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{1}: A protocol for a parallel assignment prospective, randomized, comparative trial to evaluate the safety and efficacy of intense pulsed light (IPL) combined with 3% diquafosol (DQS) ophthalmic solution in dry eye syndrome.

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Keywords:	Orbital and lacrimal disorders < OPHTHALMOLOGY, Laser therapy < DERMATOLOGY, Corneal and external diseases < OPHTHALMOLOGY

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1	Title {1}: A protocol for a parallel assignment prospective, randomized, comparative
2	trial to evaluate the safety and efficacy of intense pulsed light (IPL) combined with 3%
3	diquafosol (DQS) ophthalmic solution in dry eye syndrome.
4	
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22	

23 Word Count: 3440

25 ABSTRACT

Background: 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: A randomized clinical trial was performed at He Eye Specialty hospital in Shenyang. 150 DED patients were randomly equally divided into IPL group, DQS group, and IPL+ group (IPL combined with 3% diquafosol eye drops). All groups follow up for four weeks. The primary outcome measure was the non-invasive tear breakup time (NIBUT), Ocular Surface Disease Index (OSDI) change from baseline. The secondary outcome measures included the conjunctival and cornea staining (CFS) with fluorescein and lissamine, meibomian gland function and secretion quality, tear film lipid layer score (TFLL), Tear meniscus height (TMH), conjunctival hyperemia (RS score) change from baseline for improvement in ocular symptoms. Adverse events also were monitored and documented.

40 Discussion: This study aimed to assess whether the combination of IPL with 3%
41 diquafosol ophthalmic solution (study group) is more effective than IPL (active control
42 group) or 3% diquafosol ophthalmic solution (active control group) in participants with
43 evaporative dry eye.

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45	Trial registration {2a, 2b}: Registration number: Clniicaltrials.gov NCT05694026.
46	Name of the trial registry: Management of dry eye with Intense Pulsed Light combined
47	with 3% diquafosol ophthalmic solution, registered on Jan 10, 2023.
48	
49	Keywords: Dry eye, intense pulsed light, diquafosol ophthalmic solution, RCT
50	
51	Note: The numbers in curly brackets in this protocol refer to the SPIRIT checklist item
52	numbers. The order of the items has been modified to similar group items (see
53	http://www. equator-network.org/reporting-guidelines/spirit-2013-statement-defining-
54	standard-protocol-items-for-clinical-trials/).
55	
56	Protocol version {3}: 2023, version 2
57	
58	Funding {4}: This study was entirely funded by He Eye Specialist Hospital, Shenyang,
59	China. No support was received for the publication of this article.
60	
61	Trial sponsor {5b}: Department of Ophthalmology, He Eye Specialist Hospital,
62	Shenyang 110034, China.
63	
64	Roles and responsibilities {5c}: The study was sponsored and funded entirely by He
65	Eye Specialist Hospital, Shenyang, China.
66	

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Composition of the coordinating center and trial Steering Committee {5d}: The subject leader and the project manager will form the Steering Committee (SC). The SC 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 analyses 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. oeer (e **INTRODUCTION Background and rationale** {6a, 6b} 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 meibomian gland dysfunction (MGD).[4–6] MGD is defined as "a chronic, diffuse anomaly of the meibomian glands, often characterized by terminal duct blockage and/or qualitative/quantitative alterations in glandular secretion'' by 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 ophthalmic sodium is a P2Y2 receptor agonist, which can promote the

88 secretion of mucin and lipid. It also improves the tear film composition and stability[9–

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89 11]. It has a corneal epithelial-repairing effect and can be used to treat ocular surface 90 damage caused by dry eye[5,12,13]. By targeting the inflammation involved in the 91 pathogenesis of dry eye, it can inhibit the expression of inflammatory pathways and 92 inflammatory factors that are involved in the pathogenesis of dry eye[14–16].

Intense pulsed light (IPL) is widely used to treat dermatological conditions[17], and its noncoherent polychromatic light source with a wide wavelength range of 500– 1200 nm has been reported to stimulate facial sebaceous glands[18,19]. The photothermal effect of IPL is postulated to relieve inflammation by removing aberrant surface microvasculature and enhancing meibomian gland function[20-22]. Furthermore, an increase in fibroblast proliferation, collagen formation, and local blood flow has been associated with the application of IPL on the skin[23,24]. Several studies have documented the benefits of IPL in alleviating signs and symptoms of DED on the periocular skin[25–27] and combined it with other therapies such as heated eye mask (HEM) [28,29], 0.1% sodium hyaluronate eye drops [22], and blood extract eye drops[30]. Therefore, an RCT is warranted to assess the safety and efficacy of combining IPL with DQS for patients suffering from DED.

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OBJECTIVES {7}

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

Trial design {8}

112	This is a prospective, randomized controlled trial performed at He Eye Specialist
113	Hospital (HESH). The study adheres to the tenets of the Declaration of Helsinki and is
114	registered at ClinicalTrails.gov (NCT05694026) using the SPIRIT reporting
115	guidelines[31]. Randomization will be performed using a web-based, online, sealed
116	envelope-based system (https://www.sealedenvelope.com). Specific study information
117	sheets will be provided to patients prior to taking consent. Following a dedicated
118	screening and randomization visit for eligible patients, participants will be randomized
119	to one of three trial arms.
120	
121	Study setting {9}
122	This study will be conducted between Mar 1, 2023, and Nov 30, 2023. Participants
123	will be recruited at the Department of Ophthalmology, He Eye Specialist Hospital
124	(HESH).
125	
126	Eligibility criteria {10}
127	Inclusion criteria:
128	1. Age ≥ 18 years
129	2. Consenting participants
130	3. Able and willing to comply with the treatment/follow-up schedule
131	4. Bilateral signs and symptoms of dry eye disease: (i) Ocular Surface Disease Index
132	(OSDI) questionnaire \geq 13, (ii) Non-invasive tear breakup time (NITBUT) \leq 5

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3	400	
4 5	133	seconds, (iii) conjunctival staining score (CS) ≥ 3 points. The presence of two or
6		
7	134	more criteria was used to establish a positive DE diagnosis, based on the 2016 Asia
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9	135	Dry Eye Society criteria
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11	136	Exclusion criteria:
12 13	150	Exclusion enterna.
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15	137	1. A recent history (past 30 days) of topical ophthalmic medication use, including
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17	138	antibiotics, steroids, non-steroidal anti-inflammatory drugs, or required the chronic
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19 20	139	use of topical ophthalmic medications
20 21	100	
21	4.40	
23	140	2. Eyelids or intraocular tumors that should not put pressure
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25	141	3. Active allergy or infection or inflammatory disease that may have prevented the
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27	142	subjects from completing the study at the ocular surface
28		subjects from compreting the study at the octain surface
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30 31	143	4. Any structural change in lacrimal passage
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33	144	5. Glaucoma
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35	145	6. Diabetes or other systemic, dermatologic, or neurologic diseases that affect the
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37	4.4.0	health of ocular surface
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40	147	7. Use of any systemic anti-inflammatory drugs or medication that may interfere with
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43	148	tear production, such as antianxiety, antidepressive, and antihistamine medications
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45	149	within 3 months
46	149	within 5 months
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48 49	150	Interventions {11a, 11b, 11c, 11d}
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51	151	After enrollment in the study, Treatments were initiated after randomization
52		
53	152	immediately. None of the patients included were undergoing any topical or systemic
54	152	miniculatory. None of the patients included were undergoing any topical of systemic
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56	153	agent for DE or MGD during this study; other treatments related to DED and any other
57		
58 59	154	dry eye systemic or topical medication, treatment, or therapy will be prohibited. If dry

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eye signs and symptoms worsen, participants will be stopped and advised to use the designated device. Adverse events (AE) will be continuously monitored. In case of an AE, participants will be informed about the severity of the event, and 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 phones or computer time, and any queries regarding the study will be answered by trailed clinical staff at HESH.

Participants in DQS group and IPL+ group will be used 1 drop of 3% DQS (Diquas;
Santen Pharmaceutical Co., Ltd., Osaka, Japan) 6 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 Ltd., Yokneam, Israel) IPL system, 2 weeks apart. IPL
treatment utilizes a noncoherent polychromatic light source with a wavelength
spectrum of 500–1200 nm on the cutaneous facial sebaceous glands.

169 OUTCOMES {12}

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

Primary Outcome

Ocular Surface Disease Index (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[32]. 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 certain question is deemed irrelevant, it will be marked as 'not applicable
(N/A)' and excluded from the analysis. The OSDI total score is calculated according to
the following formula. The scale ranges from 0 to 100, with higher scores representing
more severe cases of dry eye syndrome[33,34].

Non-invasive tear breakup time (NIBUT): Non-invasive initial tear film breaking
time will be assessed using the Keratograph 5M (Oculus, Germany) topographer. Three
sequential readings will be captured, and the median value will be included in the final
analysis. The median value will be recorded[35,36].

188 Secondary outcomes

Fluorescein and lissamine conjunctival and cornea staining (CFS): Fluorescein and lissamine staining 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[37,38].

Tear meniscus height (TMH): Non-invasive first tear film breakup time using the
Keratograph 5M (Oculus, Germany) topographer will be measured three times
consecutively and the median value was recorded[35,39].

Conjunctival hyperemia (RS score): Conjunctival hyperemia (RS score) will be
assessed by Keratograph image (Oculus, Germany) of 1156*873 pixels, redness score
(RS) (accurate to 0.1 U) was displayed on the computer screen that ranged from 0.0

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> (normal) to 4.0 (severe)[36,40]. Meibomian gland function and secretion quality: Meibum quality will be assessed under a slit-lamp[41]: Five meibomian gland in the middle parts of the eyelid will be assessed using a scale of 0 to 3 for each gland (0 represented clear meibum; 1 represented cloudy meibum; 2 represented cloudy and granular meibum; and 3 represented thick, toothpaste-like consistency meibum)[42,43]. Tear Film Lipid Layer Score (TFLL): Tear Film Lipid Layer interferometry will be assessed using DR-1 (Kowa, Nagoya, Japan). The results will be graded as follows: grade 1, somewhat gray color, uniform distribution; grade 2, somewhat gray color, nonuniform distribution; grade 3, a few colors, nonuniform distribution; grade 4, many colors, nonuniform distribution; grade 5, corneal surface partially exposed[44–46]. 4.0 **Participant timeline** {13}

> 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 {14}

218 On the basis of a non-inferiority margin of 7.3, it was anticipated that 106 219 participants per treatment group would give 90% power to establish non-inferiority of 220 IPL+ group compared IPL group and DQS group in mean change from baseline in

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OSDI score at day 28. With the inclusion of the multidose treatment groups, about 350 individuals is estimated to be enrolled. The intended-to-treat population comprised all randomized individuals and was utilized for all efficacy studies.

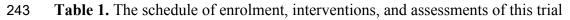
The primary and secondary efficacy analyses utilized a two-way analysis of variance that accounted for treatment and baseline OSDI score stratification in order to compare treatment differences. Using paired t-tests, within-treatment differences from baseline were evaluated (alpha level 0.05). Using analysis of variance, additional analyses of OSDI subgroups and questionnaire data were conducted. Using descriptive statistics, safety data were summarized.

Recruitment {15}

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 He Eye Specialist Hospital'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, gender, or ethnicity (Table 1).

