

BMJ Open Protocol for a parallel assignment prospective, randomised, comparative trial to evaluate the safety and efficacy of intense pulsed light (IPL) combined with 3% diquafosol (DQS) ophthalmic solution in dry eye syndrome

Jiayan Chen ¹, Guanghao Qin ¹, Liangzhe Li ¹, Yifan Qi ¹, Huixin Che ¹, He Huang ¹, Yang Xia ¹, Qing Zhang ², Yi Wu ³, Lanting Yang ⁴, Salissou Moutari ⁵, Jonathan E Moore⁶, Ling Xu ¹, Wei He ¹, Sile Yu ^{1,7}, Emmanuel Eric Pazo ¹, Xingru He ^{1,7}

To cite: Chen J, Qin G, Li L, et al. Protocol for a parallel assignment prospective, randomised, comparative trial to evaluate the safety and efficacy of intense pulsed light (IPL) combined with 3% diquafosol (DQS) ophthalmic solution in dry eye syndrome. *BMJ Open* 2023;13:e073055. doi:10.1136/bmjopen-2023-073055

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2023-073055>).

Received 24 February 2023
Accepted 27 July 2023



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Professor Xingru He;
hexingru@huh.edu.cn and
Dr Emmanuel Eric Pazo;
ericpazo@hsyk.com.cn

ABSTRACT

Introduction Evaporative dry eye (EDE) is common and can lead to ocular pain, decreased visual quality and reduced quality of life. Intense pulsed light (IPL) and 3% diquafosol ophthalmic solution have been found to be beneficial in reducing signs and symptoms of dry eye.

Methods and analysis A randomised clinical trial will be performed at He Eye Specialist Hospital in Shenyang. 360 dry eye disease patients will be equally divided randomly into the IPL group, DQS group (3% diquafosol ophthalmic solution eye-drops) and IPL+group (IPL combined with 3% diquafosol eye-drops). All groups will be followed up for 4 weeks. The primary outcome measures will be the non-invasive tear break-up time and the Ocular Surface Disease Index change from the baseline. The secondary outcome measures will include conjunctival and cornea staining with fluorescein and lissamine, meibomian gland function and secretion quality, tear film lipid layer score, tear meniscus height, conjunctival hyperemia (redness score) changes. Adverse events also will be monitored and documented.

Discussion This study aimed to assess whether the combination of IPL with 3% diquafosol ophthalmic solution (study group), IPL+ (study group), is more effective than IPL (active control group) or DQS (active control group) in participants with EDE.

Ethics and dissemination Management of dry eye with IPL combined with 3% diquafosol ophthalmic solution, registered on 23 January 2023. Ethics approval number: IRB (2022) K029.01. The study's findings will be shared regardless of the effect's direction.

Trial registration number NCT05694026.

INTRODUCTION

Background and rationale

Evaporative dry eye (EDE) has been reported to be the most prevalent form of dry eye disease (DED),^{1–3} which is primarily caused by meibomian gland hypofunction or

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The trial is designed to be embedded into routine clinical practice, providing more options for treatment.
- ⇒ The protocol promotes standardisation of therapy, enabling credible inference about benefits.
- ⇒ A large randomised controlled trial has not been conducted to understand the benefits of DQS and Intense pulsed light on dry eye disease (DED) patients.
- ⇒ The trial's data collection at a single site are limitation of the research.
- ⇒ The goal of this research is limited to assessing just tear film changes and DED symptoms.

meibomian gland dysfunction (MGD).^{4–6} MGD can be chronic or diffused anomaly of the meibomian glands, often characterised by terminal duct blockage and qualitative/quantitative alterations in glandular secretion 'b' the International Workshop on MGD.^{1,7} These glands are modified sebaceous glands that release meibum directly onto the ocular surface. Signs and symptoms of EDE and MGD can be addressed by improving the quality and quantity of meibum secretion.⁸

Diquafosol tetrasodium (DQS) topical ophthalmic solution is a dinucleotide polyphosphate which is a purinoceptor agonist; when administered to the ocular surface, it binds to P2Y₂ receptors and stimulates mucin and tear secretion.^{9–11} It also improves the tear film composition and stability.^{12–14} It has a corneal epithelial-repairing effect and can be used to treat ocular surface damage caused

by dry eye.^{5 15 16} By targeting the inflammation involved in the pathogenesis of dry eye, it can inhibit the expression of inflammatory pathways and inflammatory factors that are involved in the pathogenesis of dry eye.^{17–19} The safety and benefits of DQS in improving dry eye signs and symptoms have been demonstrated in randomised clinical trials.²⁰ At present, DQS is clinically available as a 3% ophthalmic solution (Diquas, Santen) which, due to rapid ocular clearance, requires frequent administration (six times/day).²¹

Intense pulsed light (IPL) is widely used to treat dermatological conditions,²² and its non-coherent polychromatic light source with a wide wavelength range of 500–1200 nm has been reported to stimulate facial sebaceous glands.^{23 24} The photothermal effect of IPL is postulated to relieve inflammation by removing aberrant surface microvasculature and enhancing meibomian gland function.^{25–27} Furthermore, an increase in fibroblast proliferation, collagen formation and local blood flow has been associated with the application of IPL on the skin.^{28 29} Several studies including Toyos *et al*³⁰ and Martínez-Hergueta *et al*³¹ have evaluated the safety and benefits of IPL therapy for improving signs of DED^{32–34} and combined it with other therapies such as heated eye mask (HEM),^{35 36} 0.1% sodium hyaluronate eye-drops²⁷ and blood extract eye-drops.³⁷ Therefore, a randomised controlled trial (RCT) is warranted to assess the safety and efficacy of combining IPL with DQS for patients suffering from DED.

Objectives

The primary objective of this study is to assess whether the combination of IPL with 3% diquafosol ophthalmic solution is more effective than IPL and 3% diquafosol ophthalmic solution in alleviating signs and symptoms of DED.

