the update of the American, European and UK-NICE glaucoma management guidelines.[6-8] The LiGHT trial population consisted of a large proportion of OHT and mild OAG eyes, for which IOP reduction targets are less stringent than those for more advanced disease. Eyes with advanced OAG will often require more intense treatment, whilst initial intervention might differ from that recommended for early disease.[39]

Adding to the evidence from the LiGHT trial, the Glaucoma Intensive Treatment Study (GITS)[40] has reported favourably on the use of SLT as an adjunctive therapy for patients with OAG over 3 years and the West Indies Glaucoma Laser Study (WIGLS) reported that SLT monotherapy safely provides 78% of Afro-Caribbean eyes with at least 20% IOP reduction for 12 months.[41] SLT was also recently shown to be an ideal therapeutic approach in situations where frequent monitoring visits and treatment changes are difficult.[42] With 90% of the drop-free eyes initially treated with SLT needing a maximum of 2 SLT treatments over 6 years and 55.5% requiring only a single SLT treatment, there is great potential for treating patients with SLT in such situations.

Data published previously have indicated that initial treatment with SLT might delay progression of OHT and OAG; data from the first 3 years of treatment indicated a 2% difference in eyes progressing and VF analysis suggests more eyes initially treated with IOP-lowering eye drops undergo rapid VF progression compared to eyes first treated with SLT.[5,27] After 6 years of treatment, eyes initially treated with SLT demonstrated reduced objectively defined progression compared to IOP-lowering eye drops; this was achieved despite eyes initially treated with IOP-lowering eye drops achieving lower IOP at 6 years, possibly suggesting other protective roles of SLT. Differences in progression between the two treatment arms also influence the rates of incisional glaucoma surgery. Eyes initially treated with SLT needed fewer trabeculectomies, supporting original trial data.[5] For the first three years after initial treatment, no trabeculectomies were needed in eyes receiving initial SLT, whilst at 6 years there were almost three times fewer eyes initially treated with SLT needing a trabeculectomy, compared to eyes initially treated with IOP-lowering eye drops. Excess surgeries in eyes initially treated with eye drops might have led to the slightly lower IOP at 72 months, compared to eyes initially treated with SLT. These data have significant implications for patients and healthcare systems. Trabeculectomy is performed on average 10 years after initial diagnosis and average life expectancy post glaucoma diagnosis is 9-13 years[9,43,44]; SLT can delay and potentially obviate the need for glaucoma surgery for a proportion of patients.

SLT also leads to a reduced need for cataract surgery; at least 50% more eyes initially treated with eye drops needed a cataract surgery during the 6-year course of the LiGHT trial compared to eyes initially treated with SLT, supporting evidence from the Early Manifest Glaucoma Trial on a greater need for surgical cataract removal in eyes treated with IOP lowering eye-drops.[45]

SLT appears comparable to medical IOP lowering treatment in terms of HRQL. For the first 3 years of the LiGHT trial, generic and disease specific HRQL tools indicated that patients using drops had comparable HRQL to those who received initial SLT and these findings are further supported by the LiGHT trial extension to 6 years. The single time-point where SLT appeared to lead to better GSS scores was the 72 months and is unlikely to have clinical significance. SLT has also been compared to timolol monotherapy using the WHO/PBD-VF20 vision-related quality of life instrument, which also revealed comparable results between the two treatment modalities.[42] Over the recent years the sensitivity of existing QoL tools to capture changes and their suitability as primary outcomes in clinical trials have been questioned.[46]

The safety profile of SLT remains very good, with no sight threatening complications. IOP rose more than 5 mmHg from pre-treatment IOP in only 1% of treated eyes and, of these, only 1 eye needed treatment. Other adverse events were comparable between the two groups. SLT has been shown to be a safe alternative to eye-drops in areas where advanced glaucoma is more common and where treatment resources and access to these are limited.[42] The proven safety of SLT in such areas can rapidly transform glaucoma treatment and prevent sight loss.

Conclusion

After 6 years of treatment and monitoring, SLT safely offers IOP control without the need for medical or surgical treatment in more than 70% of OHT and OAG eyes, whilst demonstrating reduced progression rates and a reduced need for glaucoma and cataract surgery. SLT is now the recommended 1st line treatment for OAG and OHT by National Institute for Health and Care Excellence (NICE)[8] in the UK and is listed as a 1st line treatment in the EU and the USA, alongside IOP-lowering eye drops.

