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Diabetic Macular Edema and Diode Subthreshold Micropulse Laser

A Randomized Double-Masked Noninferiority Clinical Trial

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Purpose: To determine clinical effectiveness, safety, and cost-effectiveness of subthreshold micropulse laser (SML), compared with standard laser (SL), for diabetic macular edema (DME) with central retinal thickness (CRT) < 400 μm.

Design: Pragmatic, multicenter, allocation-concealed, double-masked, randomized, noninferiority trial.

Participants: Adults with center-involved DME < 400 μm and best-corrected visual acuity (BCVA) of > 24 Early Treatment Diabetic Retinopathy Study (ETDRS) letters in one/both eyes.

Methods: Randomization 1:1 to 577 nm SML or SL treatment. Retreatments were allowed. Rescue with intravitreal anti–vascular endothelial growth factor therapies or steroids was permitted if 10 or more ETDRS letter loss occurred, CRT increased > 400 μm, or both.

Main Outcome Measures: Primary outcome was mean change in BCVA in the study eye at 24 months (noninferiority margin 5 ETDRS letters). Secondary outcomes were mean change from baseline to month 24 in binocular BCVA; CRT and mean deviation of Humphrey 10-2 visual field in the study eye; percentage meeting driving standards; EuroQoL EQ-5D-5L, 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25), and Vision and Quality of Life Index (VisQoL) scores; cost per quality-adjusted life-years (QALYs) gained; adverse effects; and number of laser and rescue treatments.

Results: The study recruited fully (n = 266); 87% of SML-treated and 86% of SL-treated patients had primary outcome data. Mean ± standard deviation BCVA change from baseline to month 24 was −2.43 ± 8.20 letters and −0.45 ± 6.72 letters in the SML and SL groups, respectively. Subthreshold micropulse laser therapy was deemed not only noninferior but also equivalent to SL therapy because the 95% confidence interval (CI; −3.9 to −0.04 letters) lay wholly within both upper and lower margins of the permitted maximum difference (5 ETDRS letters). No statistically significant difference was found in binocular BCVA (0.32 ETDRS letters; 95% CI, −0.99 to 1.64 ETDRS letters; $P = 0.63$); CRT (−0.64 μm; 95% CI, −14.25 to 12.98 μm; $P = 0.93$); mean deviation of the visual field (0.39 decibels (dB); 95% CI, −0.23 to 1.02 dB; $P = 0.21$); meeting driving standards (percentage point difference, 1.6%; 95% CI, −25.3% to 28.5%; $P = 0.91$); adverse effects (risk ratio, 0.28; 95% CI, 0.06−1.34; $P = 0.11$); rescue treatments (percentage point difference, −2.8%; 95% CI, −13.1% to 7.5%; $P = 0.59$); or EQ-5D, NEI-VFQ-25, or VisQoL scores. Number of laser treatments was higher in the SML group (0.48; 95% CI, 0.18−0.79; $P = 0.002$). Base-case analysis indicated no differences in costs or QALYs.

Conclusions: Subthreshold micropulse laser therapy was equivalent to SL therapy, requiring slightly higher laser treatments. *Ophthalmology 2022;■:1−14 © 2022 by the American Academy of Ophthalmology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).*

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Diabetic macular edema (DME) remains a major cause of sight loss in people with diabetes. It was estimated that, in 2020, the number of adults with diabetes and clinically significant macular edema (CSME) was 18.83 million worldwide, with a projected increase to 28.61 million by 2045.[1] High hemoglobin A1c count and longer duration

of diabetes are known to be risk factors for its occurrence.[2]

The Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated that macular laser therapy reduced the risk of visual loss ($\geq$ 3 ETDRS line loss) by 50% at 3 years in people with CSME.[3] Clinically significant macular edema was defined by the presence, as determined on slit-lamp biomicroscopy, of retinal thickening within 500 μm of the center of the macula or hard exudation within 500 μm from the center of the macula, provided it was associated with adjacent retinal thickening, or retinal thickening of 1 disc area or more within 1 disc diameter of the center of the macula.[3] Few participants in the ETDRS gained 15 letters or more after laser treatment, and as a result, it is often mentioned that macular laser therapy does not improve vision. However, ETDRS findings need to be interpreted taking into consideration that the great majority of participants (85%) in the ETDRS had excellent vision ($\geq$ 20/40) at baseline, with potentially less room for improvement. In the ETDRS, 5% of eyes assigned to immediate focal laser treatment lost > 15 letters at 1 year, 7% of eyes did so at 2 years, and 12% of eyes did so at 3 years. Randomized clinical trial (RCT) evidence has demonstrated that macular laser therapy can improve vision in people with center-involved DME, with reported gains of 10 letters or more in 32% and 44% of individuals at 2 and 3 years, respectively, after treatment.[4,5]

Even in the era of anti−vascular endothelial growth factor (VEGF) therapies, macular laser therapy remains an effective and required treatment for many patients with DME. Thus, as highlighted by the American Society of Retinal Specialists,[6] macular laser therapy remains the treatment of choice for non−center-involved CSME, and it should be offered to these patients to avoid future visual loss, as per the ETDRS. The National Institute for Health and Care Excellence (NICE) in the United Kingdom supports the use of intravitreal anti-VEGF agents to treat more severe forms of center-involved DME, with central retinal thickness (CRT) on OCT of 400 μm or more, but for people with milder forms of DME (CRT < 400 μm), macular laser treatment is preferred and advised because it is as clinically effective as anti-VEGF agents but less costly.[3,7,8] The reason for this is that, when NICE reviewed the evidence provided by the anti-VEGF manufacturers, it was found that, when the CRT was < 300 μm, no statistically significant difference was found in treatment efficacy between anti-VEGF agents and laser therapy, but laser therapy was more cost-effective. When the CRT was between 300 and 400 μm, gains in vision of approximately 7 letters in the anti-VEGF group compared with 4 letters in the macular laser group were observed; the difference (approximately 3 letters) was statistically significant but of very doubtful clinical relevance. For this group of patients, macular laser therapy dominated in cost-effectiveness, having similar efficacy but being less costly than anti-VEGF agents. Moreover, the Diabetic Retinopathy Clinical Research Network showed that between 41% and 64% of people receiving anti-VEGF agents required macular laser therapy to control DME during the 2-year period after initiation of therapy.[9] Hence, macular laser therapy is still required even in people treated with anti-VEGF agents.

Macular laser treatment can be administered using a continuous wave laser, which produces a visible burn in the retina and is referred to as *threshold laser* therapy (henceforth referred to as *standard laser* [SL] therapy). Although the mechanism of action of the macular laser is not understood completely, it is believed that it has its effect, at least in part, by acting on still viable retinal pigment epithelium (RPE) cells around the area of the burn. Given that heat spreads by conduction, it is possible that damage to the retinal layers, including photoreceptors, could occur adjacent to the area of treatment. If applied to the center of the fovea, SL treatment could cause central sight loss. Thus, this form of laser therapy requires considerable expertise by the clinician performing it because the fovea may not be identifiable easily when it is thickened by DME. Furthermore, as advised by the ETDRS,[3] ideally, fundus fluorescein angiography (FFA) should be carried out before undertaking SL therapy to identify areas of leakage that then would be targeted by the laser treatment. Side effects that have been attributed to SL therapy, besides the potential burning of the fovea, include paracentral scotomas, color vision deficits, epiretinal membrane, and subretinal fibrosis. If strong laser therapy is applied close to the fovea, expansion of the burn over time could lead to involvement of the fovea and subsequent central loss of vision.