Trial design

This is a prospective, RCT performed at He Eye Specialist Hospital (HESH) (ethics approval number: IRB (2022) K029.01). The study adheres to the tenets of the Declaration of Helsinki and is registered at ClinicalTrials.gov (NCT05694026) using the Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines.³⁸ Randomisation will be performed using a web-based, online, sealed envelope-based system (<https://www.sealedenvelope.com>). Specific study information sheets will be provided to patients prior to taking consent. Following a dedicated screening and randomisation visit for eligible patients, participants will be randomised to one of three trial arms.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

This study will be conducted between 1 March 2023 and 30 November 2023. Participants will be recruited at the Department of Ophthalmology, HESH.

Patient and public involvement

Patients and the public will not be involved in the design, implementation, reporting or dissemination plans of this study.

Eligibility criteria

Inclusion criteria

1. Age ≥18 years.
2. Consenting participants.
3. Able and willing to comply with the treatment/follow-up schedule.
4. Bilateral signs and symptoms of DED: (1) Ocular Surface Disease Index (OSDI) questionnaire ≥13, (2) non-invasive tear break-up (NITBUT) ≤5 s and (3) conjunctival staining score (CS) ≥3 points. The presence of two or more criteria was used to establish a positive DE diagnosis based on the 2016 Asia Dry Eye Society criteria.

Exclusion criteria

1. A recent history (past 30 days) of topical ophthalmic medication use, including antibiotics, steroids, non-steroidal anti-inflammatory drugs or required the chronic use of topical ophthalmic medications.
2. Eyelids or intraocular tumours.
3. Active allergy or infection, or inflammatory disease may prevent the subjects from completing the study at the ocular surface.
4. Any structural changes in the lacrimal passage.
5. Glaucoma.
6. Diabetes or other systemic, dermatological or neurological diseases that affect the health of the ocular surface.
7. Use of any systemic anti-inflammatory drugs or medication that may interfere with tear production, such as antianxiety, antidepressive and antihistamine medications, within 3 months.
8. Pregnant or breast feeding.
9. Contact lenses wearers.

Informed consent

Trained and experienced clinicians will seek informed permission from prospective participants.

Additional consent provisions for collection and use of participant data and biological specimens

This trial does not involve collecting biological specimens.

Interventions

The explanation for the choice of comparators

After enrolment in the study, treatments will be initiated immediately after randomisation. Participants in the DQS group and IPL+ group will use one drop of 3% DQS (Diquas; Santen Pharmaceutical, Osaka, Japan) six times per day for 4 weeks (28 days), whereas participants in the IPL+ group and IPL group will undergo two IPL treatment sessions of M22 (Lumenis, Yokneam, Israel) IPL system, 2 weeks apart. IPL treatment uses a non-coherent

polychromatic light source with a wavelength spectrum of 500–1200 nm on the cutaneous facial sebaceous glands.

Intervention description

In this study, patients receive either DQS, IPL or IPL combined with DQS for 4 weeks based on the group they are placed in. Two follow-up visits will be performed at week 2 and week 4 in all groups; comprehensive eye examinations will be conducted by an ophthalmologist, including primary outcomes, secondary outcomes and safety evaluation.

Criteria for discontinuing or modifying allocated interventions

If dry eye signs and symptoms worsen, participants will be stopped and advised to use the designated device. Adverse events (AEs) will be continuously monitored. In case of an AE, participants will be informed about the severity of the event, and principal investigator (PI) will decide if participants can continue further. If participants consent and agree, they will be reminded daily regarding the administration of eye-drops, recording their exposure to mobile telephones or computer time, and any queries regarding the study will be answered by trained clinical staff at HESH.

Strategies to improve adherence to interventions

Participants will be reminded by phone and email every week, and then appointments will be scheduled in advance according to their availability time. In order to improve adherence, patients will be given a medication record booklet, and their medication status will be checked at each follow-up visit. In the event of non-compliance, such as absence, participants will be contacted by phone or email to ask if they will continue or terminate the study early.

Relevant concomitant care permitted or prohibited during the trial

Any other dry eye systemic or topical medication, treatment, or therapy will be prohibited during the course of this study.

Provisions for post-trial care

There is no anticipated harm and compensation for trial participation, but participants who show signs and symptoms of deterioration in their dry eye status will be directed to their local dry eye centre for further treatment.

Outcomes

All patients will be assessed at baseline, 14 and 28 days. We plan to use primary and secondary outcomes measures, symptoms, and corneal and meibomian gland improvement will be compared between the three groups.

Primary outcome

OSDI: OSDI is a questionnaire consisting of 12 questions for evaluating the effects of dry eye syndrome on vision, ocular symptoms and any condition associated with DED.³⁹ The patient will answer each question on a scale ranging from 0 to 4, with '0' indicating 'none of the time'

and '4' indicating 'all of the time.' If a particular question is deemed irrelevant, it will be marked as 'not applicable' and excluded from the analysis. The OSDI total score is calculated according to the following formula. The total score ranges from 0 to 100, with higher scores representing more severe cases of DED symptoms.^{40 41}

NITBUT: The Keratograph 5M (Oculus, Germany) topographer will assess non-invasive tear breaking time. Three sequential readings will be captured, the median value will be included in the final analysis, and the median value will be recorded.^{42 43}

Secondary outcomes

Fluorescein and lissamine conjunctival and cornea staining: Fluorescein and lissamine staining (CS) of the ocular surface will be divided into three zones comprising nasal conjunctival, corneal and temporal conjunctival areas. The staining score ranged from 0 to 3 for each zone, yielding a total score of 0–9 for the ocular surface.^{44 45}

Tear meniscus height: Tear meniscus height (TMH) using the Keratograph 5M (Oculus, Germany) topographer will be measured three times consecutively, and the median value was recorded.^{42 46}

Conjunctival hyperaemia: Conjunctival hyperaemia (RS score) will be assessed by Keratograph image (Oculus, Germany) of 1156×873 pixels, RS (accurate to 0.1 U) was displayed on the computer screen that ranged from 0.0 (normal) to 4.0 (severe).^{43 47}

Meibomian gland function and secretion quality: Meibum quality will be assessed under a slit-lamp⁴⁸: Eight meibomian glands in the middle parts of the eyelid will be evaluated using a scale of 0–3 for each gland (0 represented clear meibum; 1 represented cloudy meibum; 2 represented cloudy and granular meibum and 3 means thick, toothpaste-like consistency meibum).^{49 50}

Tear Film Lipid Layer Score: The interferometry patterns will be assessed using DR-1 (Kowa, Nagoya, Japan). The results will be graded as follows: grade 1, somewhat grey colour, uniform distribution; grade 2, rather grey colour, non-uniform distribution; grade 3, a few colours, non-uniform distribution; grade 4, many colours, non-uniform distribution; grade 5, corneal surface partially exposed.^{34 51 52}

Participant timeline

The schedule for data collection and visits is shown in table 1. After registration for this study, the assigned treatment intervention will be administered for 4 weeks. Furthermore, the effect will be examined during the 2-week follow-up period of 4 weeks (figure 1).