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Figure 1 LiGHT trial CONSORT Flowchart. SLT: Selective Laser Trabeculoplasty. *Two patients were initially randomised twice due to IT failure, where the initial randomisation was not visible and subsequently a second randomisation was carried out. One of these patients was initially randomised to medication but was subsequently randomised to, and received, SLT. The other was initially randomised to SLT but was subsequently randomised to, and received, medication. These patients are included in the diagram according to the second randomisations.

Figure 2 Mean EQ-5D, GUI, GSS, and GQL-15 scores at each time point, across 72 months, based on all available data for patients that participated in extension study. Time-point '0' refers to pre-treatment. EQ-5D=EuroQol 5 Dimensions 5 Levels. GUI=Glaucoma Utility Index. GSS=Glaucoma Symptom Scale. GQL-15=Glaucoma Quality of Life-15. EQ-5D, GUS, GSS: Higher scores indicate better health-related quality of life. GQL-15: Higher scores indicate worse health-related quality of life. Error bars indicate ±2 standards errors.

Figure 3 Failure plot indicating time of disease progression from baseline by treatment arm (log-rank test $p< 0.006$), based on intention-to-treat analysis (the unit of analysis is eye), for all randomised patients. The number at risk at 6 years includes the patients whose last visit was ±6 months.

Figure 4 Failure plot indicating 'time to glaucoma surgery' from baseline by treatment arm (log-rank test $p< 0.001$), based on intention-to-treat analysis (y-axis on a scale of 0-10%; the unit of analyses is eye). The number at risk at 6 years includes the patients whose last visit was ±6 months.

Figure 5 Failure plot indicating 'time to phacoemulsification' from baseline by treatment arm (log-rank test $p< 0.03$), based on intention-to-treat analysis (the unit of analyses is eye). The number at risk at 6 years includes the patients whose last visit was ±6 months.

	Drops (n=320)	**SLT (n=313)**
Age (years) – Mean (SD)	63.2 (11.4)	63.1 (12.0)
Gender		
Male	170 (53.1%)	178 (56.9%)
Female	150 (46.9%)	135 (43.1%)
Diagnosis		
OHT	69 (21.6%)	71 (22.7%)
OAG	251 (78.4%)	242 (77.3%)
Race / Ethnic Origin		
Asian	26 (8.1%)	23 (7.3%)
Black	57 (17.8%)	67 (21.4%)
White	231 (72.2%)	211 (67.4%)
Other	6 (1.9%)	12 (3.8%)
Family History of Glaucoma in 1st Degree Relative		
Yes	94 (29.4%)	100 (32.1%)
No	226 (70.6%)	212 (67.9%)

Table 1 Baseline (month 0) patient characteristics of those participating in the extension. Values are either mean (SD) or number (%). There was 1 missing value for 'Family history of glaucoma for the SLT arm'. There was no evidence that the patient characteristics were significantly different between arms (all $p>0.05$).

	Drops (n=320)	SLT (n=313)	Difference (95% C.I.)
Baseline questionnaire scores			
EQ-5D	0.92 (0.11)	0.92 (0.13)	0.00 (-0.02 to 0.02)
GUI	0.89 (0.11)	0.89 (0.11)	0.00 (-0.02 to 0.01)
GSS	83.3 (16.3)	81.3 (17.0)	-2.1 (-4.7 to 0.5)
Symptom subscale	81.4 (18.7)	79.2 (19.9)	-2.2 (-5.3 to 0.8)
Function subscale	86.3 (17.1)	84.5 (17.7)	-1.8 (-4.6 to 0.9)
GQL-15	18.5 (5.4)	18.8 (6.4)	0.3 (-0.6 to 1.2)
Central subscale	2.5 (0.9)	2.5 (1.0)	0.1 (-0.1 to 0.2)
Peripheral subscale	8.3 (2.8)	8.5 (3.3)	0.2 (-0.3 to 0.6)
Dark subscale	7.8 (2.7)	7.9 (2.9)	0.0 (-0.4 to 0.5)
Outdoor subscale	1.1 (0.4)	1.1 (0.4)	0.0 (-0.1 to 0.0)

Table 1 Baseline questionnaire scores (mean, SD). EQ-5D=EuroQol 5 Dimensions 5 Levels. GUI=Glaucoma Utility Index. GSS=Glaucoma Symptom Scale. GQL-15=Glaucoma Quality of Life-15. EQ-5D, GUS, GSS: Higher scores indicate better health-related quality of life. GQL-15: Higher scores indicate worse health-related quality of life. There was 1 missing value for GUI (drops), 6 for GSS (4 drops, 2 SLT) and 1 for GLQ-15 (drops).