Macular laser therapy can be undertaken also using a subthreshold micropulse laser (SML). In SML therapy, a series of repetitive, very short pulses of laser treatment is applied, with each pulse of active "on" laser therapy separated by a long "off" period. This off period allows the retina to cool down and avoids the development of a burn, leaving the RPE and overlying neurosensory retina, including photoreceptors, intact.[10,11] It is believed SML therapy acts by stimulating the RPE directly.[9,10] Because no destruction of the retina occurs, this treatment could be applied to larger areas (not only those with leaking blood vessels or thickened by DME) in a standardized fashion and repeated as many times as needed.

Given that SML therapy does not produce any visible effects in the retina, concerns emerged about its efficacy when compared with SL therapy. Early small clinical trials[12−19] suggested that SML therapy was as effective, or even superior, to SL therapy, but stronger evidence was required. The Diabetic Macular Oedema and Diode Subthreshold Micropulse Laser (DIAMONDS) trial was undertaken to determine the clinical effectiveness, safety, and cost-effectiveness of SML therapy when compared with SL therapy in people with DME and CRT <400 μm as determined by OCT. The DIAMONDS trial was designed as a noninferiority trial but was powered also to test equivalence and superiority (if this were to exist) of SML therapy when compared with SL therapy with regard to efficacy. We chose central vision as the primary outcome because this is most important to people with diabetes and DME and set the noninferiority margin at 5 ETDRS letters (equivalence margin as ± 5 ETDRS letters) because visual changes of this size or less are unlikely to be clinically relevant to patients[7,8] and even could be attributed to test−retest variability.

Methods

Study Design and Objectives

The DIAMONDS trial was designed as a pragmatic, allocation-concealed, double-masked (participants and outcome assessors), multicenter, randomized, noninferiority clinical trial set within specialist hospital eye services (n = 16) in the United Kingdom. The DIAMONDS trial evaluated the clinical effectiveness, safety, and cost-effectiveness of SML therapy when compared with SL therapy for the treatment of patients with center-involved DME with CRT on spectral-domain OCT <400 μm. The study methodology is detailed in its published protocol[20]; a summary is provided below.

Patient Eligibility, Ethical Approval, and Trial Registration

Potential participants were identified through electronic databases, referrals to hospital eye services, or while in the clinic at each participating site. This trial was conducted following the principles that have their origin in the Declaration of Helsinki. Informed consent was obtained from all participants before the undertaking of any study procedures. Eligibility criteria for the DIAMONDS trial are presented in Table 1. If both eyes were eligible, both eyes would receive the same type of laser therapy, but one was designated as the study eye. The study eye was the eye with the best best-corrected visual acuity (BCVA) at randomization or, if vision was the same in both eyes, the eye with less CRT.

The protocol for the trial was approved by the Office for Research Ethics Committees Northern Ireland (identifier, ORECNI 15/NI/0197). A clinical trial authorization was obtained from the Medicines and Healthcare Products Regulatory Agency (identifier, 32485/0029/001-0001). The trial was registered with the European Union Drug Regulating Authorities Clinical Trials database (identifier, 2015-001940-12), in the International Standard Randomised Controlled Trial Number register (identifier, ISRCTN16962255), and at ClinicalTrials.gov (identifier, NCT03690050).

The DIAMONDS trial participants were similar to those enrolled in the original ETDRS trial[3] in that they had mild to moderate nonproliferative diabetic retinopathy and visual acuity of 20/200 or better. However, unlike those in the ETDRS, DIAMONDS participants did not necessarily have to have CSME, as per ETDRS definition, and they could have only center-involved DME as determined using spectral-domain OCT. This follows recently conducted RCTs on DME and standard clinical practice.

Interventions

Patients were randomized to 1 of 2 groups: (1) 577-nm SML therapy or (2) SL therapy (e.g., argon, frequency-doubled neodymium:yttrium–aluminium–garnet 532-nm laser treatment). Information on laser type, parameters used, and time spent applying the treatment was recorded in the patient's case report form. In participants with both eyes eligible and included in the trial, both the study eye and fellow eye in the trial received the same type of laser treatment (the laser type that was allocated randomly).

The SML therapy was delivered using a 577-nm solid-state diode laser (IQ 577; IRIDEX Corp). The SML therapy was applied confluently to the macular area using three 7 × 7 spot grids with zero-spot spacing above and below the fovea (500 μm from its center) and one 7 × 7 spot grid with zero-spot spacing at each side (temporal and nasal) of the fovea (500 μm from its center). In addition, treatment was applied to areas of thickening, if present,

located outside this central area. A contact lens with laser magnification of ×1.0 ± ×0.06 was advised to be used for all laser treatments. Before administering SML treatment, laser titration was performed using continuous-wave mode, a 200-μm spot, and a 200-ms exposure duration. An area of edematous retina of > 2 disc diameters from the foveal center (if possible) was used for titration. The threshold power was determined by increasing the laser power in 10-mW increments, starting from 50 mW, until a barely visible tissue reaction was seen. As soon as this threshold was determined, the laser was switched to micropulse mode at a 5% duty cycle, and the laser power was adjusted to 4 times the continuous-wave threshold power (e.g., if a barely visible reaction was seen at 70 mW using continuous-wave power, then micropulse laser was applied with 280 mW). The SML therapy then was delivered using a 5% micropulse duty cycle, 200-μm spot, and 200-ms exposure duration. Duty cycle is the percentage of time the laser is on during each micropulse period (e.g., a period of 2000 μs during which the laser is on for 100 μs and off for 1900 μs equates to a 5% duty cycle).

For patients allocated to SL therapy, laser treatment was applied to areas of thickened retina, macular nonperfusion (away and noncontiguous with the perifoveal capillaries), and leaking microaneurysms, in accordance with the ETDRS and the United Kingdom Royal College of Ophthalmologists guideline.[3,21] To identify areas of nonperfusion and leakage and thickening before treatment, FFA and spectral-domain OCT, respectively, were used at the discretion of the treating ophthalmologist and according to their standard clinical practice. Treatment was applied to obtain a mild gray-white burn evident beneath leaking microaneurysms and in other areas of leakage or nonperfusion not affecting the perifoveal capillaries based on FFA, if FFA had been obtained, or to cover areas of thickening if treatment was given based on spectral-domain OCT findings, or both. In the DIAMONDS trial, SL therapy was performed using a modified ETDRS technique. In the ETDRS, argon laser therapy was used, whereas in DIAMONDS, other types of lasers were allowed, given that argon laser therapy is no longer widely available. The technique and parameters used for SL therapy in the DIAMONDS trial are representative of those used in other macular laser trials[4,5] and in standard clinical practice.

If necessary, laser retreatments were carried out with the same technology allocated by randomization. When re-treating, treatment of areas within 300 to 500 μm from the center of the fovea were allowed. Rescue treatment with anti-VEGF agents or steroids, as appropriate based on judgement by the treating ophthalmologist, was allowed in both treatment groups if the CRT increased to 400 μm or more at any point during the patient's follow-up or if a loss of 10 ETDRS letters or more occurred related to DME. All treating ophthalmologists had extensive experience of diabetic retinopathy and DME, including delivering laser treatment for this condition.

Outcomes

The primary outcome was the difference between treatment groups in mean change in BCVA in the study eye at month 24. Secondary outcomes included mean change from baseline to month 24 in binocular BCVA, CRT, and mean deviation of the Humphrey 10-2 visual field in the study eye; percentage of people meeting driving standards; EuroQoL (EQ-5D-5L), 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25), and Vision and Quality of Life Index scores; cost per quality-adjusted life-year gained; adverse effects; number of laser treatments administered; and rescue treatments.