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		ST	STUDY PERIOD			
	Enrolmen	Allocation	Po	ost-alloca	tion	Close
	t					out
TIMEPOINT:	Jan 2023	2023	DAY	DAY1	DAY2	End
			0	4	8	2023
ENROLMENT:						
Eligibility screen	×					
Informed consent	×					
Allocation	C	×				
INTERVENTIONS	C					
:		6				
[IPL+DQS]		Z	•			
[IPL]					•	
[DQS]			+			
ASSESSMENTS:				5		
[The baseline	×	×				
variables]						
[The primary			×	×	×	×
outcome]						
[The second			×	×	×	×
outcome]						



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4	244	
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6	245	METHODS
7	210	
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9	246	
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12	247	Assignment of interventions (for controlled trials) {16a, 16b}
13	211	rissignment of meet ventions (for controlled erfuls) (100, 100)
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15	248	A web-based randomization application will be used (https://www.project-redcap.
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17	249	org/). Allocation will be carried out using block randomization and stratified according
18	210	org). Theorem of the organization and strained according
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20	250	to age (allocation factor: age < 80 years or ≥ 80 years).
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25	252	Implementation {16c}
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27	253	Random allocation will be conducted after the enrolment. Random numbers with
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30	254	corresponding participants will be determined in the order of the time of the visit and
31		
32	255	divided into 3 groups (IPL+, IPL, or DQS group). The allocation result will not be
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36	256	announced to the participants until the end of the data collection phase of the trial.
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38	257	Researchers collecting and analyzing data related to this trial will be blinded to the
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41	258	participant allocation results.
42		participant allocation results.
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46	260	Blinding (masking) {17a, 17b}
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48	261	The treatment assignment for the study will be triple-masked. Participants in the
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50	000	response would be weakle to responsive the contents. A meabod evention for all aliginal
51	262	research would be unable to recognize the contents. A masked examiner for all clinical
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53	263	assessments will not be involved in the data collection or group allocation procedure
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55	004	for this reasonable. The investigator will not be server of the three servers D (
56 57	264	for this research. The investigator will not be aware of the three groups. Participants
57 58		
58 59	265	will be randomly assigned to one of three treatment groups and underwent IPL
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> treatment with 12 homogeneously spaced pulsed light to both eyes and sham treatment to both eyes. The box containing the ampoules is labeled with a batch number, 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 circumstances and procedures under which unblinding is permissible will be determined and performed by the PI.

Data collection methods and management {18a, 18b, 19}

Data administration is the responsibility of Jiayan Chen, HESH, Department of
Clinical Research, as chosen by the principal investigator (Emmanuel Eric Pazo). This
research collects data using a proprietary EMR case report form and management
application. The individual responsible for statistical analysis will get the locked data
following the database lock. The data management handbook specifies the specifics.
After the study has been finished, a report on the implementation and status of data
management will be compiled and sent to the PI with the locked research data.

Statistical methods {20a, 20b, 20c}

Statistical Analysis in Social Sciences (SPSS) for MacOS software was used to analyze the data (version 26, IBM Corp.). Data from both eyes were collected at baseline, first follow-up at week 2, and second follow-up at week 4 for all patients participating in the treatment. Repeated measures analysis allowed for comparisons

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across time periods, while paired analyses allowed for comparisons of pre-and post-treatment data at specific time periods. The Kolmogorov-Smirnoff test will be used to determine the normality of variables. The background of the study's subjects will be tabulated by calculating the mean and standard deviation for continuous variables and the frequency and percentage for categorical variables. Analysis of variance will be used to analyze ordinal variables and those having nonnormal distributions (ANOVA). The primary outcome measures for this study are NITBUT OSDI scores before and after treatment. For the main endpoint, between-group comparisons using baseline as a covariate and an analysis of covariance will be made to produce the adjusted mean, its 95% confidence interval, and the p value.

299 METHODS

300 Monitoring

301 Data monitoring {21a, 21b}

Due to the projected low frequency of adverse events 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 steering committee (SC) will have oversight and access to the trial under the supervision of the trial manager (TM) at any time during the study.

review

309 Harms {22}

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Adverse events 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 harmful effects. Local symptoms may include corneal epithelium disorder (filamentary keratitis, superficial keratitis, corneal erosion, etc.), conjunctivitis, eye irritation, eye discharge, conjunctival hyperemia, eye pain, eye itching, ocular foreign body sensation, visual discomfort, hyposphagma, abnormal sensation in the eye (dry eye sensation, strange eye sensation, sticky eye sensation), blurred vision, photophobia, and lacrimation. If major adverse events occur, HESH Certified Review Board will be notified; experimental treatments will be discontinued promptly, and appropriate therapies will be offered.

Auditing {23}

322 The study will be reviewed and evaluated weekly by an independent supervisor not323 related to the PI and sponsors.

DISCUSSION

DQS 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.[47–49] At present, multi-center clinical trials have proved the advantages and efficacy of diquafosol sodium drops in the treatment of dry eyes, and the Asian Dry Eye Work Shop 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.

Literature review shows that intense pulsed light (IPL) is a relatively new method for the treatment of lipid-abnormal dry eye caused by MGD, which can relieve the symptoms and signs of MGD-related dry eye by reducing eyelid inflammation, thermal effect, sterilization, and acariasis, and light regulation[50,51]. This result should allow us to assess the effectiveness of the combination of intense pulsed light with 3% DQS ophthalmic solution. In future studies, we will further expand the sample size and conduct a deeper study on the mechanism of symptom improvement in the hope of providing clinicians with more treatment options. ETHICS AND DISSEMINATION **Research ethics approval** {24}: This study will be conducted in compliance with the tenets of the Declaration of Helsinki and the Institutional Review Board of He Eye Specialist Hospital, Shenyang, China. **Protocol amendments** {25} If there are modifications to eligibility criteria, outcomes, or analyses, a revised protocol will be submitted for approval to the HESH Medical Ethics Committee. Consent or assent {26a, 26b} Trained and experienced clinicians will seek informed permission from prospective

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354	participants.
355	
356	Confidentiality {27}
357	Participant's personal information will be kept confidential in the same way as their
358	medical histories in the hospital before, during, and after the trial.
359	
360	Declaration of interests {28}: None
361	
362	Access to data {29}: Not applicable.
363	
364	Ancillary and post-trial care {30}: Not applicable.
365	
366	Dissemination policy {31a, 31b, 31c}: The results of the trial will be reported and
367	disseminated regardless of the direction of the effect. Trial findings will be
368	disseminated to the patients and doctors. This will take the form of papers in peer-
369	reviewed open-access medical journals and presentations at conferences
370	
371	Trial Status
372	Recruitment began in April 2023 and the approximate date when recruitment will
373	be completed is June 2023. Protocol version 2.0 was approved on December 2022.
374	APPENDICES
375	Informed consent materials {32}: Not applicable

1 2		
3		
4 5	376	Biological specimens {33}: Not applicable.
6 7	377	
8 9 10	378	Author Contributions
11 12 13	379	Conception and design of the research: JC, GQ, LL, YQ, HC, HH, YX, QZ, YW, LY,
14 15	380	SM, JEM, LX, WH, SY, XH, and EEP; analysis and interpretation of the data: JC, GQ,
16 17 18	381	EEP; writing original draft preparation: JC; critical revision of the manuscript
19 20 21	382	(reviewing and editing): JC and EEP; supervision: XH, SY, and EEP.
22 23	383	
24 25 26	384	Disclosures
27 28 29	385	JC, GQ, LL, YQ, HC, HH, YX, QZ, YW, LY, SM, JEM, LX, WH, SY, XH and EEP
30 31	386	have no disclosures.
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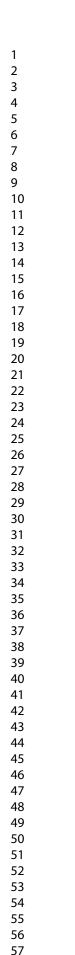
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14 15	600	Figure 1. Study flow chart (The schedule for data collection and visits)
$\begin{array}{c} 16\\ 17\\ 18\\ 19\\ 20\\ 21\\ 22\\ 23\\ 24\\ 25\\ 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 34\\ 35\\ 36\\ 37\\ 38\\ 39\\ 40\\ 41\\ 42\\ 43\\ 44\\ 45\\ 46\\ 47\\ 48\\ 49\\ 50\\ 51\\ 52\\ 53\\ 54\\ 55\\ 56\\ 57\\ 58\\ 59\\ 60\\ \end{array}$		

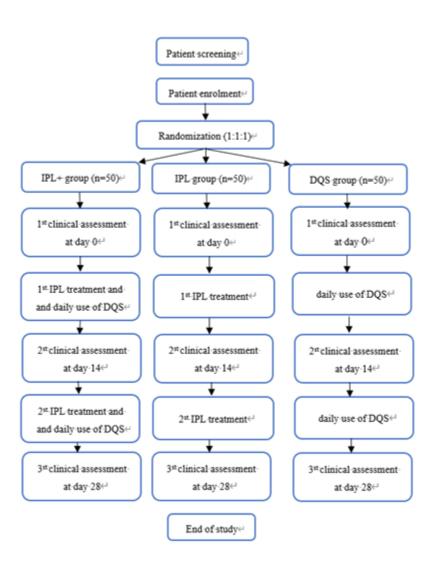
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study flow chart

36x46mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below. Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation. Upload your completed checklist as an extra file when you submit to a journal. In your methods section, say that you used the SPIRITreporting guidelines, and cite them as: Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

<u>#1</u>	Descriptive title identifying the study design, population,	
	interventions, and, if applicable, trial acronym	
<u>#2a</u>	Trial identifier and registry name. If not yet registered, name of	
	intended registry	
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	<u>#2a</u> <u>#2b</u> <u>#3</u>	 interventions, and, if applicable, trial acronym #2a Trial identifier and registry name. If not yet registered, name of intended registry #2b All items from the World Health Organization Trial Registration Data Set #3 Date and version identifier #4 Sources and types of financial, material, and other support

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1 2 3 4 5 6	Roles and responsibilities: sponsor contact information	<u>#5b</u>	Name and contact information for the trial sponsor
7 8 9 10 11 12 13 14 15	Roles and responsibilities: sponsor and funder	<u>#5c</u>	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
16 17 18 19 20 21 22 23	Roles and responsibilities: committees	<u>#5d</u>	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
24 25	Introduction		
26 27 28 29 30 31	Background and rationale	<u>#6a</u>	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
32 33 34 35	Background and rationale: choice of	<u>#6b</u>	Explanation for choice of comparators
36 37	comparators		
38	Objectives	<u>#7</u>	Specific objectives or hypotheses
 39 40 41 42 43 44 45 	Trial design	<u>#8</u>	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)
46 47	Methods:		
48	Participants,		
49 50	interventions, and		
51 52	outcomes		
53 54 55 56 57 58	Study setting	<u>#9</u>	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
59 60		For peer rev	view only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 2 3 4 5	Eligibility criteria	<u>#10</u>	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)			
6 7 8	Interventions: description	<u>#11a</u>	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered			
9	description		replication, including now and when they will be administered			
10 11	Interventions:	<u>#11b</u>	Criteria for discontinuing or modifying allocated interventions			
12 13 14	modifications		for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)			
15	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and			
16 17	adherance		any procedures for monitoring adherence (eg, drug tablet return;			
18 19	difference		laboratory tests)			
20 21	Interventions:	<u>#11d</u>	Relevant concomitant care and interventions that are permitted or			
22	concomitant care		prohibited during the trial			
23 24						
25	Outcomes	<u>#12</u>	Primary, secondary, and other outcomes, including the specific			
26 27			measurement variable (eg, systolic blood pressure), analysis			
28			metric (eg, change from baseline, final value, time to event),			
29			method of aggregation (eg, median, proportion), and time point			
30 31			for each outcome. Explanation of the clinical relevance of chosen			
32			efficacy and harm outcomes is strongly recommended			
33 34						
35	Participant timeline	<u>#13</u>	Time schedule of enrolment, interventions (including any run-ins			
36			and washouts), assessments, and visits for participants. A			
37 38			schematic diagram is highly recommended (see Figure)			
39	Sample size	#14	Estimated number of participants needed to achieve study			
40 41	Sample Size	<u>#14</u>	objectives and how it was determined, including clinical and			
42						
43 44			statistical assumptions supporting any sample size calculations			
45 46 47	Recruitment	<u>#15</u>	Strategies for achieving adequate participant enrolment to reach target sample size			
48 49	Methods: Assignment					
50 51	of interventions (for					
52 53	controlled trials)					
54 55	Allocation: sequence	<u>#16a</u>	Method of generating the allocation sequence (eg, computer-			
55 56	generation		generated random numbers), and list of any factors for			
57			stratification. To reduce predictability of a random sequence,			
58 59			details of any planned restriction (eg, blocking) should be			
60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml					

Page 3	34 of 36
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15	l3, 2025 at Α _ξ nologies.
15	jopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l training, and similar technologies.