	Drops (n=320)		SLT (n=313)		Adjusted mean difference (95% CI)*	p value
	n	Mean (SD)	n	Mean (SD)		
Intention to treat						
EQ-5D	261	0.89 (0.14)	263	0.90 (0.14)	0.01 (-0.01 to 0.04)	0.18
GUI	255	0.88 (0.13)	257	0.90 (0.13)	0.01 (-0.01 to 0.03)	
GSS	247	81.29 (17.33)	244	83.62 (18.06)	3.27 (0.54 to 6.00)	
GQL-15	208	20.57 (8.01)	203	20.80 (9.40)	-0.13 (-1.57 to 1.31)	
Per original protocol **						
EQ-5D	167	0.89 (0.14)	263	0.90 (0.14)	0.01 (-0.01 to 0.04)	
GUI	163	0.89 (0.13)	257	0.90 (0.13)	0.01 (-0.02 to 0.03)	
GSS	162	82.11 (16.76)	244	83.62 (18.06)	2.68 (-0.45 to 5.81)	
GQL-15	130	20.59 (8.44)	203	20.80 (9.40)	0.22 (-1.50 to 1.94)	

Table 1 Primary and secondary analysis: EQ-5D, GUI, GSS and GQL-15 scores at 72 months for the intention to treat and per protocol analysis. * Estimated from linear regression model adjusting for baseline EQ-5D, severity of glaucoma, site and baseline intraocular pressure ** Patients initially treated with eye drops, who switched to SLT were removed. EQ-5D=EuroQol 5 Dimensions 5 Levels. GUI=Glaucoma Utility Index. GSS=Glaucoma Symptom Scale. GQL-15=Glaucoma Quality of Life-15. EQ-5D, GUS, GSS: Higher scores indicate better health-related quality of life. GQL-15: Higher scores indicate worse health-related quality of life

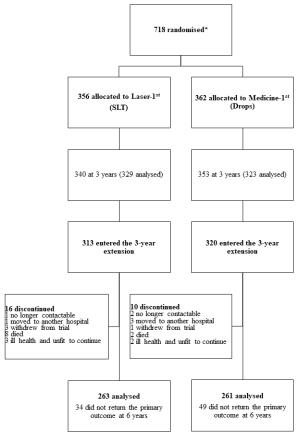
	Drops	SLT	p-value
Control of disease during the 72 months of the trial			
Visits with eyes at target (cumulative)	93.2%	92.8%	0.88
Eyes at target IOP at 72 months	429 (94.7%)	437 (94.2%)	0.73
OHT	118 (94.4%)	134 (96.3%)	0.51
Mild OAG	239 (96.4%)	227 (93.0%)	0.01
Moderate OAG	48 (88.9%)	45 (95.7%)	0.28
Severe OAG	24 (92.3%)	31 (91.2%)	1.00
Treatment escalations	477	543	0.47
Disease progression¶	147 (26.8%)	107 (19.6%)	0.01
OHT to OAG conversion	22	15	0.55
OAG progression	125	92	0.01
Algorithm-defined VF progression (OAG)	100	73	
Algorithm-defined ON progression (OAG)	9	12	
Algorithm-defined VF & ON progression (OAG)	16	7	
Ocular surgeries during the 72 months of the trial*			
Trabeculectomy at 72 months	32 (5.8%)	13 (2.4%)	<0.001
Trabeculectomy at 36 months	11	0	
Trabeculectomy revision	2 (0.4%)	0	0.50
Phacoemulsification‡	95 (17.3%)	57 (10.4%)	0.03
Treatment intensity at 72 months			
Drop freedom for eyes at Target IOP (% of all eyes reaching 6 years)			
No medications	106 (23.0%)	338 (71.9%)	<0.001
No medications, no trabeculectomy	83 (18.0%)	328 (69.8%)	<0.001
SLT only	66	295	
Phacoemulsification, no SLT	10	0	
Phacoemulsification and SLT	7	33	
Number of medications per eye at Target IOP			
1 medication	196 (42.6%)	56 (11.9%)	
2 medications	87 (18.9%)	31 (6.6%)	<0.001
3 medications	37 (8.0%)	11 (2.3%)	
4 medications	3 (0.7%)	1 (0.2%)	
Number of SLT treatments per eye			
1 SLT	164 (29.9%)	343 (62.7%)	-
2 SLTs	10 (1.8%)	169 (30.9%)	-
3 SLTs	2 (0.4%)	32 (5.9 %)	-
4 SLTs**	0 (0.0%)	3 (0.5%)	-
Number of SLT treatments per eye, for eyes with no medication and no trabeculectomy			
1 SLT	65 (78.3%)	182 (55.5%)	-
2 SLTs	6 (7.2%)	113 (34.5%)	-
3 SLTs	2 (2.4%)	31 (9.5%)	-
4 SLTs**	0	2 (0.6%)	-
IOP target revisions***	96 (89 eyes)	90 (85 eyes)	0.76
Upwards IOP target revisions	31	40	-
Downwards IOP target revisions	65	50	-
Clinical outcomes at 72 months			
Visual acuity (logMAR)	0.1 (0.2)	0.1 (0.2)	0.24
IOP	15.4 (3.9)	16.3 (4.0)	<0.001
MD	-3.9 (4.4)	-4.0 (4.5)	0.80
Clinic visits			
Total number of clinic visits	4970	5175	0.13
Number of visits excluding the 2-week IOP check	4852	4678	0.49