Sample size

The sample size calculation is based on the primary outcome measures, namely NITBUT and OSDI scores, to establish the non-inferiority of the IPL+ group compared with IPL group and DQS group in terms of the changes in the mean from the baseline in OSDI score at day 28. For the NITBUT scores, a sample size of 106 is sufficient to

Table 1 Schedule for data collection and visits

Items	Baseline	2 weeks	4 weeks
Informed consent	✓		
Patient background	✓		
Ocular Surface Disease Index scores	✓	✓	✓
IOP	✓	✓	✓
BCVA	✓	✓	✓
Non-invasive tear break-up	✓	✓	✓
Conjunctival and cornea fluorescein staining	✓	✓	✓
Tear Film Lipid Layer Score	✓	✓	✓
Corneal endothelial cells	✓	✓	✓
Tear meniscus height	✓	✓	✓
Conjunctival hyperaemia	✓	✓	✓
Meibomian gland function	✓	✓	✓
Meibomian secretion quality	✓	✓	✓
Adverse event		✓	✓
Patient background, including date of birth, sex, race, ethnicity and allergy history.			
✓: All groups.			
BCVA, best-corrected visual acuity; IOP, intraocular pressure.			

detect a clinically significant difference of 0.51 between the IPL+ group and either of the two other groups (IPL group and DQS group) while assuming a SD of 1.15, using a two-tailed t-test of difference between means with 90% power and a 5% level of significance. For the OSDI scores, a sample size of 98 is sufficient to detect a clinically significant difference of 1.2 between the IPL+ group and either of the two other groups (IPL group and DQS group) while assuming a SD of 2.6, using a two-tailed t-test of difference between means with 90% power and a 5% level of significance. Therefore, the required sample size is $\max(106, 98) = 106$ in each group.

With the inclusion of the multidose treatment groups and a drop-out rate of 8%, it is estimated that about 350 individuals. Therefore 360 individuals will be enrolled, 120 in each group. The intended-to-treat population will be randomly allocated to the three groups.

The primary and secondary efficacy analyses will use a two-way analysis of variance that will account for treatment and baseline OSDI score stratification to compare treatment differences. Using paired t-tests, within-treatment differences from baseline will be evaluated (alpha level 0.05). Additional analyses of OSDI subgroups and questionnaire data will be conducted using an analysis of variance. Using descriptive statistics, safety data will be summarised.

Recruitment

This clinical study will be done in a single site, with participants blinded to the treatment assignment. This research is open to patients diagnosed with DED at

HESH's Department of Ophthalmology. Participants will be recruited using adverts in the distribution pamphlets, the website and social media postings. Each participant's demographic information (including ocular diseases and current/previous usage of drugs and/or lubricating eye-drops) will be collected during the first (screening) appointment. Participants will not be limited based on age, sex or ethnicity (table 2).

Assignment of interventions: allocation Sequence generation

A web-based randomisation application will be used (<https://www.project-redcap.org/>). Participants will be randomised by simple randomisation process. Allocation will be carried out using block randomisation and stratified according to age (allocation factor: age <80 years or ≥80 years) (known only to the statistical team, not stated here to maintain masking). Participants will be in a 1:1:1 allocation ratio to IPL group, DQS group or IPL+ group.

Concealment mechanism

The block size will be concealed from other researchers, and the randomisation table will not be available for assessment by anyone else involved in the study.⁵³ Randomisation will be performed by an independent biostatistician. The biostatistician is the only one who has access to check the file. The allocation list will be kept in a separate file on a different computer.

Implementation

Random allocation will be conducted after the enrolment. Random numbers with corresponding participants will be determined in the order of the time of the first visit and divided into three groups (IPL+, IPL or DQS group). The allocation result will not be announced to the participants until the end of the data collection phase of the trial. Researchers collecting and analysing data related to this trial will be blinded to the participant allocation results.

Assignment of interventions

Blinding

The treatment assignment for the study will be triple-masked. Participants in the research would be unable to recognise the contents. A masked examiner for all clinical assessments will not be involved in the data collection or group allocation procedure for this research. The investigator will not be aware of the three groups. Participants will be randomly assigned to one of the three treatment groups, and they will undergo IPL treatment with 12 homogeneously spaced pulsed light to both eyes and a sham treatment to both eyes. The box containing ampoules will be labelled with a batch number, including the study reference number, participant ID, contact number, investigator name, site address, the expiration date of the eye-drops, storage instructions and a statement informing the participant that the eye-drops are for use only in clinical trials and should not be ingested. The