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24			provided in a separate document that is unavailable to those who enrol participants or assign interventions	
	Allocation concealment mechanism	<u>#16b</u>	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
	Allocation: implementation	<u>#16c</u>	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
	Blinding (masking)	<u>#17a</u>	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
	Blinding (masking): emergency unblinding	<u>#17b</u>	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	14
25 26	Methods: Data			
27	collection,			
28 29 30 31	management, and analysis			
32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54	Data collection plan	<u>#18a</u>	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15
	Data collection plan: retention	<u>#18b</u>	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
	Data management	<u>#19</u>	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
55 56 57 58 59 60	Statistics: outcomes	<u>#20a</u> or peer rev	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol iew only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	15

$\begin{array}{c}1\\2\\3\\4\\5\\6\\7\\8\\9\\10\\11\\23\\14\\15\\16\\17\\18\\19\\20\\21\\22\\23\\24\\25\\26\\27\\28\\9\\30\\31\\32\\33\\45\\36\\37\\38\\9\\40\\41\\42\\43\\44\\5\\6\\7\\8\\9\\50\\51\\55\\56\\57\\58\end{array}$	Statistics: additional analyses	<u>#20b</u>	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
	Statistics: analysis population and missing data	<u>#20c</u>	Definition of analysis population relating to protocol non- adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
	Methods: Monitoring			-
	Data monitoring: formal committee	<u>#21a</u>	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
	Data monitoring: interim analysis	<u>#21b</u>	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16
	Harms	<u>#22</u>	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16
	Auditing	<u>#23</u>	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17
	Ethics and			2
	dissemination			ų
	Research ethics approval	<u>#24</u>	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	18
	Protocol amendments	<u>#25</u>	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	18
	Consent or assent	<u>#26a</u>	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
59 60	Fo	r peer re	view only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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1 2 3 4 5	Consent or assent: ancillary studies	<u>#26b</u>	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	18 18 Protected by copyright, including for uses related 18 18 19 19 19 19
5 7 3 9 10	Confidentiality	<u>#27</u>	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18 P
11 12 13 14	Declaration of interests	<u>#28</u>	Financial and other competing interests for principal investigators for the overall trial and each study site	18 18 18 19
15 16 17 18 19	Data access	<u>#29</u>	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Protected by copyright, including for uses related 19 19 19 19 19 19 19 19 19 19 19 19 19
20 21 22 23	Ancillary and post trial care	<u>#30</u>	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	19 19 for u
24 25 26 27 28 29 30 31	Dissemination policy: trial results	<u>#31a</u>	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Enseignement Superieu ises related to text and c 19
2 3 4 5	Dissemination policy: authorship	<u>#31b</u>	Authorship eligibility guidelines and any intended use of professional writers	ur (ABES) data minin
5 7 8 9	Dissemination policy: reproducible research	<u>#31c</u>	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	g, Al training, and similar technologies
) 	Appendices			g, anc
<u>2</u> 3 4 5	Informed consent materials	<u>#32</u>	Model consent form and other related documentation given to participants and authorised surrogates	19 19 19
5 7 3 9 0	Biological specimens	<u>#33</u>	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	19 19
1 2 3 4 5 6	Attribution License CC-I	BY-NC.	boration paper is distributed under the terms of the Creative Commons This checklist was completed on 21. February 2023 using tool made by the <u>EQUATOR Network</u> in collaboration with <u>Penelope.ai</u>	 Al training, and similar technologies. 19 19 19
57 58 59 50	Fo	or peer re	view only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	indre de l

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

Journal:	BMJ Open
Manuscript ID	bmjopen-2023-073055.R1
Article Type: Protocol	
Date Submitted by the Author:	13-Jun-2023
Complete List of Authors:	Chen, Jiayan; He Eye Specialist Hospital, Ophthalmology Qin, Guanghao; He Eye Specialist Hospital, Ophthalmology Li, Liangzhe; He Eye Specialist Hospital, Ophthalmology Qi, Yifan; He Eye Specialist Hospital, Ophthalmology Che, Huixin ; He Eye Specialist Hospital, Ophthalmology Huang, He; He Eye Specialist Hospital, Ophthalmology Xia, Yang; He Eye Specialist Hospital, Ophthalmology Zhang, Qing; Tianjin Medical University Eye Hospital, Ophthalmology Wu, Yi; China Medical University Second Hospital, Ophthalmology Yang, Lanting; Wenzhou Medical University Eye Hospital Moutari, Salissou ; Queen's University Belfast Moore, Jonathan ; Cathedral Eye Clinic Xu, Ling ; He Eye Specialist Hospital, Ophthalmology He, Wei; He Eye Specialist Hospital, Ophthalmology Yu, Sile; He Eye Specialist Hospital, Ophthalmology He, Xingru; He Eye Specialist Hospital, Ophthalmology Pazo, Emmanuel Eric; He Eye Specialist Hospital, Ophthalmology
Primary Subject Heading :	Ophthalmology
Secondary Subject Heading:	Research methods, Pharmacology and therapeutics
Keywords:	Orbital and lacrimal disorders < OPHTHALMOLOGY, Laser therapy < DERMATOLOGY, Corneal and external diseases < OPHTHALMOLOGY

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9 10	3	Title: A protocol for a parallel assignment prospective, randomized, comparative trial
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12	4	to evaluate the safety and efficacy of intense pulsed light (IPL) combined with 3%
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14	5	diquafosol (DQS) ophthalmic solution in dry eye syndrome.
15	Ũ	arquarosor (BQS) opnaranne soranon in ary eye synaronie.
16 17	•	
17 18	6	Names protocol contributors : Jiayan Chen ¹ , Guanghao Qin ¹ , Liangzhe Li ¹ , Yifan
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20	7	Qi ¹ , Huixin Che ¹ , He Huang ¹ , Yang Xia ¹ , Qing Zhang ² , Yi Wu ³ , Lanting Yang ⁴ ,
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22	8	Salissou Moutari ⁵ , Jonathan E Moore ⁶ , Ling Xu ¹ , Wei He ¹ , Sile Yu ^{1,7} , Xingru He ^{1,7*} ,
23		
24 25	9	Emmanuel Eric Pazo ¹ *
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48	18	ABSTRACT
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50	10	Introduction, Evenerative dry ave (EDE) is common and can lead to couler pain
51 52	19	Introduction: Evaporative dry eye (EDE) is common and can lead to ocular pain,
52 53		
54	20	decreased visual quality, and reduced quality of life. Intense pulsed light (IPL) and 3%
55		
56	21	diquafosol ophthalmic solution have been found to be beneficial in reducing signs and
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58 59	22	symptoms of dry eye.
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Page 2 of 46

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> Methods and analysis: A randomized clinical trial will be performed at He Eye Specialist Hospital in Shenyang. 318 DED patients will be randomly equally divided into the IPL group, DQS group (diquafosol ophthalmic solution eye drops), and IPL+ group (IPL combined with 3% diguafosol eve drops). All groups will be followed up for four weeks. The primary outcome measures will be the non-invasive tear break-up time (NIBUT) and the Ocular Surface Disease Index (OSDI) change from the baseline. The secondary outcome measures included the conjunctival and cornea staining (CFS) with fluorescein and lissamine, meibomian gland function and secretion quality, tear film lipid layer score (TFLL), tear meniscus height (TMH), conjunctival hyperemia (RS score) change from the baseline for improving ocular symptoms. Adverse events also will be monitored and documented.

> 34 Discussion: This study aimed to assess whether the combination of IPL with 3%
> 35 diquafosol ophthalmic solution (study group), IPL+ (study group), is more effective
> 36 than IPL (active control group) or DQS (active control group) in participants with
> 37 evaporative dry eye.

Ethics and dissemination: Registration number: Clniicaltrials.gov NCT05694026.
Name of the trial registry: Management of dry eye with Intense Pulsed Light combined
with 3% diquafosol ophthalmic solution, registered on Jan 10, 2023. Ethics approval
number: IRB (2022) K029.01. The study's findings will be shared regardless of the
effect's direction.

43 Keywords: Dry eye, intense pulsed light, diquafosol ophthalmic solution, RCT

44 Strengths and limitations of this study:

Page 3 of 46

Title $\{1\}$

and 2b

Funding {4}

Trial registration {2a

Protocol version {3}

Author details {5a}

 BMJ Open

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thor details {5a}	Jiayan Chen. He Eye Specialist Hospital, Shenyang, China. Quanghao Qin. He Eye Specialist Hospital, Shenyang, China.					
	Shenyang, China.					
nding {4}	This study was entirely funded by He Eye Specialist Hospital,					
otocol version {3}	2023, version 2					
1 2b}	approval number: IRB (2022) K029.01					
al registration {2a	ophthalmic solution in dry eye syndrome Registration number: Clniicaltrials.gov NCT05694026. Ethics					
	pulsed light (IPL) combined with 3% diquafosol (DQS)					
	comparative trial to evaluate the safety and efficacy of intense					
le {1}	A protocol for a parallel assignment prospective, randomized,					
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http://www.equator	-network.org/reporting-guidelines/spirit-2013-statement-defining-					
numbers. The ord	er of the items has been modified to similar group items (see					
The numbers i	n curly brackets in this protocol refer to the SPIRIT checklist item					
Administrative in	formation					
symptom impr	ovement					
• In future studi	es, we will further conduct a deeper analysis on the mechanism of					
international m	nedical conferences will serve this purpose.					
	ingi impuet, open access medicar journais and tarks at national and					
Publications in	high-impact, open-access medical journals and talks at national and					
on DED patier	its.					
• A large RCT h	has not been conducted to understand the benefits of DQS and IPL					
enabling credi	ble inference about risks and benefits.					
	promotes standardization of therapy and outcome assessment,					
• The protocol	promotes standardization of therapy and outcome assessment					
options for trea	options for treatment.					
• The trial is des	The trial is designed to be embedded into routine clinical practice, providing more					

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Name and contact	This is an investigator-initiated research, so the principa		
information for the investigator acts as the sponsor. Emmanuel Eric Pazo (Princ			
trial sponsor {5b} Investigator). <u>ericpazo@outlook.com</u>			
Role of sponsor {5c}	Investigator-initiated research		

61

62 INTRODUCTION

63 **Background and rationale {6a}**

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 meibomian gland dysfunction (MGD).[4–6] MGD can be chronic or diffused anomaly of the meibomian glands, often characterized 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] Diguafosol ophthalmic sodium 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 randomized 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 (6 times/day)[21].