The safety of the treatment was assessed at each visit by noting any complications during or after the laser procedure, including self-reported visual disturbances, and 10-letter or more and

Table 1. Eligibility Criteria for DME and Diode Subthreshold Micropulse Laser Trial

Inclusion Criteria	Exclusion Criteria
1. Center involved DME, as determined by slit-lamp biomicroscopy and spectral-domain OCT, in one or both eyes, with either CRT of >300 μm but <400 μm in the central subfield (central 1 mm) resulting from DME or CRT of <300 μm in the central subfield provided that intraretinal fluid, subretinal fluid, or both were present in the central subfield (central 1 mm) because of DME. The following conditions also had to be met: 1. BCVA of >24 ETDRS letters (Snellen equivalent, >20/320) 2. Amenable to laser treatment, as judged by the treating ophthalmologist 3. 18 years of age or older	A patient's eyes were not eligible for the study 1. If the macular edema was the result of causes other than DME or if the eye was: 2. Ineligible for macular laser therapy, as judged by the treating ophthalmologist 3. Had CRT of ≥400 μm 4. Had active PDR requiring treatment 5. Received intravitreal anti-VEGF therapy within the previous 2 months 6. Received macular laser therapy within the previous 12 months 7. Received intravitreal injection of steroids 8. Underwent cataract surgery within the previous 6 weeks 9. Had PRP within the previous 3 months Patients who otherwise were eligible were not included in the study if they: 10. Were receiving pioglitazone and the drug could not be stopped 3 months before joining the trial and for its entire duration 11. Had chronic renal failure requiring dialysis or kidney transplantation 12. Had any other condition that, in the opinion of the investigator, would preclude participation in the study (e.g., unstable medical status or severe disease that would make it difficult for the patient to complete the 2-year trial) 13. Had very poor glycemic control that required starting intensive therapy within the previous 3 months 14. Was using an investigational drug

BCVA = best-corrected visual acuity; DME = diabetic macular edema; CRT = central retinal thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; PDR = proliferative diabetic retinopathy; PRP = panretinal photocoagulation; VEGF = vascular endothelial growth factor therapy.

15-letter or more score ETDRS visual acuity loss occurring from visit to visit. Patients were asked specifically, in layman's terms, about reduced color vision, presence of paracentral scotomas, or metamorphopsia at each visit. Additionally, the following also were listed in the protocol as potentially anticipated adverse events of the laser treatment and were evaluated specifically during the trial: foveal burn, epiretinal membrane formation, and choroidal neovascularization.

Randomization and Masking

After giving informed consent, eligible participants were randomized 1:1 to receive either SML or SL using a minimization algorithm within an automated randomization system (Sealed Envelope; https://www.sealedenvelope.com), with the allocation concealed to the ophthalmologist randomizing the patient until the patient had joined the trial. Only the local ophthalmologist used this automated system to ensure postrandomization masking of the outcome assessors to the allocation. Although most patients received their allocated therapy at the baseline visit, it was acceptable for it to be performed at a later visit, within 2 weeks of the baseline. If there was a longer interval between baseline and laser treatment, eligibility was reconfirmed before treatment.

The randomization system used minimization to balance allocation of patients across intervention groups for the following factors and covariates: center (participating site), distance BCVA at presentation (≥ 69 ETDRS letters [Snellen equivalent, ≥ 20/40; ≥ 0.3 logarithm of the minimum angle of resolution (logMAR)];

24−68 ETDRS letters [Snellen equivalent, ≤ 20/50; 0.4−1.2 logMAR]), and previous use of anti-VEGF agents or macular laser therapy in the study eye. A random element was used in the minimization to provide a probability of 0.85 for assigning to the treatment group that minimized imbalance.

The DIAMONDS trial was a pragmatic RCT so that its results would be applicable immediately in clinical practice as soon as the trial was completed. For this reason, ophthalmologists undertaking laser treatments for DME at each participating site delivered the treatment for the trial and thus were not masked to the laser used. However, participants and outcome assessors (optometrists measuring visual function; photographers, ophthalmic technicians, and nurses obtaining OCT images; and ophthalmic technicians obtaining visual fields) all were masked to treatment allocation. Participants remained masked until the trial ended.

Participant Assessments

Following standard clinical practice, participants were followed up at 3- to 4-month intervals after laser treatment for a total of 7 visits until trial completion (month 24). Best-corrected visual acuity was measured in both eyes using ETDRS visual acuity charts at 4 m at baseline and at months 4, 8, 12, 16, 20, and 24. Best-corrected visual acuity was obtained after refraction at baseline and 12 and 24 months by optometrists masked to treatment allocation. At all other visits, BCVA could be obtained by other masked staff using the most recently available refraction. Binocular BCVA similarly was obtained at baseline and 12 and 24 months to give indication

of the person's vision in real life (i.e., with both eyes open). A refraction protocol was followed by the optometrists to obtain BCVA and binocular vision. Both 10-2 Humphrey visual fields and an Esterman binocular visual field (to determine patient's ability to fulfil driving standards) were obtained by visual field technicians masked to treatment allocation at baseline and 12 and 24 months. Central retinal thickness measurements were obtained using the Heidelberg Spectralis spectral-domain OCT (Heidelberg Engineering) as per standard clinical practice at each of the participating centers in both eyes at baseline and at months 4, 8, 12, 16, 20, and 24 by technicians, photographers, or nurses masked to the treatment allocation.

Two vision-related quality-of-life tools, the NEI-VFQ-25 and the Vision and Quality of Life Index questionnaires, were used in the DIAMONDS trial, in addition to a generic preference-based health-related quality-of-life measure to generate utility data, the EQ-5D-5L. Questionnaires were self-completed by patients at baseline and 12 and 24 months. Baseline questionnaires were completed before the first session of laser treatment.

Power Calculation and Statistical Analysis before the Trial

The DIAMONDS trial was powered to demonstrate not only noninferiority but also equivalence of SML therapy with respect to the primary outcome (mean change in BCVA in the study eye at 24 months after treatment) because, based on the knowledge existing at the time the DIAMONDS trial was designed, it was possible that no differences could be found in the primary outcome, but differences could exist in other important secondary outcomes, such as patient-reported outcome measures. In addition, the DIAMONDS trial was sufficiently powered to determine superiority of one laser therapy over the other if this were to exist.

Based on a mean ± standard deviation (SD) BCVA change of $0.08 ± 0.23$ logMAR from baseline for the standard care laser treatment[11] and a permitted maximum difference of 0.1 logMAR (5 ETDRS letters) between groups, we estimated the trial would require 113 randomized participants per group at 90% power and 0.05 level of significance. Allowing for up to a 15% dropout rate during the 24 months of follow-up, the target recruitment was set to 266 participants. A permitted maximum difference of 5 ETDRS letters between groups was chosen as the noninferiority margin (± 5 ETDRS letters for equivalence) because a difference of this size or less is not considered clinically relevant or meaningful to patients[7,8] and even could result from test—retest variability. The 24-month data for 113 participants per group would be sufficient also to detect a mean difference between lasers of 37.7 µm in CRT (based on an SD of 86.8 µm)[13] and of 6.55 in NEI-VFQ-25 scores (based on an SD of 15.1, as per Tranos et al[22]). These are important secondary outcomes, and such differences in CRT and NEI-VFQ-25 scores have been shown to be clinically relevant.[23,24]

The primary statistical analysis was a per-protocol (PP) one, but an intention-to-treat (ITT) analysis also was undertaken. An ITT analysis is recommended for superiority trials, but for noninferiority or equivalence trials, a PP analysis is preferred because ITT analysis increases the risk of a type I error. The main analyses were as prespecified in the protocol.

The difference between lasers for change in BCVA (using 95% confidence interval [CI]) from baseline to month 24 (primary end point) was compared with the permitted maximum difference of 5 ETDRS letters (0.1 logMAR). The SML treatment would be deemed noninferior to the SL treatment if the lower limit of the 95% CI of the treatment difference was more than this noninferiority margin. If the 95% CI of the treatment difference was wholly within both upper and lower margins of the permitted maximum difference (± 5 ETDRS letters), then the SML therapy would be deemed to be equivalent to the SL therapy.

