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Evaluating the efficacy and safety of transdermal electrical stimulation on the visual functions of patients with retinitis pigmentosa: a clinical trial protocol for a prospective, multicentre, randomised, double-masked and sham-controlled design (ePICO trial)

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ABSTRACT

Introduction Previously, we conducted a clinical trial to evaluate the safety and efficacy of transdermal electrical stimulation (TdES) with skin electrodes to improve the visual functions in patients with retinitis pigmentosa (RP). No adverse events were related to the treatment during follow-up examinations, and TdES significantly improved the mean visual acuity and visual field sensitivity.

Methods and analysis We developed a study protocol for a prospective, multicentre, randomised, double-masked and sham-controlled clinical trial, planned to commence on June 2021. We intend to compare the maintenance or improvement in best-corrected visual acuity, and safety of TdES using skin electrodes between patients with RP and the sham group. The primary endpoint comprises the superiority of the logarithm of the minimum angle of resolution (logMAR) visual acuity change at week 24 from baseline in the treatment and sham groups. Secondary endpoints involve the comparison of the treatment and sham groups at week 24 for the logMAR visual acuity, early treatment diabetic retinopathy study visual acuity, the mean deviation value of Humphrey field analyser 10-2, monocular Humphrey Esterman visual field test score, ellipsoid zone length, central foveal thickness and 25-item National Eye Institute Visual Function Questionnaire score. We intend to enrol 50 patients from three Japanese institutions within 1 year and follow them up for 1 years.

Ethics and dissemination The protocol was approved by the institutional review board at the Chiba University Hospital and two other institutions, and was registered with the Japan Registry of Clinical Trials on 17 May 2021. The trial will be conducted in accordance with the principles of the Declaration of Helsinki, and is in accordance with Good Clinical Practice standards. The findings will be published in a peer-reviewed journal.

Trial registration number JRCT2032210094.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first multicentre, randomised, sham-controlled and double-masked trial aimed at verifying the maintenance or improvement in best-corrected visual acuity, and safety of transdermal electrical stimulation (TdES) using skin electrodes in patients with retinitis pigmentosa (RP).

⇒ We intend to use a less invasive and easily applicable electrical stimulator with skin electrodes, and no serious adverse events were observed in our previous study using this device.

⇒ A multicentre (three university hospitals), double-masked, sham-controlled and randomised controlled trial is the optimal study design for verifying the effectiveness of TdES.

⇒ Despite fewer patients owing to the rare occurrence of RP, the necessary sample size is estimated to comprise 50 patients based on previous study data. Second limitation is that the ideal regimen of electrical stimulation in not yet known.

INTRODUCTION

Spontaneous afferent electrical activity reportedly regulates target cell death in the developing rat visual system.[1] Short periods of low-frequency electrical stimulation accelerate the axonal regeneration of peripheral neurons.[2] Morimoto *et al* reported on significantly higher survival rate of rat retinal ganglion cells (RGCs) following optic nerve transection in rats whose optic nerves were electrically stimulated than those of the untreated group.[3] Moreover, electrical stimulation exerted a neuroprotective effect on RGCs, followed by the development of

a transcorneal electrical stimulation (TcES) device that could be used in humans.[4] Animal models of retinitis pigmentosa (RP), including rats and rabbits,[5–7] and clinical studies on patients with RP mentioned that TcES can protect retinal photoreceptors. Moreover, TcES improves the visual acuity, visual fields and electroretinograms.[8 9] Therefore, recommendation is proposed for TcES use in the treatment of RP, especially in Europe.[10] Previous TcES studies used the contact lens type or Dawson-Trick-Litzkow fiber-type corneal electrodes, and reported on an association between TcES sessions and dry eye symptoms.[11] As another attempt to establish electrical stimulation as a treatment for RP, Jackson et al reported about the safety and efficacy of intravitreal quantum dots for RP and showed that no adverse reactions were attributed to the quantum dots, and the average vision of treated eyes improved.[12]