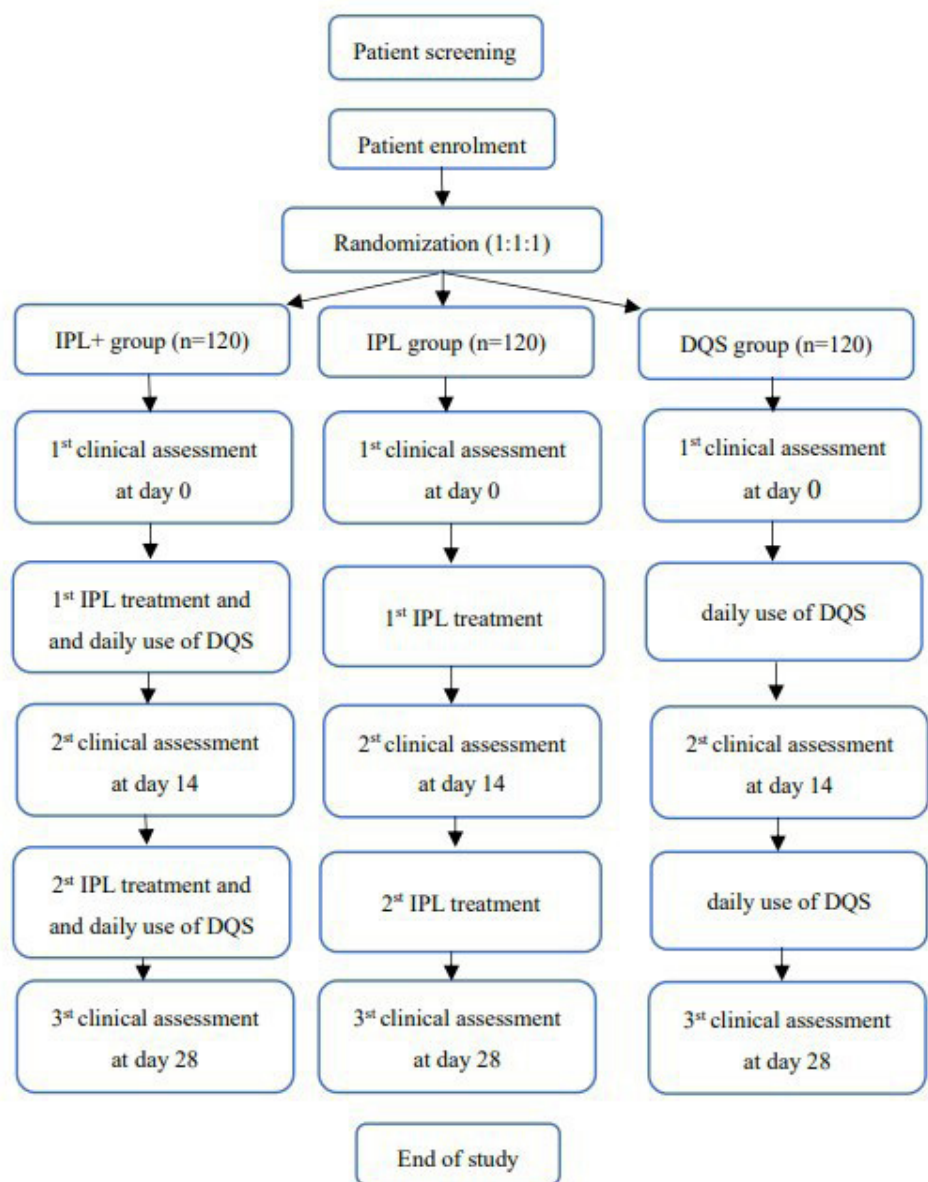


Figure 1 Study flow chart. DQS, diquafosol; IPL, intense pulsed light.

circumstances and procedures under which unblinding is permissible will be determined and performed by the PI.

Procedure for unblinding if needed

The PI will determine and perform the circumstances and procedures under which unblinding is permissible.

Participant withdrawal

Based on the following criteria, patients will be removed from the research.

1. When it is deemed challenging to continue the study owing to the emergence of new ailments.
2. When the research participant cannot be located.
3. In the case of pregnancy or pregnancy suspicion.
4. When participants or their legal guardians want to end their participation in a study.
5. When the participant's caretaker cannot guarantee their participation in the study.

6. When the research project is concluded.

7. When the lead investigator and subinvestigators believe that it is acceptable to cease the study for reasons other than those listed above.

Data collection and management

Plans for assessment and collection of outcomes

Data administration is the responsibility of Jiayan Chen, HESH, Department of Clinical Research, as chosen by the PI (Emmanuel Eric Pazo). This research will collect data using a proprietary EMR case report form and management application. Following database lock, the individual responsible for the statistical analysis will get the locked data following the database. The data management handbook will provide the details on any specific information. At the end of the study, a report

Table 2 The schedule of enrolment, interventions and assessments of this trial

Time point	Study period					
	Enrolment	Allocation	Postallocation			Close-out
	March 2023	2023	Day 0	Day 14	Day 28	End-2023
Enrolment:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
Interventions:						
(IPL+DQS)						
(DQS)						
(IPL)			X	X		
Assessments:						
(The baseline variables)	X	X				
(The primary outcome)			X	X	X	
(The second outcome)			X	X	X	

DQS, diquafosol; IPL, intense pulsed light.

on the implementation and the status of data management will be compiled and sent to the PI with the locked research data.

Plans to promote participant retention and complete follow-up

Informed consent will include information regarding follow-up assessments for all participants. In the event of participants discontinuing or deviating from intervention protocols, the study team will initiate contact and prioritise addressing any concerns that may be impacting their adherence to the intervention protocols. If these concerns cannot be resolved, the participants will be requested to complete subsequent self-assessment questionnaires online.

Data will be gathered during prerandomisation, termination and follow-up periods at 2 and 4 weeks. The method of data collection for this study will involve the use of clinical tests and self-report questionnaires, which will be administered through an online platform. In order to guarantee the completeness and accuracy of the gathered data, the online questionnaires will be encoded in a manner that necessitates respondents to provide comprehensive responses to all inquiries prior to submitting their answers.

Data management

Data collection and data entry were performed by separate experienced staff members at HESH, Department of Clinical Research. Supervision and double confirmation were performed by Jiayan Chen, along with weekly backup, to ensure data quality.

Confidentiality

Each participant's personal information will be kept confidential in the same way as their medical histories in the hospital before, during and after the trial.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use

Not applicable: There will be no biological specimens collected.

Statistical methods

Statistical methods for primary and secondary outcomes

The software Statistical Analysis in Social Sciences (SPSS, V.26, IBM) for MacOS software will be used to analyse the data. Data from both eyes will be collected for all patients participating in the treatment at the following stages: baseline, first follow-up at week 2 and second follow-up at week 4. Repeated measures analysis will be used to compare comparisons across time periods, while paired analyses will be used to compare pretreatment and post-treatment data at specific time periods. The Kolmogorov-Smirnov test will be used to determine the normality of variables. The background of the subjects will be tabulated by calculating the mean and SD for continuous variables and the frequency and percentage for categorical variables. Analysis of variance will be used to analyse ordinal variables and those having non-normal distributions. The primary outcome measures for this study are NITBUT and OSDI scores before and after treatment. For the primary endpoint, between-group comparisons using baseline as a covariate and an analysis of covariance will be performed to estimate the adjusted mean, its 95% CI and the p value.