Change in BCVA from baseline to month 24 was compared between the 2 intervention groups using an independent 2-sample *t* test with a secondary analysis using an analysis of covariance model adjusted for baseline BCVA score, baseline CRT, and minimization covariates. The primary analysis was based on data from the study eye only. When performing a secondary analysis on the subset of participants with both eyes eligible and treated, study eye was included as a random effect within the mixed model. Statistical diagnostic methods were used to check for violations of the model assumptions and data transformations or nonparametric equivalents so that the Mann—Whitney *U* test could be performed as appropriate. Statistical significance was based on 2-sided tests, with $P < 0.05$ taken as the criterion for statistical significance, with no adjustment for multiple testing. The principal analysis was based on available case data with no imputation of missing values. Intention-to-treat analyses were used for all secondary outcomes because the aim was to assess superiority for these outcomes.

Adverse effects of laser treatment and use of rescue treatments (steroids or anti-VEGF agents) were analyzed using logistic regression models with adjustment for the minimization covariates. Analyses of secondary measures of visual function and anatomic outcomes (CRT, mean deviation of the 10-2 visual field test) and number of treatments required were undertaken using linear regression models adjusted for baseline BCVA score and minimization covariates. Analysis of the proportion of participants meeting driving standards was undertaken using a logistic regression model adjusted for baseline BCVA and the minimization covariates. The number of adverse events, adverse reactions, serious adverse events, serious adverse reactions, suspected unexpected serious adverse reactions, and number (percentage) of participants experiencing these events are reported. The chi-square test (or Fisher exact test, if appropriate) and proportion test were used to check whether incidences of adverse events differed between intervention groups. Relative risks and 95% CIs are reported. Baseline characteristics, follow-up measurements, and safety data are presented using appropriate descriptive summary measures depending on the scale of measurement and distribution.

Sensitivity analyses were undertaken to assess the impact of missing data by imputing extreme values (lowest and highest) and last observation carried forward, including patients who were not treatment naive (i.e., excluding those who had undergone previous laser treatment for DME in the study eye or previous anti-VEGF treatment for DME or proliferative diabetic retinopathy in the study eye) and phakic status at baseline (i.e., no previous cataract surgery in the study eye), and using month 24 data that were collected outside ± 14 days of the due date. We conducted prespecified subgroup analyses of the primary outcome based on clinical rationale considering center, distance BCVA at baseline (≥ 69 ETDRS letters [Snellen equivalent, ≥ 20/40; ≥ 0.3 logMAR]; 24-68 ETDRS letters [Snellen equivalent, ≤20/50; 0.4—1.2 logMAR]), previous use of anti-VEGF agents, and macular laser treatment in the study eye. These analyses were carried out by including the corresponding interaction term in the regression model and 99% CIs. We also conducted an exploratory subgroup analysis to identify whether participants with a baseline hemoglobin A1c value of ≥ 53 mmol/mol (≥ 7%) were at higher risk of poorer outcomes.

Health Economics Methods

The main objective of the health economics evaluation was to conduct a short-term (baseline to 2-year follow-up) within-trial analysis comparing cost-effectiveness of SML treatment with that of SL treatment. To achieve this, a systematic comparison of costs of resource inputs used by participants in the 2 treatment groups and the consequences associated with the interventions was conducted. The primary analysis adopted a United Kingdom National Health Service and personal and social service perspective. The economic evaluation took the form of a cost-utility analysis, expressed in terms of incremental cost per quality-adjusted life-year gained. Costs and outcomes beyond the first year of follow-up were discounted at 3.5%, in line with the NICE reference case.[25]

For the health economics analysis, we adopted an ITT approach as reported in the Health Economics Analysis Plan. An ITT analysis requires that study participants are analyzed according to their treatment assignment, regardless of actual treatment received. This is the approach preferred by NICE for cost-effectiveness analyses as stated in their methods guide.[25] Results for the PP analysis also are reported in a sensitivity analysis. Detailed health economics methodology can be found in the DIAMONDS Health Economics Analysis Plan[26]; detailed results of the health economic evaluation will be published separately.

The DIAMONDS Statistical Analysis Plan and Health Economics Analysis Plan were agreed on and made accessible on the DIAMONDS website[26] before commencement of data analysis. The DIAMONDS trial was executed and reported following the Consolidated Standards of Reporting Trials guidelines for equivalence and noninferiority trials.[27]

DIAMONDS Patient and Public Involvement Group

At the very early stages of the DIAMONDS trial conception, a DIAMONDS Patient and Public Involvement (PPI) group was established with the help of the Northern Ireland branch of Diabetes UK. The DIAMONDS PPI group comprised people living with diabetes and DME, including a large group of members of the Diabetes Family Facebook group. The DIAMONDS PPI group contributed to the trial design, including selection of outcomes, preparation of patient-related materials for the trial, recruitment strategies, and interpretation of trial results. They also had a role in dissemination of results.

Results

Participant Flow, Baseline Characteristics, and Details of Laser Treatment

Recruitment of participants took place from January 18, 2017, through November 20, 2018. A total of 336 participants were assessed for eligibility, and 266 of those participants assessed as eligible (79%) agreed to join the trial and were randomized (SML group, n = 133; SL group, n = 133). One participant in the SL group withdrew consent for data to be used and was excluded from all analyses. The first month 24 follow-up visit was completed on January 25, 2019, and the final month 24 follow-up visit was completed on December 22, 2020. The Consolidated Standards of Reporting Trials flow diagram (Fig 1) details the flow of participants throughout the trial.

Patient characteristics were broadly similar across intervention groups (Table S1, available at www.aaojournal.org). All participants had DME in the study eye with an overall mean ± SD duration of diagnosis of 2.5 ± 4.5 years; 24% (n = 64) had

received previous macular laser treatment before joining the trial, with a median number of laser sessions of 1 (interquartile range, 1−2 sessions) and a mean ± SD length of time since the last laser session of 4.2 ± 4.8 years. In the study eye, the mean ± SD CRT was 329.2 ± 37.3 μm, and the mean ± SD BCVA was 80.2 ± 8.4 ETDRS letters. Most participants were men (70.2% [n = 186]) with a mean ± SD age of 62 ± 10.3 years. Eighty-five percent (n = 226) had type 2 diabetes, with a mean ± SD duration of 15.7 ± 7.6 years. Most participants were overweight, obese, or morbidly obese (88%) with a mean ± SD hemoglobin A1c value of 69.5 ± 18.4 mmol/mol (or 8.5 ± 3.8%). Details of the laser procedures performed after trial entry are presented in Table S2 (available at www.aaojournal.org).

Primary Outcome

Of the 266 participants who were randomized in the trial, primary outcome data were available for 87% (n = 231; n = 116 in the SML group and n = 115 in the SL group). The PP analysis found that the mean ± SD change in BCVA in the study eye from baseline to month 24 was −2.43 ± 8.2 ETDRS letters in the SML group and −0.45 ± 6.72 ETDRS letters in the SL group, with a difference of −1.98 (95% CI, −3.93 to −0.035 ETDRS letters; P = 0.046), which, although just statistically significant, is not clinically relevant. Therefore, SML treatment was deemed to be noninferior to SL treatment because the lower limit of the 95% CI of the treatment difference (−3.93 ETDRS letters) was more than the noninferiority margin (−5.0 ETDRS letters; Fig 2). Furthermore, SML treatment also was deemed to be equivalent to SL treatment because the 95% CI (−3.9 to −0.04) was wholly within both the upper and lower margins of the permitted maximum difference (−5.0 to +5.0). An ITT analysis also was undertaken that supported the findings from the PP analysis. Table 2 displays the analysis results for the primary outcome for both PP and ITT analyses.

In accordance with the Statistical Analysis Plan, the primary outcome also was adjusted for baseline BCVA score, baseline CRT, and previous cataract surgery in the study eye before enrollment in the trial, as well as the minimization factors on both the PP and the ITT populations (Table S3, available at www.aaojournal.org). These results support findings from the unadjusted analyses.