Based on this information, we previously conducted a prospective, non-randomised, open-label, uncontrolled clinical trial with 20 eyes of 10 RP patients to evaluate the safety and efficacy of transdermal electrical stimulation (TdES) on the visual function. That was a 12-week trial consisting of six TdES treatments every 2 weeks.[13] We used a prototype equipment with a patch containing an electrode applied to the skin. Electric stimulation was delivered through the skin, developed jointly with the Mayo. No adverse events (AEs) were reported during the follow-up examinations, and the mean logarithm of the minimum angle of resolution (logMAR), Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity, and the mean deviation of the Humphrey field analyser (HFA) 10-2 significantly improved post-TdES. Therefore, we planned a prospective, multi-centre, randomised, double-masked and sham-controlled clinical trial to compare the maintenance or improvement in best-corrected visual acuity (BCVA), and safety of TdES using skin electrodes between patients with RP and the sham group. The trial protocol was approved in May 2021 by the Pharmaceuticals and Medical Devices Agency (PMDA), Japan, and the trial was initiated in June 2021. Approval was obtained from the institutional review board (IRB) prior to patient recruitment at each institution.

METHODS AND ANALYSIS
Objectives
We aimed to verify the long-term efficacy and safety of TdES with a skin electrode as a novel treatment for patients with RP. Furthermore, we intended to investigate the long-term course and safety following the discontinuation of TdES.

Trial design
We proposed a prospective, multicentre, randomised, double-masked and sham-controlled clinical trial. The original protocol and informed consent forms written in Japanese are provided in online supplemental appendices 1 and 2, and this protocol meets the criteria of the Standard Protocol Items: Recommendations for Interventional Trials 2013 statement. The trial was conceived and initiated at the Chiba University Hospital and will be conducted across three institutions (Chiba University Hospital, Kobe University Hospital, and Nagoya City University Hospital) in Japan. Patients were randomly assigned to receive either TdES (intervention) or sham (control), immediately before treatment (details below).

Figure 1 illustrates the study design. This study consists of three periods, namely preobservation, treatment and postobservation. After obtaining informed consent, patients were randomly assigned 1:1 to the TdES and sham groups. The permissible range for the preobservation period is 4 weeks. TdES will be performed 12 times. The primary and secondary endpoints will be evaluated at week 24. In contrast, the exploratory endpoints will be evaluated at weeks 36 and 48. Table 1 lists all schedules for each period to be performed in this study.

In this trial, FUJITSU Life Science Solution tsClinical DDworks NX, which is a clinical trial work support system is used for communicating important protocol modifications to relevant parties.

Primary endpoint
The primary endpoint comprises the superiority of the logMAR visual acuity in the change from baseline at week 24 in the TdES group, compared with the sham group.

Secondary endpoints
The secondary endpoints include a comparison of the TdES and sham groups at baseline to week 24 for the logMAR visual acuity, ETDRS visual acuity, the mean deviation (MD) value of HFA 10-2 (dB), monocular Humphrey Esterman visual field test score, ellipsoid zone length (μm), central foveal thickness (μm) and compo 9 score of the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) (details below).
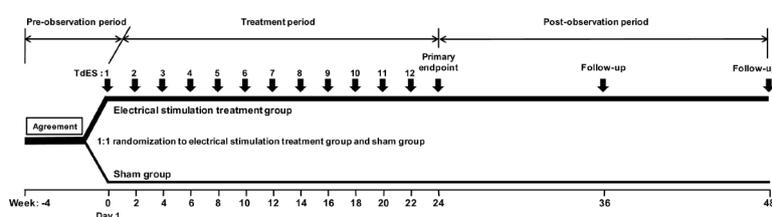

Figure 1 Trial design. TdES, transdermal electrical stimulation.

Table 1 Treatment and examination schedule

Visit	Preobservation	Treatment													Postobservation		Drop-out
Week	1	0	2	4	6	8	10	12	14	16	18	20	22	24	36	48	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Allowable range (days)	0–31	0	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±14	±14	+7
Informed consent	●																
Registration/randomisation		●															
Patient information	●																
TdES		●	●	●	●	●	●	●	●	●	●	●	●				●
Subjective symptoms review	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Blood pressure measurement		○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Blood test	●																○
logMAR VA	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
ETDRS VA	●	●						●						●	●	●	●
HFA 10–2	●							●								●	●
HFA esterman	●							●						●		●	●
OCT	●							●	●					●	●	●	●
NEI VFQ-25	●							●						●		●	●
Slit lamp microscopy	●				●			●						●	●	●	●
IOP/fds	●				●			●						●	●	●	●
Pregnancy test	●																○
Adverse event observation	◄───►																

Black circles are items that must be performed. White circles are items to be performed only when the investigator deems it necessary.