Interim analyses

Not applicable: No anticipated problems are detrimental to the participant, so interim analysis is not warranted.

Methods for additional analyses (eg, subgroup analyses)

Subgroup analyses are not planned for this study.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data

After accounting for lost to follow-up and missing data in sample size calculations. Using a two-tailed t-test of difference between means with a power of 80% and a significance level of 5%, we allowed for a drop-out rate of 10%, using an additional 10% to compensate for potential deviations of dry eye measures from the normal distribution.

Plans to give access to the complete protocol, participant-level data and statistical code

The datasets analysed during the current study and statistical code are available from the corresponding author on reasonable request, as is the complete protocol.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee

The subject leader and the project manager will form the steering committee (SC). The SC is accountable for managing the whole project. The monitor group's (MG) inspectors are appointed by the SC. The MG will oversee the entire research procedure in compliance with the GCP requirements. The inspector will analyse the investigator's adherence to the protocol, the protection of participants' rights and interests, the quality of the CRF form, and the investigators' understanding of different standards before submitting inspection reports to the SC.

Composition of the data monitoring committee, its role and reporting structure

Due to the projected low frequency of AEs and the modest numbers in each location, no data monitoring committee has been convened for this trial. The database will be constructed using Excel (Microsoft, USA 2022 version), and regular data monitoring will be undertaken in accordance with the sponsor's standard operating procedures. The SC will have oversight and access to the trial under the supervision of the trial manager at any time during the study.

AE reporting and harms

AEs are unanticipated indications, symptoms or illnesses seen during a clinical study, regardless of their relationship to the treatment. There may be local, general and psychological unwanted effects (table 3). If any discomfort or new changes in condition during the study period, or any unexpected situation, whether related to the study or not, one should promptly notify the doctor, who will make a judgement and give appropriate medical treatment. At the end of each examination, the doctor will evaluate eye health status according to the examination results. If the condition deteriorates or is no longer suitable for the study, the study may be terminated early. At the same time, the doctor will provide other treatment options that are more suitable for the current situation to ensure health to the greatest extent. If major AEs occur, HESH Certified Review Board will be notified;

Table 3 Possible adverse events and solutions

Adverse events	Solutions
Visual discomfort	Standard operation
Eye irritation, conjunctival hyperaemia, eye pain	No special treatment was required, relieve and subside within 1–3 days
Periocular swelling	Resolve within a few hours
Bluish-purple bruise (purpura)	Rare cases may last from five to fifteen days; no special treatment is required
The skin around the eye becomes sensitive and fragile	Avoiding makeup and rubbing
Burn injury occurs	In rare cases, follow instructions
Allergy, abnormal sensation in the eye, etc.	Excluded and treatment

experimental treatments will be discontinued promptly, and appropriate therapies will be offered.

Frequency and plans for auditing trial conduct

The study will be reviewed and evaluated weekly by an independent supervisor not related to the PI and sponsors.

Plans for communicating significant protocol amendments to relevant parties (eg, trial participants, ethical committees)

If there are modifications to eligibility criteria, outcomes or analyses, a revised protocol will be submitted for approval to the HESH Medical Ethics Committee.

Dissemination plans

The study's findings will be shared regardless of the effect's direction. All possible beneficiaries of the research, including patients, caretakers, family, doctors, advisory boards and medical boards, will receive trial data. Publications in high-impact, open-access medical journals and talks at national and international medical conferences will serve this purpose.

DISCUSSION

DQS stimulates P2Y₂ receptors on the ocular surface, which enhances the secretion of water and secretory mucin from conjunctival tissue. At present, multicentre clinical trials have proved the advantages and efficacy of diquafosol sodium drops in the treatment of dry eyes, and the Asian Dry Eye Workshop identifies it as the current first-choice treatment for aqueous tear deficiency dry eyes and as one of the first choices for the treatment of mucin deficiency dry eyes. The primary untoward effects observed were ocular discharge, ocular irritation, and ocular pain; however, these manifestations resolved within a period of 28 days.⁵⁴ These events will be assessed and mentored continually during the study and follow-up phase of the study.

Literature review shows that IPL is a relatively new method for the treatment of lipid-abnormal dry eye caused by MGD. IPL can relieve the symptoms and signs of MGD-related dry eye by reducing eyelid inflammation, thermal effect, sterilisation, acariasis and light regulation.^{55 56} With respect to the adverse effects, the majority of studies have reported that participants did not experience any significant negative effects, apart from temporary occurrences of erythema, oedema and pain. Nevertheless, the likelihood of hyperpigmentation, blisters and a burning sensation cannot be ruled out in certain instances, particularly in patients with darker skin phototypes.⁵⁷ Potential corneal and/or retinal toxicity will be assessed and monitored continuously. Therefore, this study aims to assess the effectiveness of the combination of IPL with 3% DQS ophthalmic solution, providing more options for treatment. In future studies, we will further expand the sample size and conduct a deeper analysis of the mechanism of symptom improvement in the hope of providing clinicians with more treatment options.

Trial status

Recruitment began in March 2023, and the approximate date when recruitment will be completed is November 2023. Protocol version 2.0 was approved on January 2023.

Author affiliations

¹Department of Ophthalmology, He Eye Specialist Hospital, Shenyang, China

²Department of Ophthalmology, Tianjin Medical University Eye Hospital, Tianjin, China

³Department of Ophthalmology, China Medical University Second Hospital, Shenyang, China

⁴Department of Ophthalmology, Wenzhou Medical University Eye Hospital, Wenzhou, China

⁵School of Mathematics and Physics, Queen's University Belfast, Belfast, UK

⁶Department of Ophthalmology, Cathedral Eye Clinic, Belfast, UK

⁷School of Public Health, He University, Shenyang, China

Acknowledgements The authors would like to express their appreciation for the effort of all personnel involved in this trial.

Contributors Conception and design of the research: JC, GQ, LL, YQ, HC, HH, YX, QZ, YW, LY, SM, JM, LX, WH, SY, XH and EEP; analysis and interpretation of the data: JC, GQ and EEP; writing original draft preparation: JC; critical revision of the manuscript (reviewing and editing): JC and EEP; supervision: XH, SY and EEP.