A secondary analysis was performed on the subset of participants with both eyes included in the trial (study eye and fellow eye if fellow eye was eligible and randomized), including the study eye as a random effect within the mixed model. The findings also support those of the main analysis (Table S4, available at www.aaojournal.org).

When the primary outcome was analyzed within prespecified subgroups (Table S5, available at www.aaojournal.org), a statistically significant interaction only for the center (study site) was found (P = 0.013), but this result was unreliable because of the wide variability in the number of participants recruited at each center. No other statistically significant interactions were identified. Sensitivity analyses supported findings of the unadjusted analyses (Table S6, available at www.aaojournal.org).

For completeness, baseline and 24-month ETDRS BCVAs, as well as change from baseline to month 24 in ETDRS letter score, number and proportion of participants gaining and losing vision, and number and proportion of participants at baseline and at month 24 in the different bands of visual acuity, are presented in Table S7 (available at www.aaojournal.org). However, any interpretation of these data needs to take account of the potential dangers of analyses of small subgroups of participants, especially given that these analyses were not prespecified in the protocol or statistical analysis plan.
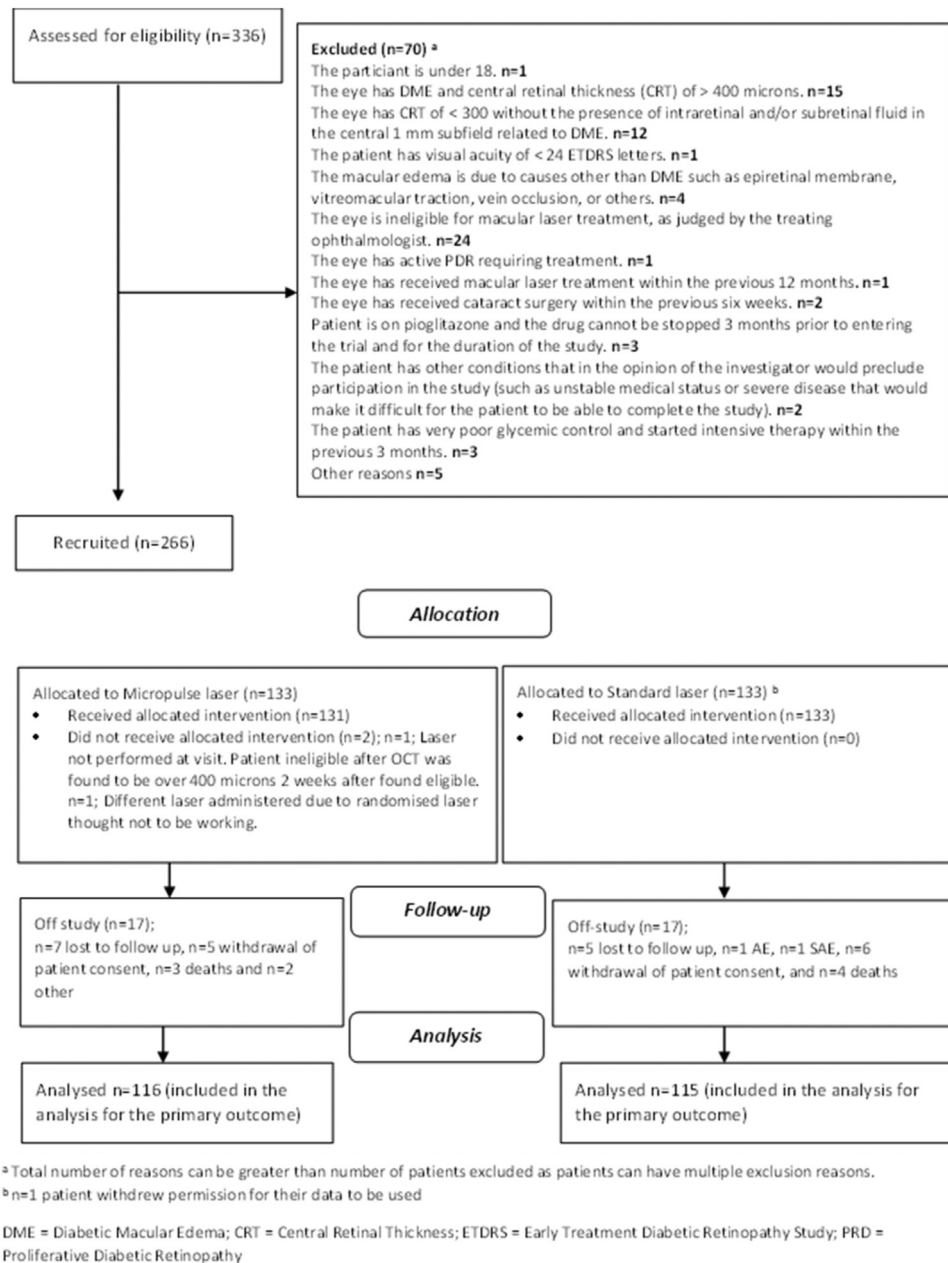
Assessed for eligibility (n=336)

Excluded (n=70) [a]
The participant is under 18. n=1
The eye has DME and central retinal thickness (CRT) of > 400 microns. n=15
The eye has CRT of < 300 without the presence of intraretinal and/or subretinal fluid in the central 1 mm subfield related to DME. n=12
The patient has visual acuity of < 24 ETDRS letters. n=1
The macular edema is due to causes other than DME such as epiretinal membrane, vitreomacular traction, vein occlusion, or others. n=4
The eye is ineligible for macular laser treatment, as judged by the treating ophthalmologist. n=24
The eye has active PDR requiring treatment. n=1
The eye has received macular laser treatment within the previous 12 months. n=1
The eye has received cataract surgery within the previous six weeks. n=2
Patient is on pioglitazone and the drug cannot be stopped 3 months prior to entering the trial and for the duration of the study. n=3
The patient has other conditions that in the opinion of the investigator would preclude participation in the study (such as unstable medical status or severe disease that would make it difficult for the patient to be able to complete the study). n=2
The patient has very poor glycemic control and started intensive therapy within the previous 3 months. n=3
Other reasons n=5

Recruited (n=266)

Allocation

Allocated to Micropulse laser (n=133)
• Received allocated intervention (n=131)
• Did not receive allocated intervention (n=2); n=1; Laser not performed at visit. Patient ineligible after OCT was found to be over 400 microns 2 weeks after found eligible. n=1; Different laser administered due to randomised laser thought not to be working.

Allocated to Standard laser (n=133) [b]
• Received allocated intervention (n=133)
• Did not receive allocated intervention (n=0)

Follow-up

Off study (n=17);
n=7 lost to follow up, n=5 withdrawal of patient consent, n=3 deaths and n=2 other

Off-study (n=17);
n=5 lost to follow up, n=1 AE, n=1 SAE, n=6 withdrawal of patient consent, and n=4 deaths

Analysis

Analysed n=116 (included in the analysis for the primary outcome)

Analysed n=115 (included in the analysis for the primary outcome)

[a] Total number of reasons can be greater than number of patients excluded as patients can have multiple exclusion reasons.
[b] n=1 patient withdrew permission for their data to be used

DME = Diabetic Macular Edema; CRT = Central Retinal Thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; PRD = Proliferative Diabetic Retinopathy

Figure 1. Consolidated Standards of Reporting Trials participant flow diagram for the DIAMONDS trial. AE = severe adverse event; CRT = central retinal thickness; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; PDR = prolifertive diabetic retinopathy; SAE = severe adverse event.