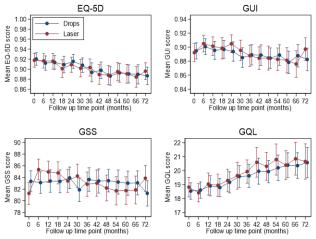
Table 4 Measurement of pathway effectiveness and visual function for eyes at 72 months (± 6 months). Data are n (%) unless otherwise stated. Diagnosis indicates diagnosis at baseline. SLT=selective laser trabeculoplasty. IOP=intraocular pressure. OHT=ocular hypertension. OAG=primary open angle glaucoma. VF=visual field. MD=mean deviation. ¶Conversion of OHT to OAG required a sign of progression derived from the decision support software and verification by a consultant ophthalmologist; OAG progression OAG required a sign of progression derived from the decision support software; 4 OHT eyes had a single OAG diagnosis during the trial and these were assumed to be errors. See Figure 3 for a full statistical comparison. An analysis of progression by disease severity is available in Appendix 4 ‡ Minimally invasive glaucoma surgery combined phacoemulsification was performed in 11 eyes of 6 patients initially treated with IOP-lowering eye drops during the extension of the trial. * See Figure 4 and Figure 5 for a full statistical comparison. **Protocol deviation; 3 eyes of 2 patients. ***Target IOP was reassessed when VF and sequential disc imaging provided evidence of disease stability; IOP was revised following a decision support software recommendation, according to pre-set criteria[21].