Funding This study was entirely funded and sponsored by He Eye Specialist Hospital, Shenyang, China, which included study design, data collection, analysis, interpretation and manuscript writing. No support was received for the publication of this article.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Jiayan Chen <http://orcid.org/0000-0002-3425-8486>

Guanghao Qin <http://orcid.org/0000-0003-1596-7970>

Liangzhe Li <http://orcid.org/0000-0002-3620-9805>

Yifan Qi <http://orcid.org/0000-0001-7750-6729>

Huixin Che <http://orcid.org/0000-0002-7777-6777>

He Huang <http://orcid.org/0000-0002-7777-6777>

Yang Xia <http://orcid.org/0000-0002-7777-6777>

Qing Zhang <http://orcid.org/0000-0002-7777-6777>

Yi Wu <http://orcid.org/0000-0002-6163-6737>

Lanting Yang <http://orcid.org/0000-0002-9723-3972>

Salissou Moutari <http://orcid.org/0000-0002-9723-3972>

Ling Xu <http://orcid.org/0000-0002-8024-1263>

Wei He <http://orcid.org/0000-0002-8024-1263>

Sile Yu <http://orcid.org/0000-0002-9956-2526>

Emmanuel Eric Pazo <http://orcid.org/0000-0002-0848-827X>

Xingru He <http://orcid.org/0000-0002-4180-9290>

REFERENCES

- Ma J, Pazo EE, Zou Z, et al. Prevalence of symptomatic dry eye in breast cancer patients undergoing systemic adjuvant treatment: A cross-sectional study. *Breast* 2020;53:164–71.
- Bron AJ, de Paiva CS, Chauhan SK, et al. TFOS DEWS II pathophysiology report. *Ocul Surf* 2017;15:438–510.
- Bron AJ, Tiffany JM. The contribution of Meibomian disease to dry eye. *Ocul Surf* 2004;2:149–65. 10.1016/s1542-0124(12)70150-7 Available: <https://pubmed.ncbi.nlm.nih.gov/17216085/>
- Chhadva P, Goldhardt R, Galor A. Meibomian gland disease: the role of gland dysfunction in dry eye disease. *Ophthalmology* 2017;124:S20–6.
- Georgiev GA, Eftimov P, Yokoi N. Contribution of Mucins towards the physical properties of the tear film: A modern update. *Int J Mol Sci* 2019;20:6132. 10.3390/ijms20246132 Available: <https://www.mdpi.com/1422-0067/20/24/6132/htm>
- Zhang X, M VJ, Qu Y, et al. Dry eye management: targeting the ocular surface Microenvironment. *Int J Mol Sci* 2017;18:1398. 10.3390/ijms18071398 Available: <https://www.mdpi.com/1422-0067/18/7/1398/htm>
- Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II definition and classification report. *Ocul Surf* 2017;15:276–83. 10.1016/j.jtos.2017.05.008 Available: <https://pubmed.ncbi.nlm.nih.gov/28736335/>
- Heidari M, Noorizadeh F, Wu K, et al. Dry eye disease: emerging approaches to disease analysis and therapy. *J Clin Med* 2019;8:1439. 10.3390/jcm8091439 Available: <https://www.mdpi.com/2077-0383/8/9/1439/htm>
- Kulkarni AA, Trousdale MD, Stevenson D, et al. Nucleotide-induced restoration of Conjunctival chloride and fluid secretion in adenovirus type 5-infected pigmented Rabbit eyes. *J Pharmacol Exp Ther* 2003;305:1206–11. 10.1124/jpet.103.049221 Available: <https://pubmed.ncbi.nlm.nih.gov/12649304/>
- Dota A, Sakamoto A, Nagano T, et al. Effect of Diquafosol ophthalmic solution on airflow-induced ocular surface disorder in diabetic rats. *Clin Ophthalmol* 2020;14:1019–24. 10.2147/OPTh.S242764 Available: <https://pubmed.ncbi.nlm.nih.gov/32280196/>
- Jumblatt JE, Jumblatt MM. Regulation of ocular Mucin secretion by P2Y2 nucleotide receptors in Rabbit and human conjunctiva. *Exp Eye Res* 1998;67:341–6. 10.1006/exer.1998.0520 Available: <https://pubmed.ncbi.nlm.nih.gov/9778415/>
- Yokoi N, Kato H, Kinoshita S. The increase of aqueous tear volume by diquafosol sodium in dry-eye patients with sjögren's syndrome: a pilot study. *Eye* 2016;30:857–64. 10.1038/eye.2016.54 Available: <https://pubmed.ncbi.nlm.nih.gov/27055679/>
- Endo K, Sakamoto A, Fujisawa K. Diquafosol tetrasodium elicits total cholesterol release from Rabbit Meibomian gland cells via P2Y2 Purinergic receptor signalling. *Sci Rep* 2021;11. 10.1038/s41598-021-86433-6 Available: <https://pubmed.ncbi.nlm.nih.gov/33772064/>
- Fujihara T, Murakami T, Nagano T, et al. Ins365 suppresses loss of corneal epithelial integrity by secretion of Mucin-like glycoprotein in a rabbit short-term dry eye model. *J Ocul Pharmacol Ther* 2002;18:363–70. 10.1089/10807680260218524 Available: <https://pubmed.ncbi.nlm.nih.gov/12222766/>
- Byun Y-S, Yoo Y-S, Kwon J-Y, et al. Diquafosol promotes corneal epithelial healing via intracellular calcium-mediated ERK activation. *Exp Eye Res* 2016;143:89–97.
- Yagi-Yaguchi Y, Kojima T, Higa K, et al. The effects of 3% Diquafosol sodium eye drops on tear function and the ocular surface of cu, Zn-superoxide Dismutase-1 (Sod1) knockout mice treated with Antiglaucoma eye medications. *Diagnostics (Basel)* 2020;10:20.