ETDRS, Early Treatment Diabetic Retinopathy Study; fds, fundus examination; HFA, Humphrey field analyser; IOP, intraocular pressure; LogMAR, logarithm of the minimum angle of resolution; NEI VFQ-25, 25-item National Eye Institute Visual Function Questionnaire; OCT, optical coherence tomography; TdES, transdermal electrical stimulation; VA, visual acuity.

Exploratory endpoints

The exploratory endpoints comprised a comparison of the TdES and sham groups at weeks 36 and 48 for items of the secondary endpoints.

Safety endpoints

We intend to evaluate the number and rate of AEs while analysing the safety endpoints. In addition to the evaluation of possible keratitis, dermatitis, anterior segment, optic media and fundus, we will determine the effects on the facial and trigeminal nerves during the scheduled visit. Moreover, the patients will undergo safety assessment by optical coherence tomography (OCT). All AEs are coded in MedDRA (vas.6.0) and recorded.

Outcome measures

The BCVA was measured monocularly using a Japanese standard Landolt ring chart (System Charts SC-2000 Nidek Instruments, Gamagori, Japan) at 3 m. Decimal visual acuities were converted to logMAR units using the formula logMAR = -log (decimal acuity)[14] for statistical analyses. Furthermore, we assessed the BCVA using the ETDRS chart (CSV-1000LanC VectorVision, Ohio, USA) at a distance of 2.5 m. The luminance for the tests was 85 cd/m^2, which is recommended for vision testing by the US National Academy of Sciences. It has been adopted by the FDA as the required testing light level for clinical trials. Refraction measurement was done every time visual acuity measurements.

The MD of retinal sensitivity was determined by the HFA III (Model 850; Carl Zeiss Meditec, Dublin, California, USA) using the Swedish Interactive Threshold Algorithm Standard 10-2 protocol. We also analysed monocular Humphrey Esterman visual field test scores. Visual acuity, visual field and OCT tests were all performed by a certified orthoptist. We requested the patients to respond to the Japanese version of the NEI VFQ-25[15] to evaluate their subjective symptoms and the quality of life. The NEI VFQ-25 consists of 25 questions that address 12 aspects of daily living as follows: general health, general vision, near vision, distance vision, driving, peripheral vision, colour vision, ocular pain, role limitation, dependency, social function, and mental health. Compo 9 comprehensively evaluates nine aspects (general vision, near vision, distance vision, peripheral vision, colour vision, role limitation, dependency, social function and mental health), and was analysed in this study. VFQ-25 is self-administered and was answered by the patients themselves. The primary outcome was the only protected comparison in this trial.

Eligibility criteria

Those who met all of the following inclusion criteria and did not have any listed exclusion criteria were considered eligible:

Inclusion criteria

1. Clinically diagnosed with typical RP, with age ≥20 years and ≤80 years.
2. HFA 10-2 performed twice within 6 months with a reliability fixation defect rate <20%, false positive rate <15%, false negative rate <33% and a difference in the mean centre four points of retinal sensitivity within 5 dB; both values were <30 dB.
3. Decimal visual acuity ranging from 0.1 to 0.7 during screening.
4. HFA 10-2 MD values up to −10 dB.
5. Provided written informed consent with a sufficient understanding of the responsibilities of participating in this trial.
6. Regular hospital visits every 2 weeks for 6 months and follow-up at 36 and 48 weeks.
7. Could adopt appropriate contraceptive measures during the trial period.