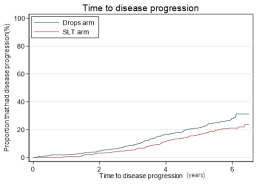
	Total (n=633)		Drops (n=320)		SLT (n=313)		p-value
Adverse events							
Total number of events	3647		2069		1578		
Total number of patients	557 (88.0%)		286 (89.4%)		271 (86.6%)		0.33
	N of events	**N of patients (%)**	**N of events**	**N of patients (%)**	**N of events**	**N of patients (%)**	
Ocular	2367	495 (78.2%)	1470	271 (84.7%)	897	224 (71.6%)	<0.001
Aesthetic side effects of	195	71 (11.2%)	164	57 (17.8%)	31	14 (4.5%)	<0.001
Ophthalmic allergic	81	48 (7.6%)	54	27 (8.4%)	27	21 (6.7%)	0.41
Reactivation of herpes	2	2 (0.3%)	1	1 (0.3%)	1	1 (0.3%)	1.00
Uveitis	17	10 (1.6%)	7	5 (1.6%)	10	5 (1.6%)	0.97
Vision changes	43	38 (6.0%)	26	22 (6.9%)	17	16 (5.1%)	0.35
Other [c]	2029	484 (76.5%)	1218	262 (81.9%)	811	222 (70.9%)	0.001
Systemic [g]	1006	287 (45.3%)	544	154 (48.1%)	462	133 (42.5%)	0.16
Pulmonary problems [h]	86	41 (6.5%)	44	23 (7.2%)	42	18 (5.8%)	0.46
Cardiac events	27	19 (3.0%)	11	10 (3.1%)	16	9 (2.9%)	0.85
Drug related events [i]	345	89 (14.1%)	202	59 (18.4%)	143	30 (9.6%)	0.001
Other [j]	548	237 (37.4%)	287	121 (37.8%)	261	116 (37.1%)	0.85
	N of events	**% of SLT treatments**	**N of events**	**% of SLT treatments**	**N of events**	**% of SLT treatments**	
SLT related	274	28.0%	55	28.9%	219	27.8%	0.74
Inflammation post SLT	3	0.3%	1	0.5%	2	0.3%	0.48
IOP spike post SLT [d]	10	1.0%	4	2.1%	6	0.8%	0.11
Other transient events [e]	241	24.6%	50	26.3%	191	24.2%	0.55
AE during SLT procedure [f]	20	2.0%	0	0%	20	2.5%	0.02
Serious adverse events							
Total number of events	389		180		209		
Total number of patients	217		110		107		0.003
	N of events	**N of patients (%)**	**N of events**	**N of patients (%)**	**N of events**	**N of patients (%)**	
Ocular [k]	43	34 (5.4%)	18	15 (4.7%)	25	19 (6.0%)	0.6
Pulmonary problems [l]	10	10 (1.6%)	4	4 (1.2%)	6	6 (1.9%)	0.50
Cerebrovascular accidents	7	7 (1.1%)	5	5 (1.6%)	2	2 (0.6%)	0.45
Cardiac events	29	26 (4.1%)	15	14 (4·4%)	14	12 (3.8%)	0.73
Cancer	44	38 (6.0%)	14	12 (3.8%)	30	26 (8.3%)	0.02
Death	25	25 (3.9%)	10	10 (3.1%)	15	15 (4.8%)	0.28
Other Systemic	231	193 (30.5%)	114	77 (24.1%)	117	79 (25.2%)	0.73

Table 1: Adverse events. Adverse events. a: includes excessive lash growth, peri-ocular pigmentation, change in iris colour. b: includes peri-ocular skin rash c: Includes ocular irritation, discomfort, dry eye, retinal haemorrhages, flashes, floater, conjunctivitis, blepharitis, vascular occlusions, diabetic retinopathy, macular

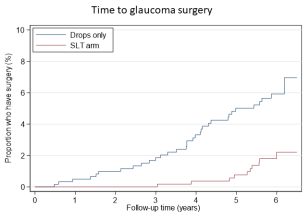
pathology d: IOP spike defined as >5mmHg; 2 eyes had an IOP rise >10mmHg, 1 eye was monitored and received no treatment and 1 eye received treatment e: Includes discomfort, transient blurred vision, transient photophobia, hyperemia f: Includes discomfort, variation in the number of laser shots, angle visualisation issues g: not requiring hospitalisation h: asthma, shortness of breath, reduced exercise tolerance i: includes impotence, depression, somnolence/tiredness, nightmares, taste disturbance, generalised skin rash j: unrelated events, such as headaches, pain, falls etc. k: excludes cataract and glaucoma surgery; includes central retinal artery occlusion, choroidal neovascularisation, epi-retinal membrane, angle closure, anterior chamber surgery, corneal pathologies, orbital cellulitis, retinal detachment, trauma and any treatment required for these pathologies l: requiring hospitalisation.



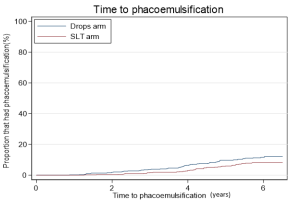




Number of patients at risk / years	0	2	4	6*
Drops arm	361	335	282	235
SLT arm	355	339	287	243



Number of patients at risk / years	0	1	2	3	4	5	6*
Drops arm	361	352	342	334	307	291	266
SLT arm	355	351	345	328	304	287	270



Number of patients at risk / years	0	2	4	6*
Drops arm	353	331	287	240
SLT arm	351	340	296	256

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Selective laser trabeculoplasty offers drop- and surgery-free IOP control to 70% of treated eyes and a reduced need for glaucoma and cataract surgery over 6 years, compared to eyes treated with eye drops.