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Intense pulsed light (IPL) is widely used to treat dermatological conditions[22], and its noncoherent 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 [30] et al. and Martínez-Hergueta [31] et al. have evaluated the safety

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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
drops [27], and blood extract eye drops[37]. Therefore, an RCT is warranted to assess
the safety and efficacy of combining IPL with DQS for patients suffering from DED.

96 **Objectives** {7}

97 The primary objective of this study is to assess whether the combination of intense
98 pulsed light with 3% diquafosol ophthalmic solution is more effective than intense
99 pulsed light and 3% diquafosol ophthalmic solution in alleviating signs and symptoms
100 of DED.

101

102 Trial design {8}

This is a prospective, randomized controlled trial performed at He Eye Specialist 103 Hospital (HESH) [ethics approval number: IRB (2022) K029.01]. The study adheres to 104 the tenets of the Declaration of Helsinki and is registered at ClinicalTrails.gov 105 (NCT05694026) using the SPIRIT reporting guidelines[38]. Randomization will be 106 107 performed using web-based, online. sealed envelope-based а system (https://www.sealedenvelope.com). Specific study information sheets will be provided 108 to patients prior to taking consent. Following a dedicated screening and randomization 109 visit for eligible patients, participants will be randomized to one of three trial arms. 110

111

112 Methods: Participants, interventions, and outcomes

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4	113	Study setting {9}
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6	114	This study will be conducted between Mar 1, 2023, and Nov 30, 2023. Participants
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10	115	will be recruited at the Department of Ophthalmology, He Eye Specialist Hospital
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12	116	(HESH).
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17	118	Eligibility criteria {10}
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19	119	Inclusion criteria:
20	113	inclusion effectia.
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22 23	120	1. Age ≥ 18 years
23 24		
25	121	2. Consenting participants.
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27	400	
28	122	3. Able and willing to comply with the treatment/follow-up schedule.
29		
30	123	4. Bilateral signs and symptoms of dry eye disease: (i) Ocular Surface Disease Index
31		
32	104	(OSDI) questionnaire \geq 13, (ii) Non-invasive tear break-up (NITBUT) \leq 5 seconds,
33	124	$(OSDI)$ questionnance ≥ 15 , (ii) Non-invasive tear break-up $(NIIBOI) \geq 5$ seconds,
34		
35	125	(iii) conjunctival staining score (CS) \geq 3 points. The presence of two or more criteria
36 27		
37 38	126	was used to establish a positive DE diagnosis based on the 2016 Asia Dry Eye
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41	127	Society criteria.
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43	128	Exclusion criteria:
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45	120	1 A recent history (next 20 days) of tenical entitlelinic medication use including
46	129	1. A recent history (past 30 days) of topical ophthalmic medication use, including
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48	130	antibiotics, steroids, non-steroidal anti-inflammatory drugs, or required the chronic
49		
50 51	131	use of topical ophthalmic medications.
52	101	use of topfour opficiumite moulourons.
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54	132	2. Eyelids or intraocular tumors.
55		
56	133	3. Active allergy or infection, or inflammatory disease may prevent the subjects from
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58	104	completing the study at the equilar surface
59	134	completing the study at the ocular surface.
60		7

135	4. Any structural changes in the lacrimal passage.
136	5. Glaucoma.
137	6. Diabetes or other systemic, dermatologic, or neurologic diseases that affect the
138	health of the ocular surface.
139	7. Use of any systemic anti-inflammatory drugs or medication that may interfere with
140	tear production, such as antianxiety, anti-depressive, and antihistamine medications,
141	within three months.
142	8. Pregnant or breastfeeding.
143	9. Contact lenses wearers.
144	
145	Informed consent {26a}
146	Trained and experienced clinicians will seek informed permission from prospective
147	participants.
148	
149	Additional consent provisions for collection and use of participant data and
150	biological specimens {26b}
151	This trial does not involve collecting biological specimens.
152	
153	Interventions
154	The explanation for the choice of comparators {6b}
155	After enrollment in the study, treatments will be initiated immediately after

DQS (Diquas; Santen Pharmaceutical Co., Ltd., Osaka, Japan) 6 times per day for four weeks (28 days), whereas participants in the IPL+ group and IPL group will undergo two IPL treatment sessions of M22 (Lumenis Ltd., Yokneam, Israel) IPL system, two weeks apart. IPL treatment utilizes a noncoherent polychromatic light source with a wavelength spectrum of 500–1200 nm on the cutaneous facial sebaceous glands.

Intervention description {11a}

In this study, patients receive either DQS, IPL, or IPL combined with DQS for four weeks based on the group they are placed in. Two follow-up visits were performed at week two and week 4 in all groups; comprehensive eye exams will be conducted by an ophthalmologist, including primary outcomes, secondary outcomes, and safety 4.2 evaluation.

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Criteria for discontinuing or modifying allocated interventions {11b}

If dry eye signs and symptoms worsen, participants will be stopped and advised to use the designated device. Adverse events (AE) will be continuously monitored. In case of an AE, participants will be informed about the severity of the event, and 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.

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179 Strategies to improve adherence to interventions {11c}

Participants will be reminded by phone and email every week, and then 180 181 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 182 183 medication status will be checked at each follow-up visit. In the event of noncompliance, such as absence, participants will be contacted by phone or email to ask if 184 they will continue or terminate the study early. 185

186

Relevant concomitant care permitted or prohibited during the trial {11d} 187

Any other dry eye systemic or topical medication, treatment, or therapy will be 188 prohibited during the course of this study. 189

190

Provisions for post-trial care {30} 191

There is no anticipated harm and compensation for trial participation, but 192 participants who show signs and symptoms of deterioration in their dry eye status will 193 be directed to their local dry eye center for further treatment. 194

195

Outcomes {12} 196

All patients will be assessed at baseline, 14, and 28 days. We plan to use primary 197 and secondary outcomes measures, symptoms, and corneal and meibomian gland 198 199 improvement will be compared between the three groups.

201 Primary Outco	ome
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202	Ocular Surface Disease Index (OSDI): OSDI is a questionnaire consisting of 12
203	questions for evaluating the effects of dry eye syndrome on vision, ocular symptoms,
204	and any condition associated with DED[39]. The patient will answer each question on
205	a scale ranging from 0 to 4, with '0' indicating 'none of the time' and '4' indicating 'all
206	of the time.' If a particular question is deemed irrelevant, it will be marked as 'not
207	applicable (N/A)' and excluded from the analysis. The OSDI total score is calculated
208	according to the following formula. The total score ranges from 0 to 100, with higher
209	scores representing more severe cases of dry eye disease symptoms [40,41].
210	Non-invasive tear break-up (NIBUT): The Keratograph 5M (Oculus, Germany)
211	topographer will assess non-invasive initial tear film breaking time. Three sequential
212	readings will be captured, the median value will be included in the final analysis, and
213	the median value will be recorded [42,43].
214	

215 Secondary outcomes

Fluorescein and lissamine conjunctival and cornea staining (CFS): Fluorescein and lissamine staining 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]. Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Tear meniscus height (TMH): Non-invasive first tear film break-up using the Keratograph 5M (Oculus, Germany) topographer will be measured three times consecutively, and the median value was recorded[42,46].

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Conjunctival hyperemia (RS score): Conjunctival hyperemia (RS score) will be
assessed by Keratograph image (Oculus, Germany) of 1156*873 pixels, redness score
(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-lamp[48]: Five meibomian glands in the middle parts of the eyelid will be evaluated using a scale of 0 to 3 for each gland (0 represented clear meibum; 1 represented cloudy meibum; 2 represented cloudy and granular meibum; and three means thick, toothpaste-like consistency meibum)[49,50].

Tear Film Lipid Layer Score (TFLL): The interferometry patterns will be assessed
using DR-1 (Kowa, Nagoya, Japan). The results will be graded as follows: grade 1,
somewhat gray color, uniform distribution; grade 2, rather gray color, nonuniform
distribution; grade 3, a few colors, nonuniform distribution; grade 4, many colors,
nonuniform distribution; grade 5, corneal surface partially exposed [51–53].

Participant timeline {13}

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 four weeks. Furthermore, the effect will be examined during the 2-week follow-up period of 4 weeks (**Figure 1**).

244 Sample size {14}

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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 to 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 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 standard deviation 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 standard deviation 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.

With the inclusion of the multidose treatment groups and a dropout rate of 8%, it is estimated that about 350 individuals will be enrolled. The intended-to-treat population comprised all randomized individuals and was utilized for all efficacy studies. Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

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

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267				
268	Recruitment {15}			
269	This clinical study will be done in a single site,	with participan	ts blind	led to
270	treatment assignment. This research is open to patients			
		-		
71	Specialist Hospital's Department of Ophthalmology. Pa	-		
72	adverts in the distribution pamphlets, the website, a	nd social media	a postii	ngs. E
73	participant's demographic information (including ocul	ar diseases and	current	t/previ
274	usage of drugs and/or lubricating eye drops) will be col	llected during th	e first (screen
275	appointment. Participants will not be limited based on	age, gender, or	ethnic	ity (Ta
276				
	2).			
277	2).			
	2). Items	Baseline	2w	4w
		Baseline √	2w	4w
	Items	Baseline √ √	2w	4w
	Items Informed consent	Baseline √ √	2w √	4w √
	Items Informed consent Patient background	Baseline \checkmark \checkmark \checkmark	2w √ √	4w √
	Items Informed consent Patient background Ocular Surface Disease Index (OSDI) scores	Baseline 	2w √ √ √	4w √ √
	Items Informed consent Patient background Ocular Surface Disease Index (OSDI) scores IOP	Baseline 	2w √ √ √	4w
	Items Informed consent Patient background Ocular Surface Disease Index (OSDI) scores IOP BCVA	Baseline 	2w √ √ √ √ √	4w
	Items Informed consent Patient background Ocular Surface Disease Index (OSDI) scores IOP BCVA Non-invasive tear break-up (NIBUT)	Baseline 	2w √ √ √ √ √ √ √	4 w
	Items Informed consent Patient background Ocular Surface Disease Index (OSDI) scores IOP BCVA Non-invasive tear break-up (NIBUT) conjunctival and cornea staining (CFS)	Baseline $}$ 	2w √ √ √ √ √ √ √	4 w イ イ イ イ イ イ イ イ イ イ イ イ

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	Conjunctival hypere	emia (RS scor	e)			\checkmark	١
			()		,		
	Meibomian gland fu	inction					٦
	Meibomian secretio	n quality			\checkmark		٦
	Adverse event (AE)					\checkmark	٦
278	: All groups						
279	Patient background, i	ncluding date	of birth, geno	der, race	, ethnicity,	, and allerg	gy hist
280							
281	Table 1. Schedule fo	r data collecti	on and visits				
		R	ST	TUDY P	ERIOD		
		Enrolmen	Allocation	P	ost-alloca	tion	Clo
		t	6				0
	TIMEPOINT:	Jan 2023	2023	DAY	DAY1	DAY2	Er
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	Eligibility screen		×				
	Eligibility screen Informed consent		×				
	Eligibility screen Informed consent Allocation		×				
	Eligibility screen Informed consent Allocation INTERVENTIONS		×				

			-			
[DQS]						
ASSESSMENTS:						
[The baseline	×	×				
variables]						
[The primary			×	×	×	×
outcome]						
[The second			×	×	×	×
outcome]	6					

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

284 Assignment of interventions: Allocation

285 Sequence generation {16a}

A web-based randomization application will be used (https://www.project-redcap.
org/). Randomization will be by simple randomization. Allocation will be carried out
using block randomization 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.