Exclusion criteria

1. Patients with a history of electrical stimulation treatment for ocular diseases.
2. Underwent intraocular surgery within 3 months of beginning this trial.
3. Modified the dose and usage of isopropyl unoprostone,[16] calcium antagonist and helenien within 31 days before the screening examination.
4. A history of allergy to mydriatic agents and ophthalmic surface anaesthetic.
5. The presence of ocular diseases, such as vitreous macular traction syndrome, macular oedema, epiretinal membrane, myopia with posterior staphyloma, diabetic retinopathy, the inflammation or infection of accessory visual structures, severe dry eye, central retinal vein occlusion, ischaemic optic neuropathy, optic nerve disease, Emery-Little cataract ≥grade 3[17] or posterior capsular opacification.
6. Without any deterioration in visual acuity, OCT findings, Goldmann perimetry findings and HFA 10-2 visual field sensitivities in last 3 years.
7. With a pacemaker or defibrillator.
8. With a history of malignant tumour. However, patients without a relapse for more than 5 years can be enrolled.
9. With psychosis, dementia or mental symptoms that could hinder participation.
10. With diabetes and poor glycaemic control (Hemoglobin A1c>10.0%).
11. With hypertension (systole ≥180 mm Hg and/or diastole ≥110 mm Hg) and difficulty in controlling blood pressure by treatment.
12. With hepatic or renal dysfunction that meets any of the following criteria during screening: (1) AST (aspartate aminotransferase), ALT (alanine aminotransferase): More than thrice the upper limit of the facility's standard value; (2) creatinine: More than 1.5 times the upper limit of the facility's standard value.
13. Pregnant, breast feeding or planning to get pregnant during the trial period.
14. Participating in other clinical trials.

15. Under investigational responsibility (shared) judged inappropriate by doctors for participation in this trial.

Registration and randomisation

After confirming the fulfilment of the eligibility criteria, patients were randomly assigned to the TdES and sham groups in a 1:1 allocation via a dynamic and centralised randomisation procedure, implemented with the DATA-TRAK Electronic Data Capture system (DATATRAK ONE V.14.6.3; https:// secure.datatrak.net). The participants were randomised by the Academic Clinical Research Center of Osaka University Hospital as a neutral third party, and the masking codes will be retained by the Osaka University, thus effectively guaranteeing the implementation of masking in clinical trials. An electronic data capture system was used for the registration, randomisation and data collection. The registration and allocation sequences were generated and managed by the Academic Clinical Research Center of Osaka University Hospital. Viedoc's dynamic allocation incorporates the Pocock-Simon method, which aims to minimise imbalances in the distribution of patients across treatment groups with respect to prognostic factors that may affect the effect of treatment on patients. This is done by hypothetically assigning a new patient to each treatment group and calculating the level of imbalance for each assignment. Patients are then assigned to treatment groups in such a way that imbalance is minimised. When setting up allocations for the Pocock-Simon method, we set the relative importance of factors and the desired distribution of treatments to be assigned.

Data collection was managed by the Data Management Office, Clinical Trial Centre of the Chiba University Hospital. The allocation factor is the BCVA (>0.3, <0.4), based on dynamic allocation method.

Operators are divided into masked group and unmasked group. The unmasked operator only operates the device to treat the TdES and sham treatment groups. The masked operator performs examinations, safety assessment, confirmation of results during trial period. After the trial is completed, they become unmask and perform evaluation of results. Participants are masked, in which they are not known which group they are in. The Statistician accesses and analyses the data after the test is completed.

Treatment methods

TdES group: The patients received TdES every 2 weeks for 12 sessions. They underwent TdES consisting of 10 ms biphasic pulses at 20 Hz for 30 min. All patients were simultaneously stimulated bilaterally with 1.0 mA at the Chiba University Hospital by physicians. Electrical pulses were obtained from a prototype equipment (figure 2) jointly developed by Mayo (Aichi, Japan). While one electrode was placed on the lower eyelid lateral to the midline of both eyes, the other was placed at the centre of the forehead in a similar way as in our previous study.[13]
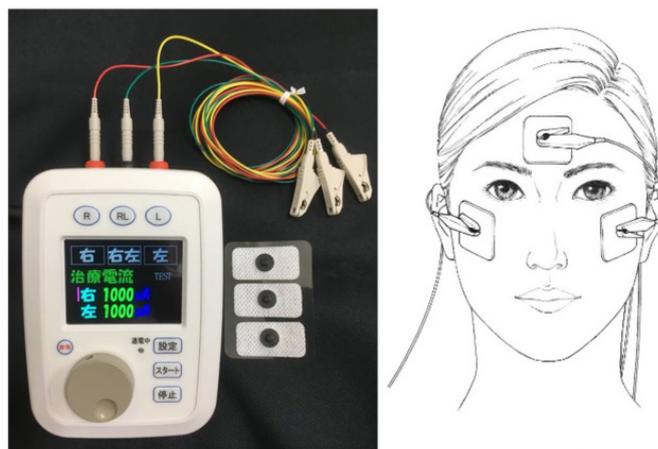