Secondary Outcomes

No statistically significant difference was found in most secondary outcomes, including mean change in binocular BCVA (mean difference, 0.32 ETDRS letters; 95% CI, −0.99 to 1.64 ETDRS letters; $P = 0.63$), CRT (mean difference, −0.64 μm; 95% CI, −14.25 to 12.98 μm; $P = 0.93$), 10-2 Humphrey visual field mean deviation (0.39 decibels [dB]; 95% CI, −0.23 to 1.02 dB; $P = 0.21$), percentage meeting driving standards (percentage point difference, 1.6%; 95% CI, −25.3% to 28.5%; $P = 0.91$), side effects (risk ratio [RR], 0.28; 95% CI, 0.06−1.34; $P = 0.11$), and rescue treatments (percentage point difference, −2.8%; 95% CI,

−13.1% to 7.5%; $P = 0.59$; Table 3). The number of laser treatments performed was higher in the SML group (mean difference, 0.48; 95% CI, 0.18−0.79; $P = 0.002$; Table 3). The difference was driven by a small number of participants requiring a larger number of laser treatments in the SML group. Specifically, 13 participants required 6 or 7 laser treatments in the SML group compared with 2 participants in the SL group.

A total of 70 severe adverse events was reported during the trial affecting 46 participants (17%), with no statistically significant differences between laser groups (RR, 0.8; 95% CI, 0.5−1.4; $P = 0.50$ for SML vs. SL groups). No serious adverse reactions were reported that were deemed to be related to study treatments.
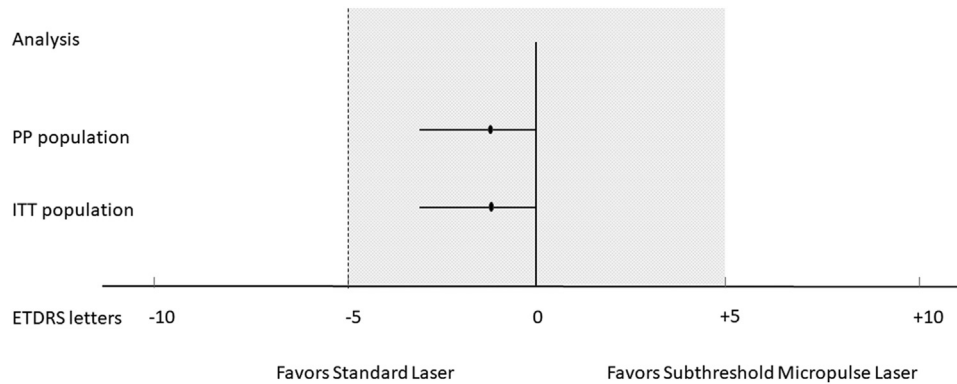
Figure 2. Graph showing the results of the Diabetic Macular Oedema and Diode Subthreshold Micropulse Laser trial primary outcome (observed values). Dash line shows the noninferiority margin of −5 Early Treatment Diabetic Retinopathy Study (ETDRS) letters. The shaded area represents the equivalence zone (−5 to +5 ETDRS letters). The 95% confidence intervals from both per-protocol (PP) and intention-to-treat (ITT) analyses lie wholly within the equivalence zone and also above the noninferiority margin, suggesting that subthreshold micropulse laser therapy is not only noninferior but also equivalent to standard laser therapy.

A total of 418 adverse events was reported affecting 157 participants (59%), with no statistically significant differences between laser groups (RR, 0.9; 95% CI, 0.8–1.1; $P = 0.48$ for SML vs. SL groups). Ten adverse events were reported that were deemed to be related to study treatments (i.e., adverse reactions), affecting 6 participants (2%), with no statistically significant differences between laser groups (RR, 0.5; 95% CI, 0.1–2.7; $P = 0.45$ for SML vs. SL groups; Table S8, available at www.aaojournal.org).

The EQ-5D-5L utility scores showed no statistically significant differences between the 2 laser groups (Table S9, available at www.aaojournal.org). The EQ-5D visual analog scale scores followed a similar pattern across periods for the 2 treatment groups with no statistically significant differences (Table S10, available at www.aaojournal.org). Similarly, the Vision and Quality of Life Index (Table S11, available at www.aaojournal.org) and NEI-VFQ-25 (Table S12, available at www.aaojournal.org) scores were not statistically significantly different between laser groups.

Economic Costs, Resource Use, and Cost-effectiveness

For participants with complete cost data, mean total National Health Service and personal and social service costs were lower in the SML group compared with the SL group (£897.83 vs. £1125.66) from baseline to 24 months after randomization; however, the mean difference of £227.83 was not statistically significant at the 5% level (Table S13, available at www.aaojournal.org).

The mean numbers of laser treatments were 2.4 in the SML group and 1.9 in the SL group, a difference of 0.48 ($P = 0.002$; Table 3). Of these treatments, 80% and 86%, respectively, were administered in the first 12 months (Table S14, available at www.aaojournal.org). The proportions of participants receiving rescue treatment (almost all rescue treatments were with anti-VEGF drugs; only 1 participant received a steroid injection in addition to anti-VEGF agents) in the study eye were 18% with SML therapy and 21% with SL therapy during the 24 months of the trial (the difference was not statistically significant; Table 3). About half of the participants receiving anti-VEGF agents did so in the first 12 months of the trial (9.8% in the SML group and 12.9% in the SL group, respectively; Table S14). It should be noted that the proportion of participants who met the criteria for rescue at

least once during the trial was 33% for the SML group and 31% for the SL group (the difference was not statistically significant), so of those who at any one point met the criteria, only 54% and 68%, respectively, were treated (Table S14). Some of those not treated showed only temporary increases of a few micrometers in CRT that resolved without treatment. The mean number of anti-VEGF treatments in the SL group was skewed by 5 patients who received > 10 treatments; none of the participants in the SML group required 10 or more injections.

The mean ± SD time to deliver the first session of laser treatment (measured from the time the participant entered the laser room for the treatment to be delivered until the participant left the laser room after the treatment was completed) was 19 ± 9.8 minutes for the SML group (median, 19 minutes) and 18 ± 7.3 minutes for the SL group (median, 17 minutes).

Base-case analysis demonstrated that, over the 24-month period of the trial, participants in the SML group, compared with those in the SL group, experienced a nonstatistically significant increase in quality-adjusted life-years of 0.008 (circa 3 days of good quality of life; 95% CI, −0.059 to 0.075 quality-adjusted life-years). The National Health Service and personal and social service costs were lower in the SML group than in the SL group, but the CI for the cost difference was wide and ranged from cost saving to cost increasing.

Discussion

The DIAMONDS trial found SML therapy to be equivalent to SL therapy. No statistically significant differences were found in all predefined secondary outcomes with the exception of the number of laser treatments performed, which was slightly higher (2.4 vs. 1.9; i.e., <1 further session of laser during the 2-year trial) in the SML group. The latter finding was driven by a small number of participants (n = 13) in the SML group who required a larger number of laser treatments. Most participants (approximately 80% and 90% of participants in SML and SL groups, respectively) required 1 to 3 laser sessions throughout the 2-year period. A similar number of participants in each laser treatment group (approximately one-third) met eligibility criteria to

Table 2. Primary Outcome (Observed Values): Change in Best-Corrected Visual Acuity in the Study Eye from Baseline to Month 24

Primary Outcome	Subthreshold Micropulse Laser Therapy (n = 116)*	Standard Threshold Laser Therapy (n = 115)*	Difference (95% Confidence Interval)	P Value[†]
PP analysis	−2.43 ± 8.20 (n = 115)	−0.45 ± 6.72	−1.98 (−3.93 to −0.035)	0.046
ITT analysis	−2.41 ± 8.16	−0.45 ± 6.72	−1.96 (−3.90 to −0.022)	0.047

ITT = intention-to-treat; PP = per-protocol.
Data are presented as mean ± standard deviation unless otherwise indicated.
*Number of participants with best-corrected visual acuity data available at baseline and month 24.
[†]Independent 2-sample *t* test.

receive rescue treatment at any time during the 2-year period of the study. However, fewer were actually treated (24 [18%] in the SML group and 28 [21%] in the SL group; the difference was not statistically significant), all receiving anti-VEGF agents and 1 participant in the SL group in addition receiving intravitreal steroids. Most participants maintained good vision throughout the trial, with only 9% (25 of 266) of those recruited experiencing a drop of 10 or more ETDRS letters, which would be considered a clinically relevant change, by month 24. Among the 231 participants with data at both baseline and month 24 (shown in Supplemental Table 7), this proportion is 10.8%. Most participants (> 95%) met driving standards at the 24-month trial visit. Meeting driving standards was identified at the time of trial conception by the DIAMONDS PPI group to be a very important outcome to people with diabetes, so it was incorporated as one of the secondary outcomes investigated. Similarly, most participants maintained good health-related and visual-related quality of life throughout the trial period. The total cost of the treatment, including first session and subsequent laser sessions, rescue treatments required, and follow-up for the 2 years, was £897.83 and £1125.66 for the SML and SL groups, respectively.