293 Concealment mechanism {16b}

The block size will be concealed from other researchers, and the randomization table will not be available for assessment by anyone else involved in the study [54].

ician is the	
nbers with e visit and will not be f the trial. ded to the	Enseignement Superieur (A Protected by copyright, including for uses related to text and data
ants in the all clinical procedure articipants	ent Superieur (ABES) . to text and data mining, Al training, and similar technologies.
ll undergo nd a sham th a batch t number,	schnologies.

Randomization is performed by an independent biostatistician. The biostatisti only one who has access to check the file. The allocation list is kept in a se on a different computer.

Implementation {16c}

Random allocation will be conducted after the enrolment. Random nun corresponding participants will be determined in the order of the time of the divided into three groups (IPL+, IPL, or DQS group). The allocation result v announced to the participants until the end of the data collection phase of Researchers collecting and analyzing data related to this trial will be blind review participant allocation results.

Assignment of interventions:

Blinding {17a}

The treatment assignment for the study will be triple-masked. Participa research would be unable to recognize the contents. A masked examiner for assessments will not be involved in the data collection or group allocation for this research. The investigator will not be aware of the three groups. Pa will be randomly assigned to one of the three treatment groups, and they will IPL treatment with 12 homogeneously spaced pulsed light to both eyes ar treatment to both eyes. The box containing ampoules will be labeled with number, including the study reference number, participant ID, contact

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3 4	318	investigator name, site address, the expiration date of the eye drops, storage instructions,
5 6 7	319	and a statement informing the participant that the eye drops are for use only in clinical
7 8		
9 10	320	trials and should not be ingested. The circumstances and procedures under which
11 12	321	unblinding is permissible will be determined and performed by the PI.
13 14 15	322	
16 17 18	323	Procedure for unblinding if needed {17b}
19 20	324	The PI will determine and perform the circumstances and procedures under which
21 22 23	325	unblinding is permissible.
24 25 26	326	Participant withdrawal
27 28	327	Based on the following criteria, patients will be removed from the research.
29 30 31	328	1. When it is deemed challenging to continue the study owing to the emergence of
32 33 34	329	new ailments.
35 36	330	2. When the research participant cannot be located.
37 38 39	331	3. In the case of pregnancy or pregnancy suspicion.
40 41	332	4. When participants or their legal guardians want to end their participation in a
42 43 44	333	study.
45 46 47	334	5. When the participant's caretaker cannot guarantee their participation in the study.
48 49	335	6. When the research project is concluded.
50 51 52	336	7. When the lead investigator and sub-investigators believe that it is acceptable to
53 54	337	cease the study for reasons other than those listed above.
55 56 57	338	
58 59 60	339	Data collection and management
00		18

340	Plans for assessment and collection of outcomes {18a}
-----	---

Data administration is the responsibility of Jiayan Chen, HESH, Department of Clinical Research, as chosen by the principal investigator (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 on the implementation and the status of data management will be compiled and sent to the PI with the locked research data.

350 Plans to promote participant retention and complete follow-up {18b}

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 prioritize 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 selfassessment questionnaires online. Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Data will be gathered during pre-randomization, termination, and follow-up periods at four and eight 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

362	that necessitates respondents to provide comprehensive responses to all inquiries prior
363	to submitting their answers.
364	
365	Data management {19}
366	Data collection and data entry were performed by separate experienced staff
367	members at HESH, Department of Clinical Research. Supervision and double
368	confirmation were performed by Jiayan Chen, along with weekly backup, to ensure data
369	quality.
370	
371	Confidentiality {27}
372	Each participant's personal information will be kept confidential in the same way
373	as their medical histories in the hospital before, during, and after the trial.
374	
375	Plans for collection, laboratory evaluation, and storage of biological specimens for
376	genetic or molecular analysis in this trial/future use {33}
377	Not Applicable-There will be no biological specimens collected.
378	
379	Statistical methods
380	Statistical methods for primary and secondary outcomes {20a}
381	The software Statistical Analysis in Social Sciences (SPSS, version 26, IBM Corp)
382	for MacOS software will be used to analyze the data. Data from both eyes will be
383	collected for all patients participating in the treatment at the following stages: baseline,
	20

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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 pre-and post-treatment data at specific time periods. The Kolmogorov-Smirnoff test will be used to determine the normality of variables. The background of the subjects will be tabulated by calculating the mean and standard deviation for continuous variables and the frequency and percentage for categorical variables. Analysis of variance will be used to analyze ordinal variables and those having nonnormal distributions (ANOVA). 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% confidence interval, and the Zie4 p-value.

Interim analyses {21b}

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

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- Methods for additional analyses (e.g., subgroup analyses) {20b}
- Subgroup analyses are not planned for this study.

- Methods in analysis to handle protocol non-adherence and any statistical methods
- to handle missing data {20c}

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406	After accounting for loss to follow-up and missing data in sample-size calculations.
407	Using a two-tailed t-test of difference between means with a power of 80% and a
408	significance level of 5%, we allowed for a dropout rate of 10%, using an additional 10%
409	to compensate for potential deviations of dry eye measures from the normal distribution.
410	
411	Plans to give access to the complete protocol, participant-level data, and statistical
412	code {31c}
413	The datasets analyzed during the current study and statistical code are available
414	from the corresponding author on reasonable request, as is the complete protocol.
415	
416	Oversight and monitoring
417	Composition of the coordinating center and trial steering committee {5d}
417 418	Composition of the coordinating center and trial steering committee {5d} The subject leader and the project manager will form the Steering Committee (SC).
418	The subject leader and the project manager will form the Steering Committee (SC).
418 419	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)
418 419 420	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
418 419 420 421	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 analyze the investigator's
418 419 420 421 422	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 analyze the investigator's adherence to the protocol, the protection of participants' rights and interests, the quality
418 419 420 421 422 423	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 analyze 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
418 419 420 421 422 423 424	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 analyze 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

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Due to the projected low frequency of adverse events 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 steering committee (SC) will have oversight and access to the trial under the supervision of the trial manager (TM) at any time during the study.

435 Adverse event reporting and harms {22}

Adverse events 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 judgment and give appropriate medical treatment. At the end of each examination, the doctor will evaluate eve 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 adverse events occur, HESH Certified Review Board will be notified; experimental treatments will be discontinued promptly, and appropriate therapies will be offered.

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Adverse events	Solutions
Visual discomfort	Standard operation

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	Eye irritation, conjunctival hyperemia, eye	No special treatment was required
	pain	relieve and subside within 1-3 days
	Periocular swelling	Resolve within a few hours
	6	
	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
	5 0	
	Allergy, abnormal sensation in the eye, etc.	Excluded and treatment
449	Table 3. Possible adverse events and solution	15
450		
450		
451	Frequency and plans for auditing trial con-	duct {23}
452	The study will be reviewed and evaluated	weekly by an independent supervisor not
453	related to the PI and sponsors.	
400	Tendred to the FF and sponsors.	
. – .		
454		
455	Plans for communicating significant protoc	ol amendments to relevant parties (e.g.,
456	trial participants, ethical committees) {25}	
	······ F········ F······· ······· · ······	
457	If there are modifications to aligibility of	ritaria autoomaa or analyzaa a raviaad
457	If there are modifications to eligibility c	interna, outcomes, or analyses, a revised
458	protocol will be submitted for approval to the	HESH Medical Ethics Committee.
459		
460	Dissemination plans {31a}	
404	The study is findings will be shound as some	lless of the official direction. All reasible
461	The study's findings will be shared regard	liess of the effect's direction. All possible
462	beneficiaries of the research, including patient	nts, caretakers, family, doctors, advisory
463	boards, and medical boards, will receive trial	data. Publications in high-impact. open-
464	accord medical insumals and talles at mating -1 -	nd international modical conferences
464	access medical journals and talks at national a	nu memational medical conferences will
465	serve this purpose.	
466		

467	Discu	ission

DQS stimulates P2Y2 receptors on the ocular surface, which enhances the secretion of water and secretory mucin from conjunctival tissue. At present, multi-center 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 [55]. These events will be assessed and mentored continually during the study and follow-up phase of the study. Literature review shows that intense pulsed light (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, sterilization, acariasis, and light regulation [56,57]. With respect to the adverse effects, the majority of studies have reported that participants didn't experience any significant negative effects, apart from temporary occurrences of erythema, edema, 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 [58]. 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

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> analysis of the mechanism of symptom improvement in the hope of providing clinicians with more treatment options. **Trial status** Recruitment began in August 2023, and the approximate date when recruitment will be completed is December 2023. Protocol version 2.0 was approved on December 2022. Abbreviations BCVA: Best-corrected visual acuity; DED: Dry eye disease; DQS; Diquafosol; HRT II: Heidelberg Retina Tomography II; IOP: Intraocular pressure; GCP: Good Clinical Practice; RCT: Randomized control trial; SOPs: Standard operating procedures; AEs: Adverse events; CRF: Case report form **Declarations** Acknowledgments The authors would like to express their appreciation for the effort of all personnel involved in this trial. Authors' contributions {31b} Conception and design of the research: JC, GQ, LL, YQ, HC, HH, YX, QZ, YW, LY, SM, JEM, LX, WH, SY, XH, and EEP; analysis and interpretation of the data: JC,

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2		
3 4 5	511	GQ, EEP; writing original draft preparation: JC; critical revision of the manuscript
6 7	512	(reviewing and editing): JC and EEP; supervision: XH, SY, and EEP.
8 9 10	513	
11 12	514	Funding statement {4}
13 14	515	This study was entirely funded and sponsored by He Eye Specialist Hospital,
15 16	516	Shenyang, China, which included study design, data collection, analysis, interpretation,
17 18 19	517	and manuscript writing. No support was received for the publication of this article.
20 21	518	
22 23	519	Availability of data and materials {29}
24 25 26	520	Any data required to support the protocol can be supplied on request.
20 27 28	521	
29 30	522	Ethics and dissemination {24}
31 32 33	523	The study was registered with the trial number NCT05694026 and was conducted
34 35	524	in compliance with the tenets of the Declaration of Helsinki and the Institutional
36 37	525	Review Board of the He Eye Specialist Hospital, Shenyang, China: IRB (2022)
38 39 40	526	K029.01. Documented informed consent was obtained from all participants in this
41 42	527	study. In the present study, all components with any individually identifiable
43 44	528	information have been removed from the dataset.
45 46 47	529	
47 48 49	530	Consent for publication {32}
50 51	531	Not applicable - no identifying images or other personal or clinical details of
52 53	532	participants are presented here or will be presented in reports of the trial results. The
54 55 56	533	participant information materials and informed consent form are available from the
57 58 59	534	corresponding author on request.