- 10.3390/diagnostics10010020 Available: <https://www.mdpi.com/2075-4418/10/1/20/htm>
- 17 Kim YH, Yang IJ, Nguyen LTH, *et al.* Effect of Diquafosol on Hyperosmotic stress-induced tumor necrosis factor- α and Interleukin-6 expression in human corneal epithelial cells. *Korean J Ophthalmol* 2020;34:1–10. 10.3341/kjo.2019.0046 Available: <https://pubmed.ncbi.nlm.nih.gov/32037744/>
- 18 Zhang Q, Zhang H, Qin G, *et al.* Impact of Diquafosol ophthalmic solution on tear film and dry eye symptom in type 2 diabetic dry eye: A pilot study. *J Ocul Pharmacol Ther* 2022;38:133–40. 10.1089/jop.2021.0083 Available: <https://www.liebertpub.com/doi/10.1089/jop.2021.0083>
- 19 Matsumoto Y, Ibrahim OMA, Kojima T, *et al.* Corneal in vivo laser-scanning confocal microscopy findings in dry eye patients with Sjögren's syndrome. *Diagnostics (Basel)* 2020;10:497.
- 20 Ohashi Y, Munesue M, Shimazaki J, *et al.* Long-term safety and effectiveness of diquafosol for the treatment of dry eye in A real-world setting: A prospective observational study. *Adv Ther* 2020;37:707–17. 10.1007/s12325-019-01188-x Available: <https://link.springer.com/article/10.1007/s12325-019-01188-x>
- 21 Wang J, Liu X, Zhu C, *et al.* Improving ocular Bioavailability of hydrophilic drugs through dynamic Covalent Complexation. *Journal of Controlled Release* 2023;355:395–405.
- 22 Raulin C, Greve B, Grema H. IPL technology: a review. *Lasers Surg Med* 2003;32:78–87. 10.1002/lsm.10145 Available: <https://pubmed.ncbi.nlm.nih.gov/12561039/>
- 23 Heymann WR. Intense pulsed light. *J Am Acad Dermatol* 2007;56:466–7. 10.1016/j.jaad.2006.10.031 Available: <https://pubmed.ncbi.nlm.nih.gov/17317488/>
- 24 Qin G, Chen J, Li L, *et al.* Managing severe evaporative dry eye with intense pulsed light therapy. *Ophthalmol Ther* 2023;12:1059–71. 10.1007/s40123-023-00649-5 Available: <https://link.springer.com/article/10.1007/s40123-023-00649-5>
- 25 Liu R, Rong B, Tu P, *et al.* Analysis of cytokine levels in tears and clinical correlations after intense pulsed light treating Meibomian gland dysfunction. *Am J Ophthalmol* 2017;183:81–90.
- 26 Bäumler W, Vural E, Landthaler M, *et al.* The effects of intense pulsed light (IPL) on blood vessels investigated by mathematical modeling. *Lasers Surg Med* 2007;39:132–9. 10.1002/lsm.20408 Available: <http://doi.wiley.com/10.1002/lsm.v39:2>
- 27 Wu Y, Xu L, Song Y, *et al.* Management of post-LASIK dry eye with intense pulsed light in combination with 0.1% sodium Hyaluronate and heated eye mask. *Ophthalmol Ther* 2022;11:161–76.
- 28 Jeng S, Chen J, Chang L, *et al.* Beneficial effect of intense pulsed light on the wound healing in diabetic rats. *Lasers Surg Med* 2020;52:530–6. 10.1002/lsm.23183 Available: <https://onlinelibrary.wiley.com/toc/10969101/52/6>
- 29 Cao Y, Huo R, Feng Y, *et al.* Effects of intense pulsed light on the biological properties and Ultrastructure of skin Dermal fibroblasts: potential roles in Photoaging. *Photomed Laser Surg* 2011;29:327–32. 10.1089/pho.2010.2867 Available: <https://www.liebertpub.com/doi/10.1089/pho.2010.2867>
- 30 Toyos R, Desai NR, Toyos M, *et al.* Intense pulsed light improves signs and symptoms of dry eye disease due to Meibomian gland dysfunction: A randomized controlled study. *PLoS One* 2022;17:e0270268.
- 31 Martínez-Hergueta MC, Alió Del Barrio JL, Canto-Cerdan M, *et al.* Efficacy and safety of intense pulsed light direct eyelid application. *Sci Rep* 2022;12:15592. 10.1038/s41598-022-17986-3 Available: <https://doi.org/10.1038/s41598-022-17986-3>
- 32 Chen Y, Li J, Wu Y, *et al.* Comparative evaluation in intense pulsed light therapy combined with or without Meibomian gland expression for the treatment of Meibomian gland dysfunction. *Current Eye Research* 2021;46:1125–31. 10.1080/02713683.2020.1867750 Available: <https://pubmed.ncbi.nlm.nih.gov/33342317/>
- 33 Pazo EE, Huang H, Fan Q, *et al.* Intense pulse light for treating post-LASIK refractory dry eye. *Photobiomodul Photomed Laser Surg* 2021;39:155–63. 10.1089/photob.2020.4931 Available: <https://www.liebertpub.com/doi/10.1089/photob.2020.4931>
- 34 Song Y, Yu S, He X, *et al.* Tear film Interferometry assessment after intense pulsed light in dry eye disease: A randomized, single masked, sham-controlled study. *Cont Lens Anterior Eye* 2022;45:S1367-0484(21)00128-4.
- 35 Xu L, Wu Y, Song Y, *et al.* Comparison between heated eye mask and intense pulsed light treatment for contact lens-related dry eye. *Photobiomodul Photomed Laser Surg* 2022;40:189–97. 10.1089/photob.2021.0094 Available: <https://www.liebertpub.com/doi/10.1089/photob.2021.0094>
- 36 Vigo L, Pellegrini M, Carones F, *et al.* Outcomes of serial sessions of Activa mask combined with intense pulsed light therapy in patients with Meibomian gland dysfunction. *BMC Ophthalmol* 2022;22:313.
- 37 Wu Y, Mou Y, Zhang Y, *et al.* Efficacy of intense pulsed light combined blood extract eye drops for treatment of nociceptive pain in dry eye patients. *JCM* 2022;11:1312. 10.3390/jcm11051312 Available: <https://www.mdpi.com/2077-0383/11/5/1312/htm>