Although participants in the SML group required slightly more laser sessions (on average 0.5 session more), total costs of care were slightly higher (not statistically significantly) in the SL group. This seemed to be driven by the higher number of anti-VEGF rescue injections in the SL group, largely resulting from 5 patients who received 10 or more injections.

Both types of lasers proved to be very safe, with only a very small number of participants (the highest for any of the following events being approximately 2%) experiencing adverse events potentially related to the laser treatment, including central or paracentral scotomas, epiretinal membrane, and self-reported reduced color vision and metamorphopsia. These potential adverse events of laser therapy were identified, a priori, before the trial commenced; patients were questioned at each of the follow-up visits about their occurrence, and ophthalmologists evaluated participants to determine whether any of these had happened. However, none of these adverse events reported were attributed by the investigators to clearly be the result of the laser treatment.

Other previously conducted smaller RCTs have compared SML with SL therapy. Lavinsky et al[12] conducted a 3-arm trial that included 123 participants with CSME (n = 42 and n = 39 randomized to high-density and low-density SML therapy, respectively, and n = 42 randomized to SL therapy) and showed superiority with regard to visual acuity improvement and reduction in CRT at 12 months after high-density SML. Similarly, Fazel et al[18] (68 participants, 68 eyes) in a very short-term RCT (4 months) comparing SML with SL therapy in people with CSME with CRT < 450 μm found a statistically significantly higher CRT reduction in the SML group when compared with the SL group, with changes in macular volume and visual acuity being only statistically significant after SML therapy. In contrast, smaller trials by Xie et al[19] (n = 84 participants, 99 eyes), Figueira et al[14] (n = 53 participants, 84 eyes), Vujosevic et al[13] (n = 50 participants, 62 eyes), Venkatesh et al[15] (n = 33 participants, 46 eyes), Kumar et al[16] (n = 20 participants, 30 eyes), and Laursen et al[17] (n = 16 participants, 23 eyes), with follow-up of 6 months, 12 months, 12 months, 6 months, 18 weeks, and 5 months, respectively, found no statistically significant differences in vision or CRT between the SML and SL groups.

Several systematic reviews and meta-analysis comparing SML with SL therapy for the treatment of DME have been published.[28–31] Among these was the Cochrane systematic review and meta-analysis by Jorge et al[31] that concluded that SML may be as effective as SL therapy, but this conclusion was made with a low degree of certainty, following the Grading of Recommendation, Assessment, Development, and Evaluation working group.[32] All conducted meta-analyses were restricted by the inherent limitations of available RCTs, including the short follow-up and the unclear information with regard to the proportion of participants with CRT < 400 μm in the RCTs included, which would be those most likely to respond to macular laser therapy.[7,8,33] Furthermore, none of these RCTs included patient-reported outcomes or an economic evaluation.

A recent publicly funded Diabetic Retinopathy Clinical Research Network RCT comparing observation, standard macular laser therapy, and aflibercept treatment in people with central-involved DME with good vision found no statistically significant difference in vision loss or change in CRT at 2 years among groups.[34] Participants in this trial had

Table 3. Secondary Outcomes (Intention-to-Treat Analysis)

Variable	Subthreshold Micropulse Laser Therapy	Standard Threshold Laser Therapy	Difference (95% Confidence Interval)	P Value
Mean change in binocular BCVA from baseline to mo 24[*][†]	−1.36 (0.47) (n = 115)	−1.68 (0.47) (n = 115)	0.32 (−0.99 to 1.64)	0.63
Mean change in CRT in the study eye from baseline to mo 24[*][†]	−17.45 (4.84) (n = 115)	−16.81 (4.84) (n = 115)	−0.64 (−14.25 to 12.98)	0.93
Mean change in the MD of the Humphrey 10-2 visual field in the study eye from baseline to mo 24[*][†]	−0.47 (0.22) (n = 91)	−0.87 (0.22) (n = 95)	0.39 (−0.23 to 1.02)	0.21
Percentage of people meeting driving standards at mo 24[‡]	104 (95.4%) (n = 108)	106 (97.3%) (n = 109)	OR, 0.84 (0.14−5.27) % point difference, 1.6 (−25.3 to 28.5)	0.86 0.91
No. of participants experiencing side effects from baseline to mo 24[§]	2 (1.5%) (n = 133)	7 (5.3%) (n = 132)	OR, 0.27 (0.056−1.34) RR, 0.28 (0.060−1.34)	0.11 0.11
No. of laser treatments used from baseline to mo 24 in the study eye[*][†]	2.37 (0.11) (n = 133)	1.89 (0.11) (n = 132)	0.48 (0.18−0.79)	0.002
No. of participants receiving at least 1 additional rescue treatment from baseline to mo 24 (anti-VEGF agents or steroids)[§]	24 (18.1%) (n = 133)	28 (21.2%) (n = 132)	OR, 0.78 (0.42−1.45) % point difference, −2.8 (−13.1 to 7.5)	0.44 0.59

BCVA = best-corrected visual acuity; CRT = central retinal thickness; MD = mean deviation; OR = odds ratio; RR = risk ratio; VEGF = vascular endothelial growth factor.

Data are presented as no. (%) for categorical outcomes. Percentage point difference and RR presented for binary outcomes when models achieved convergence.

[*]Mean (standard error) presented for continuous outcomes.

[†]Secondary measures of visual function and anatomic outcomes (MD of the 10-2 visual field test, CRT, and macular volume) and number of treatments required were undertaken using linear regression models adjusted for baseline BCVA score and minimization variables.

[‡]Analysis of driving ability (meeting standards for driving) was undertaken using a logistic regression model adjusted for baseline driving standards, baseline BCVA, and the minimization variables (site was not included in the adjusted model because numbers who did not meet driving standards at sites 1, 2, 4, 6, 13, and 14 were small and all participants achieved driving standards at all other sites).

[§]Side effects of the treatment and use of additional treatments (defined as the use of at least 1 anti-VEGF agent or steroids) were analyzed using logistic regression models with adjustment for the minimization covariates. (Note that side effects only adjusted for the previous macular laser treatment use in the study eye because numbers of complications at sites 1, 5, 6, 10, 11, and 14 were small and no complications occurred at all at other sites, and all participants who had side effects were in the no anti-VEGF category and the BCVA ≥ 20/40 category).

better glycemic control (median hemoglobin A1c, 7.6%) and normal vision (mean ETDRS letter score, 85 ETDRS letters [Snellen equivalent, 6/6]). Patients had less severe DME (mean CRT, approximately 300 μm [306 μm, 314 μm, and 314 μm in the aflibercept, laser therapy, and observation groups, respectively]) than those included in the DIAMONDS trial. As in the DIAMONDS trial, a small proportion of participants (9%, 7%, and 7% in the aflibercept, macular laser therapy, and observation arms, respectively) in this RCT experienced a loss of 10 or more ETDRS letters from baseline to month 24. The authors concluded that observation without treatment, unless visual acuity worsens, was a reasonable strategy for eyes with central-involving DME. Given that DIAMONDS participants had poor diabetes control (mean hemoglobin A1c, 8.5%), reduced vision (mean ETDRS score, 80 letters [Snellen equivalent, 6/7.5]), and more severe DME (mean CRT, 329.2 μm), observation would not be considered the right approach for their management.