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536	Competing interests statement {28}			
537	The authors declare that they have no competing interests.			
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547 548	Figure legends			
549	Figure 1. Study flow chart			
550	Word count: 5374			
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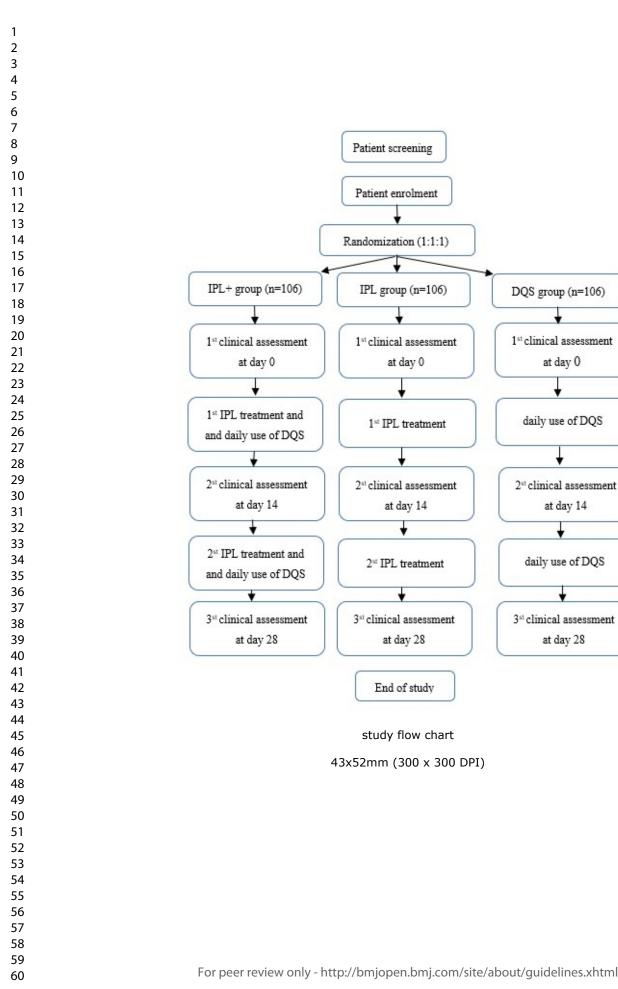
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CHECKLIST

Title: <u>Line 3</u>

Names protocol contributors: *Line 6*

Abstract: *Line 18*

• Introduction: <u>Line 19</u>

• Methods and analysis: *Line 23*

• Discussion: <u>Line 34</u>

Ethics and dissemination: *Line 38*

Keywords: <u>Line 43</u>

Administrative information: <u>Line 60</u>

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order of the items has been modified to group similar items (see <u>http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/</u>).

Title {1}: <u>line 60</u>	SPIRIT guidance: Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym.
Trial registration {2a and 2b}. <u>line 60</u>	SPIRIT guidance: Trial identifier and registry name. If not yet registered, name of intended registry.Item 2b is met if the register used for registration collects all items from the World Health Organization Trial Registration Data Set.
Protocol version {3} <i>line 60</i>	SPIRIT guidance: Date and version identifier.
Funding {4} <u>line 60</u>	SPIRIT guidance: Sources and types of financial, material, and other support.
Author details {5a} line 60	SPIRIT guidance: Affiliations of protocol contributors.
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Role of sponsor {5c} line 60	SPIRIT guidance: Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities.

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Competing interests {28}: *Line 536*

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

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Article Type:	Protocol
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12	4	to evaluate the safety and efficacy of intense pulsed light (IPL) combined with 3%
13		
14	5	diquafosol (DQS) ophthalmic solution in dry eye syndrome.
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16 17	•	
17 18	6	Names protocol contributors : Jiayan Chen ¹ , Guanghao Qin ¹ , Liangzhe Li ¹ , Yifan
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45	17	
46 47		
48	18	ABSTRACT
49	10	ADSTRACT
50		
51	19	Introduction: Evaporative dry eye (EDE) is common and can lead to ocular pain,
52		
53 54	20	decreased visual quality, and reduced quality of life. Intense pulsed light (IPL) and 3%
54 55		
56	21	diquafosol ophthalmic solution have been found to be beneficial in reducing signs and
57		
58	22	symptoms of dry eye.
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> Methods and analysis: A randomized clinical trial will be performed at He Eye Specialist Hospital in Shenyang. 360 DED patients will be randomly equally divided into the IPL group, DQS group (diquafosol ophthalmic solution eye drops), and IPL+ group (IPL combined with 3% diguafosol eve drops). All groups will be followed up for four weeks. The primary outcome measures will be the non-invasive tear break-up time (NIBUT) and the Ocular Surface Disease Index (OSDI) change from the baseline. The secondary outcome measures included the conjunctival and cornea staining (CFS) with fluorescein and lissamine, meibomian gland function and secretion quality, tear film lipid layer score (TFLL), tear meniscus height (TMH), conjunctival hyperemia (RS score) change from the baseline for improving ocular symptoms. Adverse events also will be monitored and documented.

> 34 Discussion: This study aimed to assess whether the combination of IPL with 3%
> 35 diquafosol ophthalmic solution (study group), IPL+ (study group), is more effective
> 36 than IPL (active control group) or DQS (active control group) in participants with
> 37 evaporative dry eye.

Ethics and dissemination: Registration number: Clniicaltrials.gov NCT05694026.
Name of the trial registry: Management of dry eye with Intense Pulsed Light combined
with 3% diquafosol ophthalmic solution, registered on Jan 10, 2023. Ethics approval
number: IRB (2022) K029.01. The study's findings will be shared regardless of the
effect's direction.

43 Keywords: Dry eye, intense pulsed light, diquafosol ophthalmic solution, RCT

44 Strengths and limitations of this study:

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Title $\{1\}$

and 2b

Funding {4}

Trial registration {2a

Protocol version {3}

Author details {5a}

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• The trial is des	signed to be embedded into routine clinical practice, providing more		
options for trea	options for treatment.		
• The protocol	promotes standardization of therapy, enabling credible inference		
aboutbenefits.			
• A large RCT h	has not been conducted to understand the benefits of DQS and IPL		
on DED patier	nts.		
• The trial's data	a collection at a single site are limitation of the research		
• The goal of the	nis research is limited to assessing just tear film changes and DED		
symptoms			
Administrative in	formation		
The numbers i	n curly brackets in this protocol refer to the SPIRIT checklist item		
numbers. The ord	er of the items has been modified to similar group items (see		
http://www.equator	r-network.org/reporting-guidelines/spirit-2013-statement-defining-		
standard-protocol-i	tems-for-clinical-trials/).		
le {1}	A protocol for a parallel assignment prospective, randomized, comparative trial to evaluate the safety and efficacy of intense pulsed light (IPL) combined with 3% diquafosol (DQS) ophthalmic solution in dry eye syndrome		
al registration {2a l 2b}	Registration number: Clniicaltrials.gov NCT05694026. Ethics approval number: IRB (2022) K029.01		
tocol version {3}	2023, version 2		
nding {4}	This study was entirely funded by He Eye Specialist Hospital,		
thor details {5a}	Shenyang, China.Jiayan Chen. He Eye Specialist Hospital, Shenyang, China.Quanghao Qin. He Eye Specialist Hospital, Shenyang, China.Liangzhe Li. He Eye Specialist Hospital, Shenyang, China.Yifan Qi. He Eye Specialist Hospital, Shenyang, China.		
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Role of sponsor {5c}	Investigator-initiated research
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1 INTRODUCTION	
2 Background and 1	rationale {6a}
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INTRODUCTION 61

62 **Background and rationale {6a}**

Evaporative dry eye (EDE) has been reported to be the most prevalent form of dry 63 eye disease (DED), [1-3] which is primarily caused by meibomian gland hypofunction 64 or meibomian gland dysfunction (MGD).[4-6] MGD can be chronic or diffused 65 anomaly of the meibomian glands, often characterized by terminal duct blockage and 66 qualitative/quantitative alterations in glandular secretion" b" the International 67 68 Workshop on MGD.[1,7] These glands are modified sebaceous glands that release Page 5 of 44

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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 ophthalmic sodium 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 randomized 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 (6 times/day)[21]. Intense pulsed light (IPL) is widely used to treat dermatological conditions[22], and its noncoherent 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 [30] et al. and Martínez-Hergueta [31] et al. have evaluated the safety and benefits of IPL therapy for improving signs of DED. [32–34] and combined it with

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other therapies such as heated eye mask (HEM) [35,36], 0.1% sodium hyaluronate eye
drops [27], and blood extract eye drops[37]. Therefore, an RCT is warranted to assess
the safety and efficacy of combining IPL with DQS for patients suffering from DED.

Objectives {7}

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

101 Trial design {8}

This is a prospective, randomized controlled trial 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 ClinicalTrails.gov (NCT05694026) using the SPIRIT reporting guidelines[38]. Randomization will be performed using web-based. online. sealed envelope-based а system (https://www.sealedenvelope.com). Specific study information sheets will be provided to patients prior to taking consent. Following a dedicated screening and randomization visit for eligible patients, participants will be randomized to one of three trial arms.

111 Methods: Participants, interventions, and outcomes

112 Study setting {9}

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2		
3 4 5	113	This study will be conducted between Mar 1, 2023, and Nov 30, 2023. Participants
6 7	114	will be recruited at the Department of Ophthalmology, He Eye Specialist Hospital
8 9 10	115	(HESH).
11 12 12	116	
13 14 15	117	Patient and Public Involvement
16 17 18	118	Patients and the public will not be involved in the design, implementation,
19 20	119	reporting, or dissemination plans of this study.
21 22 23	120	
24 25 26	121	Eligibility criteria {10}
27 28	122	Inclusion criteria:
29 30 31	123	1. Age ≥18 years
32 33	124	2. Consenting participants.
34 35 36	125	3. Able and willing to comply with the treatment/follow-up schedule.
37 38 39	126	4. Bilateral signs and symptoms of dry eye disease: (i) Ocular Surface Disease Index
40 41	127	(OSDI) questionnaire \geq 13, (ii) Non-invasive tear break-up (NITBUT) \leq 5 seconds,
42 43 44	128	(iii) conjunctival staining score (CS) \geq 3 points. The presence of two or more criteria
45 46	129	was used to establish a positive DE diagnosis based on the 2016 Asia Dry Eye
47 48 49	130	Society criteria.
50 51	131	Exclusion criteria:
52 53 54	132	1. A recent history (past 30 days) of topical ophthalmic medication use, including
55 56 57	133	antibiotics, steroids, non-steroidal anti-inflammatory drugs, or required the chronic
57 58 59 60	134	use of topical ophthalmic medications.

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3 4 5	135	2. Eyelids or intraocular tumors.
6 7	136	3. Active allergy or infection, or inflammatory disease may prevent the subjects from
8 9 10	137	completing the study at the ocular surface.
11 12 13	138	4. Any structural changes in the lacrimal passage.
14 15	139	5. Glaucoma.
16 17 18	140	6. Diabetes or other systemic, dermatologic, or neurologic diseases that affect the
19 20 21	141	health of the ocular surface.
22 23	142	7. Use of any systemic anti-inflammatory drugs or medication that may interfere with
24 25 26	143	tear production, such as antianxiety, anti-depressive, and antihistamine medications,
27 28	144	within three months.
29 30 31	145	8. Pregnant or breastfeeding.
32 33 34	146	9. Contact lenses wearers.
35 36	147	
37 38 39	148	Informed consent {26a}
40 41	149	Trained and experienced clinicians will seek informed permission from prospective
42 43 44	150	participants.
45 46 47	151	
48 49	152	Additional consent provisions for collection and use of participant data and
50 51 52	153	biological specimens {26b}
53 54	154	This trial does not involve collecting biological specimens.
55 56 57	155	
58 59 60	156	Interventions

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157	The explanation for the choice of comparators {6b}
158	After enrollment in the study, treatments will be initiated immediately after
159	randomization. Participants in the DQS group and IPL+ group will use one drop of 3%
160	DQS (Diquas; Santen Pharmaceutical Co., Ltd., Osaka, Japan) 6 times per day for four
161	weeks (28 days), whereas participants in the IPL+ group and IPL group will undergo
162	two IPL treatment sessions of M22 (Lumenis Ltd., Yokneam, Israel) IPL system, two
163	weeks apart. IPL treatment utilizes a noncoherent polychromatic light source with a
164	wavelength spectrum of 500–1200 nm on the cutaneous facial sebaceous glands.
165	
166	Intervention description {11a}
167	In this study, patients receive either DQS, IPL, or IPL combined with DQS for
168	four weeks based on the group they are placed in. Two follow-up visits were performed
169	at week two and week 4 in all groups; comprehensive eye exams will be conducted by
170	an ophthalmologist, including primary outcomes, secondary outcomes, and safety
171	evaluation.
172	
173	Criteria for discontinuing or modifying allocated interventions {11b}
174	If dry eye signs and symptoms worsen, participants will be stopped and advised to
175	use the designated device. Adverse events (AE) will be continuously monitored. In case
176	of an AE, participants will be informed about the severity of the event, and PI will
177	decide if participants can continue further. If participants consent and agree, they will
178	be reminded daily regarding the administration of eye drops, recording their exposure
	9

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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 {11c} 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 {11d} 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 {30}** 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 center for further treatment. **Outcomes {12}** All patients will be assessed at baseline, 14, and 28 days. We plan to use primary

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and secondary outcomes measures, symptoms, and corneal and meibomian glandimprovement will be compared between the three groups.