- 38 Chan A-W, Tetzlaff JM, Götzsche PC, *et al.* SPIRIT 2013 explanation and guidance for protocols of clinical trials. *BMJ* 2013;346:e7586. 10.1136/bmj.e7586 Available: <https://pubmed.ncbi.nlm.nih.gov/23303884/>
- 39 Zhang X-M, Yang L-T, Zhang Q, *et al.* Reliability of Chinese web-based ocular surface disease index questionnaire in dry eye patients: a randomized, crossover study. *Int J Ophthalmol* 2021;14:834–43. 10.18240/ijo.2021.06.07 Available: <https://pubmed.ncbi.nlm.nih.gov/34150537/>
- 40 Pult H, Wolffsohn JS. The development and evaluation of the new ocular surface disease Index-6. *Ocul Surf* 2019;17:817–21.
- 41 Dougherty BE, Nichols JJ, Nichols KK. Rasch analysis of the ocular surface disease index (OSDI). *Invest Ophthalmol Vis Sci* 2011;52:8630–5. 10.1167/iov.11-8027 Available: <https://pubmed.ncbi.nlm.nih.gov/21948646/>
- 42 García-Marqués JV, Martínez-Albert N, Talens-Estrelles C, *et al.* Repeatability of non-invasive Keratograph break-up time measurements obtained using Oculus Keratograph 5m. *Int Ophthalmol* 2021;41:2473–83. 10.1007/s10792-021-01802-4 Available: <https://pubmed.ncbi.nlm.nih.gov/33728492/>
- 43 Fydanaki O, Chalkiadaki E, Tsiogka A, *et al.* Preoperative dry eyes disease in cataract patients with deficient tear break up time: evaluation of OSDI questionnaire, its Subcategories and Keratograph 5m device results. *Int Ophthalmol* 2022;42:3017–25. 10.1007/s10792-022-02287-5 Available: <https://link.springer.com/article/10.1007/s10792-022-02287-5>
- 44 Tsubota K, Yokoi N, Shimazaki J, *et al.* New perspectives on dry eye definition and diagnosis: A consensus report by the Asia dry eye society. *The Ocular Surface* 2017;15:65–76. 10.1016/j.jtos.2016.09.003 Available: <https://pubmed.ncbi.nlm.nih.gov/27725302/>
- 45 Najafi L, Malek M, Valojerdi AE, *et al.* Dry eye disease in type 2 diabetes mellitus: comparison of the tear Osmolarity test with other common diagnostic tests: a diagnostic accuracy study using STARD standard. *J Diabetes Metab Disord* 2015;14:39. 10.1186/s40200-015-0157-y Available: <https://pubmed.ncbi.nlm.nih.gov/26020035/>
- 46 Fydanaki O, Chalkiadaki E, Tsiogka A, *et al.* Preoperative dry eyes disease in cataract patients with deficient tear break up time: evaluation of OSDI questionnaire, its Subcategories and Keratograph 5m device results. *Int Ophthalmol* 2022;42:3017–25. 10.1007/s10792-022-02287-5 Available: <https://pubmed.ncbi.nlm.nih.gov/35394587/>
- 47 Pérez-Bartolomé F, Sanz-Pozo C, Martínez-de la Casa JM, *et al.* Assessment of ocular redness measurements obtained with Keratograph 5m and correlation with subjective grading scales. *J Fr Ophthalmol* 2018;41:836–46. 10.1016/j.jfo.2018.03.007 Available: <https://pubmed.ncbi.nlm.nih.gov/30293826/>
- 48 Mathers WD, Lane JA. Meibomian gland lipids, evaporation, and tear film stability. *Adv Exp Med Biol* 1998;438:349–60. 10.1007/978-1-4615-5359-5_50 Available: <https://pubmed.ncbi.nlm.nih.gov/9634908/>
- 49 Yang L, Pazo EE, Zhang Q, *et al.* Treatment of contact lens related dry eye with intense pulsed light. *Cont Lens Anterior Eye* 2022;45:S1367-0484(21)00060-6.
- 50 Mathers WD, Lane JA. Meibomian gland lipids, evaporation, and tear film stability. *Adv Exp Med Biol* 1998;438:349–60.
- 51 Hosaka E, Kawamorita T, Ogasawara Y, *et al.* Interferometry in the evaluation of Precorneal tear film thickness in dry eye. *Am J Ophthalmol* 2011;151:18–23. 10.1016/j.ajo.2010.07.019 Available: <https://pubmed.ncbi.nlm.nih.gov/20970770/>
- 52 King-Smith PE, Fink BA, Nichols JJ, *et al.* Interferometric imaging of the full thickness of the Precorneal tear film. *J Opt Soc Am A Opt Image Sci Vis* 2006;23:2097–104. 10.1364/josaa.23.002097 Available: <https://pubmed.ncbi.nlm.nih.gov/16912736/>
- 53 Miura M, Inomata T, Nojiri S, *et al.* Clinical efficacy of Diquafosol sodium 3% versus Hyaluronic acid 0.1% in patients with dry eye disease after cataract surgery: a protocol for a single-centre, randomised controlled trial. *BMJ Open* 2022;12:e052488. 10.1136/bmjopen-2021-052488 Available: <https://pubmed.ncbi.nlm.nih.gov/35105626/>
- 54 Science HW-IO & V. Medical treatment for dry eye in Japan. 2018. Available: <https://iovs.arvojournals.org/article.aspx?articleid=2717221>
- 55 Tashbayev B, Yazdani M, Arita R, *et al.* Intense pulsed light treatment in meibomian gland dysfunction: a concise review. *The Ocular Surface* 2020;18:583–94.



- 56 Vergés C, Salgado-Borges J, March de Ribot F, *et al.* Current developments of intensive pulsed light treatment for dry eye disease and Meibomian gland dysfunction. *Expert Rev Ophthalmol* 2021;16:401–9.
- 57 Qin G, Chen J, Li L, *et al.* Efficacy of intense pulsed light therapy on signs and symptoms of dry eye disease: A meta-analysis and

systematic review. *Indian J Ophthalmol* 2023;71:1316–25. 10.4103/IJO.IJO_2987_22 Available: https://journals.lww.com/ijo/Fulltext/2023/04000/Efficacy_of_intense_pulsed_light_therapy_on_signs.35.aspx