Midena et al,[35] in an exploratory, post hoc (not prespecified) analysis of data from the VIVID and VISTA[36] trials, concluded that intravitreal aflibercept showed benefits over laser therapy regardless of baseline CRT. Adjustment for multiple hypothesis testing was not undertaken in this post hoc analysis. Statistically significant differences in mean change in BCVA at the

week 100 favoring the aflibercept arm were observed between the laser group and the 2q8-week aflibercept arm. Aflibercept was administered as per the current summary of product characteristics (i.e., 5 monthly intravitreal injections followed by injections every 8 weeks until week 100 for a total of 15 intravitreal injections). A difference of only 5.7 letters was observed at week 100, which is of questionable clinical relevance, with wide CIs ranging from 1.9 to 9.4. Furthermore, and importantly, in VIVID and VISTA, laser re-treatments were allowed only when CSME was noted, rather than when central-involved DME was present on OCT, just as was carried out at baseline and as carried out currently in standard clinical practice. Moreover, in VIVID and VISTA, rescue treatment with aflibercept was not allowed in the laser arm even if worsening of fluid was observed on OCT but only when there had been a 10-letter drop in vision on 2 consecutive visits. Hence, it could be argued that the study design in VIVID and VISTA may have disfavored the laser arm. Other important outcomes, such as patient acceptability, patient disutility of the treatments, and costs, were not measured or considered.

In many countries, anti-VEGF agents are used by ophthalmologists as the first-line therapy for patients with DME, regardless of its severity based on CRT. In the DIAMONDS trial, people with DME with CRT < 400 μm who were

judged suitable for laser treatment by their treating ophthalmologist were recruited to evaluate the clinical effectiveness and cost-effectiveness of SML therapy compared with SL therapy for this group of patients. Macular laser therapy was not compared with anti-VEGF agents.

The DIAMONDS trial was designed as a pragmatic trial.[37] On its conception, we followed the Pragmatic Explanatory Continuum Indicator Summary 2 (PRECIS-2) tool[38] to ensure as much as possible that trial results would be generalizable and reproducible when implemented in clinical practice. Input from the DIAMONDS PPI ensured that outcomes in the trial included those important to people with DME. Thus, BCVA was selected as the primary outcome. The noninferiority margin of 5 ETDRS letters (equivalence margin of ± 5 ETDRS letters) was chosen because changes of this magnitude are not considered to be clinically relevant and could be the result of test−retest variability.

The strengths of the DIAMONDS trial include its robust design and power to detect not only noninferiority of SML therapy when compared with SL therapy but also equivalence and superiority if these were to exist. It was powered also to detect differences not only in the primary outcome but also in important secondary outcomes (CRT and vision-related quality of life). It was estimated at the trial conception that 113 participants in each laser arm were required to complete the primary outcome data at month 24, and a higher number of participants (116 and 115 in SML and SL groups, respectively) actually were available at this time point. Unlike many RCTs evaluating treatments for DME, in which the primary outcome was measured at 1 year, the DIAMONDS trial set the primary outcome at 2 years because it is possible that benefits of treatments may wane overtime or, as shown in some laser trials, may improve over time. Similarly, unlike many RCTs evaluating treatments for DME, the DIAMONDS trial included patient-reported outcome measures and importantly incorporated a clinical outcome that was suggested by people with diabetes and DME, namely, meeting driving standards. Unlike most trials of treatments for DME, it included a prospective health economic within-trial evaluation to compare the cost-effectiveness of the alternative treatments investigated. Limitations include the fact that the great majority of participants enrolled had poorly controlled diabetes, and it is possible that better outcomes in both treatment groups may be achieved in people with more adequately controlled diabetes. Screened individuals were excluded to participate in the trial if they were considered not to be amenable to laser treatment by the examining ophthalmologists; the reasons for this decision were not always recorded fully. Nonetheless, only 24 of the 336 screened individuals (0.07%) fell in this category. Diffuse macular edema was not a contraindication or exclusion criterion for macular laser in the DIAMONDS trial. We used ±5 ETDRS letters as the margin allowed for equivalence. However, no robust data prove that changes of this magnitude are not perceived by people with DME. Margins of 4 to 5 ETDRS letters have been considered previously not to be clinically relevant and thus have been used to set the margin of noninferiority in other large clinical trials of treatment for DME and other retinal diseases.[39−41] A change of 5 ETDRS letters is not considered to be a clinically relevant change either by NICE[7,8] or by the European Medicines Agency,[42] who consider 10 or more ETDRS letters to be a clinically important change. The fact that, in the DIAMONDS trial, we did not observe statistically significant or clinically important differences in measurements of health-related or vision-related quality of life from baseline to month 24 or between laser groups suggests that differences observed in visual acuity in the DIAMONDS trial were not clinically relevant to participants. The DIAMONDS trial was not designed to compare SL or SML therapy with anti-VEGF therapy for patients with DME with CRT < 400 μm. Thus, conclusions regarding clinical effectiveness and cost-effectiveness of macular laser therapy (SL or SML) versus anti-VEGF therapy for this patient population cannot be made and require further investigation.

The DIAMONDS trial showed that SML therapy had comparable (equivalent) efficacy and cost to SL therapy, suggesting that either treatment could be offered to patients with central-involved DME < 400 μm suitable for macular laser therapy. Given that SML therapy has been shown to preserve photoreceptor cells,[43−45] RPE, and neurosensory retina[43,44] and to produce no burn or objective damage, it should be easier and safer to perform and to teach to, for example, junior ophthalmologists, general ophthalmologists, or even allied nonmedical staff in settings with a lack of ophthalmologists (e.g., low- to middle-income countries, the United Kingdom[46]) because a foveal burn would be avoided. The possibility of having trained nonmedical staff contributing to the management of people living with complications of diabetic retinopathy could help coping with the high and ever-increasing demand of care for diabetes in the developed and developing world.[47−49]

Footnotes and Disclosures

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C.B.: Consultant — Alcon, Bayer, Novartis, Alimera Sciences, Allergan

V.C.: Employee — Janssen Biopharma LLC; Lecturer — Quantel Medical

L.D.: Advisory board — Bayer, Novartis, Allergan, Alimera Thrombogenics, Alcon; Financial support — Bayer, Novartis, Allergan, Roche, Alimera

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Abbreviations and Acronyms:

BCVA = best-corrected visual acuity; **CI** = confidence interval; **CRT** = central retinal thickness; **CSME** = clinically significant macular edema; **dB** = decibels; **DIAMONDS** = Diabetic Macular Oedema and Diode Subthreshold Micropulse Laser; **DME** = diabetic macular edema; **EQ-5D-5L** = EuroQoL; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **FFA** = fundus fluorescein angiography; **ITT** = intention-to-treat; **logMAR** = logarithm of the minimum angle of resolution; **NEI-VFQ-25** = 25-item National Eye Institute Visual Function Questionnaire; **NICE** = National Institute for Health and Care Excellence; **PP** = per-protocol; **PPI** = Patient and Public Involvement; **QALY** = quality-adjusted life-year; **RCT** = randomized clinical trial; **RPE** = retinal pigment epithelium; **RR** = risk ratio; **SD** = standard deviation; **SL** = standard laser; **SML** = subthreshold micropulse laser; **VEGF** = vascular endothelial growth factor; **VisQoL** = Vision and Quality of Life Index.

Keywords:

Anti-VEGF, Diabetic macular edema, DME, Macular laser, Micropulse.

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