204 Primary Outcome

Ocular Surface Disease Index (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 (N/A)' 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 dry eye disease symptoms [40,41].

Non-invasive tear break-up (NIBUT): The Keratograph 5M (Oculus, Germany)
topographer will assess non-invasive initial tear film 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].

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218 Secondary outcomes

Fluorescein and lissamine conjunctival and cornea staining (CFS): Fluorescein and lissamine staining 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].

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> Tear meniscus height (TMH): Non-invasive first tear film break-up using the Keratograph 5M (Oculus, Germany) topographer will be measured three times consecutively, and the median value was recorded[42,46].

Conjunctival hyperemia (RS score): Conjunctival hyperemia (RS score) will be
assessed by Keratograph image (Oculus, Germany) of 1156*873 pixels, redness score
(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-lamp[48]: Five meibomian glands in the middle parts of the eyelid will be evaluated using a scale of 0 to 3 for each gland (0 represented clear meibum; 1 represented cloudy meibum; 2 represented cloudy and granular meibum; and three means thick, toothpaste-like consistency meibum)[49,50].

Tear Film Lipid Layer Score (TFLL): The interferometry patterns will be assessed
using DR-1 (Kowa, Nagoya, Japan). The results will be graded as follows: grade 1,
somewhat gray color, uniform distribution; grade 2, rather gray color, nonuniform
distribution; grade 3, a few colors, nonuniform distribution; grade 4, many colors,
nonuniform distribution; grade 5, corneal surface partially exposed [51–53].

Participant timeline {13}

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 four weeks.
Furthermore, the effect will be examined during the 2-week follow-up period of 4

245 v	veeks (Figure 1).
-------	-------------------

Sample size {14} 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 to 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 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 standard deviation 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 standard deviation 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. With the inclusion of the multidose treatment groups and a dropout rate of 8%, it

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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 utilize 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

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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 summarized.

271 Recruitment {15}

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 He Eye Specialist Hospital'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, gender, or ethnicity (Table 2).

Items	Baseline	2w	4 w
Informed consent	V		
Patient background	\checkmark		
Ocular Surface Disease Index (OSDI) scores	\checkmark	\checkmark	
IOP		\checkmark	
BCVA	\checkmark	\checkmark	
Non-invasive tear break-up (NIBUT)	\checkmark		
conjunctival and cornea staining (CFS)	\checkmark	\checkmark	

	Toor Film Linid Los	uor Sooro (TE	11)				
	Tear Film Lipid Lay		LLJ		N	N	
	Corneal endothelial	cells					
	Tear meniscus heigl	ht (TMH)			\checkmark	\checkmark	
	Conjunctival hypere	emia (RS scor	re)		\checkmark	\checkmark	
	Meibomian gland fu	unction			\checkmark	\checkmark	
	Meibomian secretio	n quality			\checkmark	\checkmark	
	Adverse event (AE)					\checkmark	
281	√: All groups						
200	Patient background, i			1		1 11	
28Z	i anom background, i	including date	e of birth, gene	uer, race,	ethnicity,	and allerg	gy hi
				der, race,	ethnicity,	, and allerg	gy hi
283	Table 1. Schedule for			uer, race,	ethnicity,	, and allers	gy hi
282 283 284				der, race,	ethnicity,	, and allers	gy hi
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[IPL+DQS]			•			
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ASSESSMENTS:						
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outcome]	C					
[The second	C		×	×	×	×
outcome]		6				

Table 2. The schedule of enrolment, interventions, and assessments of this trial .0.Z.(

Assignment of interventions: Allocation

Sequence generation {16a}

A web-based randomization application will be used (https://www.project-redcap. org/). Randomization will be by simple randomization. Allocation will be carried out using block randomization 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.

296 Concealment mechanism {16b}

The block size will be concealed from other researchers, and the randomization table will not be available for assessment by anyone else involved in the study [54]. Randomization is performed by an independent biostatistician. The biostatistician is the only one who has access to check the file. The allocation list is kept in a separate file on a different computer.

Implementation {16c}

Random allocation will be conducted after the enrolment. Random numbers with corresponding participants will be determined in the order of the time of the 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 analyzing data related to this trial will be blinded to the participant allocation results. Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

311 Assignment of interventions:

312 Blinding {17a}

The treatment assignment for the study will be triple-masked. Participants in the research would be unable to recognize 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

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318	IPL treatment with 12 homogeneously spaced pulsed light to both eyes and a sham
319	treatment to both eyes. The box containing ampoules will be labeled with a batch
320	number, including the study reference number, participant ID, contact number,
321	investigator name, site address, the expiration date of the eye drops, storage instructions,
322	and a statement informing the participant that the eye drops are for use only in clinical
323	trials and should not be ingested. The circumstances and procedures under which
324	unblinding is permissible will be determined and performed by the PI.
325	
326	Procedure for unblinding if needed {17b}
327	The PI will determine and perform the circumstances and procedures under which
328	unblinding is permissible.
329	Participant withdrawal
330	Based on the following criteria, patients will be removed from the research.
331	1. When it is deemed challenging to continue the study owing to the emergence of
332	new ailments.
333	2. When the research participant cannot be located.
334	3. In the case of pregnancy or pregnancy suspicion.
335	4. When participants or their legal guardians want to end their participation in a
336	study.
337	5. When the participant's caretaker cannot guarantee their participation in the study.
338	6. When the research project is concluded.
339	7. When the lead investigator and sub-investigators believe that it is acceptable to
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cease the study for reasons other than those listed above. **Data collection and management** Plans for assessment and collection of outcomes {18a} Data administration is the responsibility of Jiayan Chen, HESH, Department of Clinical Research, as chosen by the principal investigator (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 on the implementation and the status of data management will be compiled and sent to the PI with the locked research data.

353 Plans to promote participant retention and complete follow-up {18b}

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 prioritize 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 selfassessment questionnaires online. Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

360 Data will be gathered during pre-randomization, termination, and follow-up361 periods at four and eight weeks. The method of data collection for this study will

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> 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 {19}

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 (elie quality.

Confidentiality {27}

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 {33}
- Not Applicable-There will be no biological specimens collected.

- **Statistical methods**
- Statistical methods for primary and secondary outcomes {20a}

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The software Statistical Analysis in Social Sciences (SPSS, version 26, IBM Corp) for MacOS software will be used to analyze 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 pre-and post-treatment data at specific time periods. The Kolmogorov-Smirnoff test will be used to determine the normality of variables. The background of the subjects will be tabulated by calculating the mean and standard deviation for continuous variables and the frequency and percentage for categorical variables. Analysis of variance will be used to analyze ordinal variables and those having nonnormal distributions (ANOVA). 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% confidence interval, and the p-value.

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400 Interim analyses {21b}

401 Not applicable- no anticipated problems are detrimental to the participant, so402 interim analysis is not warranted.

404 Methods for additional analyses (e.g., subgroup analyses) {20b}

405 Subgroup analyses are not planned for this study.

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407	Methods in analysis to handle protocol non-adherence and any statistical methods
408	to handle missing data {20c}
409	After accounting for loss to follow-up and missing data in sample-size calculations.
410	Using a two-tailed t-test of difference between means with a power of 80% and a
411	significance level of 5%, we allowed for a dropout rate of 10%, using an additional 10%
412	to compensate for potential deviations of dry eye measures from the normal distribution.
413	
414	Plans to give access to the complete protocol, participant-level data, and statistical
415	code {31c}
416	The datasets analyzed during the current study and statistical code are available
417	from the corresponding author on reasonable request, as is the complete protocol.
418	
419	Oversight and monitoring
420	Composition of the coordinating center and trial steering committee {5d}
421	The subject leader and the project manager will form the Steering Committee (SC).
422	The SC is accountable for managing the whole project. The Monitor Group's (MG)
423	inspectors are appointed by the SC. The MG will oversee the entire research procedure
424	in compliance with the GCP requirements. The inspector will analyze the investigator's
425	adherence to the protocol, the protection of participants' rights and interests, the quality
426	of the CRF form, and the investigators' understanding of different standards before
427	submitting inspection reports to the SC.

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2 3		
4 5	428	
6 7	429	Composition of the data monitoring committee, its role and reporting structure
8 9 10	430	{ 21 a}
11 12 13	431	Due to the projected low frequency of adverse events and the modest numbers in
14 15 16	432	each location, no data monitoring committee has been convened for this trial. The
17 18	433	database will be constructed using Excel (Microsoft, USA 2022 version), and regular
19 20 21	434	data monitoring will be undertaken in accordance with the sponsor's standard operating
22 23 24	435	procedures. The steering committee (SC) will have oversight and access to the trial
25 26	436	under the supervision of the trial manager (TM) at any time during the study.
27 28 29	437	
30 31 32	438	Adverse event reporting and harms {22}
33 34	439	Adverse events are unanticipated indications, symptoms, or illnesses seen during a
35 36 37	440	clinical study, regardless of their relationship to the treatment. There may be local,
38 39 40	441	general, and psychological unwanted effects (Table 3). If any discomfort or new
41 42	442	changes in condition during the study period, or any unexpected situation, whether
43 44 45	443	related to the study or not, one should promptly notify the doctor, who will make a
46 47	444	judgment and give appropriate medical treatment. At the end of each examination, the
48 49 50	445	doctor will evaluate eye health status according to the examination results. If the
51 52 53	446	condition deteriorates or is no longer suitable for the study, the study may be terminated
54 55	447	early. At the same time, the doctor will provide other treatment options that are more
56 57 58	448	suitable for the current situation to ensure health to the greatest extent. If major adverse
59 60	449	events occur, HESH Certified Review Board will be notified; experimental treatments

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450 will be discontinued promptly, and appropriate therapies will be offered.

verse events ual discomfort irritation, conjunctival hyperemia, eye ocular swelling ish-purple bruise (purpura)	Solutions Standard operation No special treatment was required, relieve and subside within 1-3 days Resolve within a few hours	
irritation, conjunctival hyperemia, eye ocular swelling ish-purple bruise (purpura)	No special treatment was required, relieve and subside within 1-3 days Resolve within a few hours	
n locular swelling ish-purple bruise (purpura)	relieve and subside within 1-3 days Resolve within a few hours	
ocular swelling ish-purple bruise (purpura)	Resolve within a few hours	
ish-purple bruise (purpura)		
	Rare cases may last from five to fifteen days; no special treatment is required	
skin around the eye becomes sensitive fragile	Avoiding makeup and rubbing	
n injury occurs	In rare cases, follow instructions	
ergy, abnormal sensation in the eye, etc.	Excluded and treatment	
e 3. Possible adverse events and solutions	S	
uency and plans for auditing trial conc	luct {23}	
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 (e.g.,		
trial participants, ethical committees) {25}		
If there are modifications to eligibility criteria, outcomes, or analyses, a revised		
protocol will be submitted for approval to the HESH Medical Ethics Committee.		
mination plane (21.)		
emination plans {31a}	less of the effect's direction. All possible	
Fhe study's findings will be shared regard	-	
2	nts, caretakers, family, doctors, advisory	
	-	

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470 Discussion

DQS stimulates P2Y2 receptors on the ocular surface, which enhances the secretion of water and secretory mucin from conjunctival tissue. At present, multi-center 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 [55]. These events will be assessed and mentored continually during the study and follow-up phase of the study. Literature review shows that intense pulsed light (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, sterilization, acariasis, and light regulation [56,57]. With respect to the adverse effects, the majority of studies have reported that participants didn't experience any significant negative effects, apart from temporary occurrences of erythema, edema, 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 [58]. Potential corneal and/or retinal toxicity will be assessed and

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489	monitored continuously. Therefore, this study aims to assess the effectiveness of the
490	combination of IPL with 3% DQS ophthalmic solution, providing more options for
491	treatment. In future studies, we will further expand the sample size and conduct a deeper
492	analysis of the mechanism of symptom improvement in the hope of providing clinicians
493	with more treatment options.
494	
495	Trial status
496	Recruitment began in August 2023, and the approximate date when recruitment
497	will be completed is December 2023. Protocol version 2.0 was approved on December
498	2022.
499	
500	Abbreviations
500 501	Abbreviations BCVA: Best-corrected visual acuity; DED: Dry eye disease; DQS; Diquafosol;
501	BCVA: Best-corrected visual acuity; DED: Dry eye disease; DQS; Diquafosol;
501 502	BCVA: Best-corrected visual acuity; DED: Dry eye disease; DQS; Diquafosol; HRT II: Heidelberg Retina Tomography II; IOP: Intraocular pressure; GCP: Good
501 502 503	BCVA: Best-corrected visual acuity; DED: Dry eye disease; DQS; Diquafosol; HRT II: Heidelberg Retina Tomography II; IOP: Intraocular pressure; GCP: Good Clinical Practice; RCT: Randomized control trial; SOPs: Standard operating procedures;
501 502 503 504	BCVA: Best-corrected visual acuity; DED: Dry eye disease; DQS; Diquafosol; HRT II: Heidelberg Retina Tomography II; IOP: Intraocular pressure; GCP: Good Clinical Practice; RCT: Randomized control trial; SOPs: Standard operating procedures;
501 502 503 504 505	BCVA: Best-corrected visual acuity; DED: Dry eye disease; DQS; Diquafosol; HRT II: Heidelberg Retina Tomography II; IOP: Intraocular pressure; GCP: Good Clinical Practice; RCT: Randomized control trial; SOPs: Standard operating procedures; AEs: Adverse events; CRF: Case report form
501 502 503 504 505 506	BCVA: Best-corrected visual acuity; DED: Dry eye disease; DQS; Diquafosol; HRT II: Heidelberg Retina Tomography II; IOP: Intraocular pressure; GCP: Good Clinical Practice; RCT: Randomized control trial; SOPs: Standard operating procedures; AEs: Adverse events; CRF: Case report form Declarations
501 502 503 504 505 506 507	BCVA: Best-corrected visual acuity; DED: Dry eye disease; DQS; Diquafosol; HRT II: Heidelberg Retina Tomography II; IOP: Intraocular pressure; GCP: Good Clinical Practice; RCT: Randomized control trial; SOPs: Standard operating procedures; AEs: Adverse events; CRF: Case report form Declarations Acknowledgments

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2 3 4 5	511	Authors' contributions {31b}
6 7	512	Conception and design of the research: JC, GQ, LL, YQ, HC, HH, YX, QZ, YW,
8 9 10	513	LY, SM, JEM, LX, WH, SY, XH, and EEP; analysis and interpretation of the data: JC,
11 12 13	514	GQ, EEP; writing original draft preparation: JC; critical revision of the manuscript
14 15	515	(reviewing and editing): JC and EEP; supervision: XH, SY, and EEP.
16 17	516	
18 19	517	Funding statement {4}
20 21 22	518	This study was entirely funded and sponsored by He Eye Specialist Hospital,
23 24	519	Shenyang, China, which included study design, data collection, analysis, interpretation,
25 26 27	520	and manuscript writing. No support was received for the publication of this article.
28 29	521	
30 31	522	Availability of data and materials {29}
32 33	523	Any data required to support the protocol can be supplied on request.
34 35 36	524	
37 38	525	Ethics and dissemination {24}
39 40	526	The study was registered with the trial number NCT05694026 and was conducted
41 42 43	527	in compliance with the tenets of the Declaration of Helsinki and the Institutional
44 45	528	Review Board of the He Eye Specialist Hospital, Shenyang, China: IRB (2022)
46 47	529	K029.01. Documented informed consent was obtained from all participants in this
48 49 50	530	study. In the present study, all components with any individually identifiable
50 51 52	531	information have been removed from the dataset.
53 54 55	532	
56 57	533	Consent for publication {32}
58 59 60	534	Not applicable - no identifying images or other personal or clinical details of

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3 4	535	participants are presented here or will be presented in reports of the tria	al results. The		
5 6	536	participant information materials and informed consent form are avail	able from the		
7 8 9	537	corresponding author on request.			
10 11	538				
12 13 14	539	Competing interests statement {28}			
14 15 16	540	The authors declare that they have no competing interests.			
17 18	541				
19 20	542	Authors' information			
21					
22 23 24	543	1 He Eye Specialist Hospital, Shenyang, China.			
25 26	544	2 Tianjin Medical University, Tianjin, China.			
27 28	545	3 China Medical University, Shenyang, China.			
29 30 31	546	4 Wenzhou Medical University, Wenzhou, China.			
32 33	547	5 Queens University Belfast, United Kingdom.			
34 35 36	548	6 Cathedral Eye Clinic, Belfast, United Kingdom.			
37 38 39	549	7 He University, Shenyang, China.			
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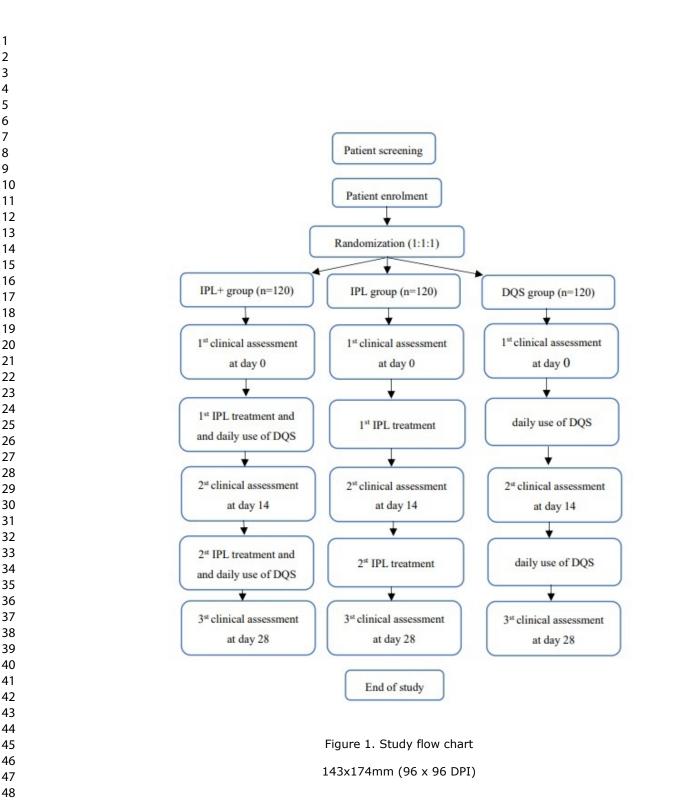
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ltem No	Description
Administrative in	format	ion
Title	1 <mark>Page 1</mark>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a <mark>Page 2</mark>	Trial identifier and registry name. If not yet registered, name of intended registry
	2b <mark>Page 2</mark>	All items from the World Health Organization Trial Registration Data Set
Protocol version	3 <mark>Page 3</mark>	Date and version identifier
Funding	4 <mark>Page 3</mark>	Sources and types of financial, material, and other support
Roles and responsibilities	5a <mark>Page 4</mark>	Names, affiliations, and roles of protocol contributors
	5b <mark>Page 4</mark>	Name and contact information for the trial sponsor
	5c <mark>Page 4</mark>	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d <mark>Page</mark> 22	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a <mark>Page 4</mark>	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b <mark>Page 8</mark>	Explanation for choice of comparators

Objectives	7 <mark>Page 6</mark>	Specific objectives or hypotheses
Trial design	8 <mark>Page 6</mark>	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (e superiority, equivalence, noninferiority, exploratory)
Methods: Particip	oants, i	nterventions, and outcomes
Study setting	9 <mark>Page 7</mark>	Description of study settings (eg, community clinic, academic hospit and list of countries where data will be collected. Reference to wher list of study sites can be obtained
Eligibility criteria	10 <mark>Page 7</mark>	Inclusion and exclusion criteria for participants. If applicable, eligibil criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a <mark>Page 9</mark>	Interventions for each group with sufficient detail to allow replication including how and when they will be administered
	11b <mark>Page 9</mark>	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c <mark>Page</mark> 10	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d Page 10	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12 Page 10	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy ar harm outcomes is strongly recommended
Participant timeline	13 <mark>Page</mark> 12	Time schedule of enrolment, interventions (including any run-ins an washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14 <mark>Page</mark> 13	Estimated number of participants needed to achieve study objective and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15 <mark>Page</mark> 14	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a Page 16	Method of generating the allocation sequence (eg, computer- generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b <mark>Page</mark> 16	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c Page <mark>17</mark>	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a ^{Page} 17	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b Page 18	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data co	llectio	n, management, and analysis
Data collection methods	18a Page 19	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b Page 19	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19 <mark>Page</mark> 20	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a <mark>Page</mark> 20	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol

	20b Page 21	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c Page 22	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitor	ing	
Data monitoring	21a Page 22	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b ^{Page} 21	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22 Page <mark>23</mark>	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23 Page <mark>24</mark>	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissen	ninatio	n
Research ethics approval	24 <mark>Page</mark> 27	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25 <mark>Page</mark> 24	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a <mark>Page 8</mark>	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b <mark>Page 8</mark>	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27 Page <mark>20</mark>	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28 Page <mark>28</mark>	Financial and other competing interests for principal investigators for the overall trial and each study site

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Access to data	29 <mark>Page</mark> 27	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30 <mark>Page</mark> 10	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a <mark>Page</mark> 24	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevan groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b <mark>Page</mark> 26	Authorship eligibility guidelines and any intended use of professiona writers
	31c Page 22	Plans, if any, for granting public access to the full protocol, participa level dataset, and statistical code
Appendices		
Informed consent materials	32 <mark>Page</mark> 27	Model consent form and other related documentation given to participants and authorised surrogates
Biological	33 <mark>Page</mark>	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and future use in ancillary studies, if applicable

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