Figure 2 The prototype equipment for transdermal electrical stimulation.

Sham treatment group: The electrodes were attached in place similar to the TdES group. A normally energised electric cord is used for the treatment group, and a broken electric cord is used for the sham group, but the difference was not apparent to the patient. The display of the treatment device used in the sham group was also displayed as 1000 µV, which is exactly the same as in the treatment group, but the amount of current actually energised was 0 µA. When the unmasked operator pressed the start button, 30 min timer would automatically start, and after 30 min it would automatically end, just like in the treatment group. Therefore, the sham treatment was administered at same interval as the live treatment in Treatment method part. This was exactly the same process for both groups. Participants were only patients who have never experienced electrical stimulation therapy. The setting, the display of the device and the treatment time were exactly the same as in the treatment group, and the only difference was that no current flows, so the effect of masking was maintained in this way.

The procedure manual for the provision and management of investigational equipment written in Japanese is provided in online supplemental appendix 3.

Postobservation period

Following TdES, all patients entered the postobservation period. They will be admitted at 36 and 48 weeks and evaluated for the applicable items and safety (table 1).

Criteria for the discontinuation of trial treatment

The defined criteria for the discontinuation of trial treatment are as follows:

1. Offer to decline participation in the clinical trial or consent withdrawal.
2. Found ineligible after enrolment.
3. Difficult to continue the clinical trial because of an exacerbation of complications.
4. Difficult to continue the clinical trial owing to AEs.

5. Pregnancy.
6. If the entire clinical trial is discontinued.
7. Other serious violations of the trial protocol.
8. Other situations, judged by the principal investigator, in which TdES cannot be continued.

Data management, monitoring, safety and auditing

The monitors will ensure the following aspects:
► The investigational team complied with the study protocol based on Good Clinical Practice standards.
► The data, results and AEs have been appropriately and accurately recorded in the electronic case report forms.
► Serious AEs are reported to the trial coordinator and the treatment device provider (Mayo), and patients meeting the aforementioned criteria have been reported to the IRB.

The classification of AEs is determined according to the Medical Dictionary for Regulatory Activities, Japanese translation MedDRA/J V.22.1 (MedDRA Japanese Maintenance Organisation, Tokyo, Japan). All participants with AEs were followed up until they resolved the AE or for 4 weeks after the end of the trial. All serious AEs were reported to the investigators, discussed through an AE reporting system on the web, and reported to the PMDA (as required). All patients will be recruited into a clinical trial insurance provided by the Mitsui Sumitomo Insurance for a compensation to those who suffer harm from trial participation.

Data monitoring committee

The data monitoring committee comprises three clinical trial specialists, including a biostatistician, an ophthalmology specialist and an otolaryngology specialist who were not included in this study. These data monitoring committee members were all independent. This committee will meet twice a year and will check all data obtained from this trial.

Statistical analysis plan

We will perform statistical analyses and reporting of this trial in accordance with the Consolidated Standards of Reporting Trials statement guidelines. All efficacy analyses will be primarily based on the complete analysis set, including all patients who received at least one stimulation of the trial treatment. For the primary analysis aimed at comparing the effects, we will estimate a change in logMAR from the baseline to 24 weeks and its 95% CI using the analysis of covariance, adjusted for the allocation factor at the registration period.

To supplement the analysis of the primary endpoints, we will analyse the secondary endpoints of the efficacy. There are no multiplicity adjustments in the analysis of the secondary endpoints. In a secondary analysis, we will use the linear mixed-effects model to compare the secondary efficacy of the change score

between groups at each time point. The frequency of AEs and 95% CI were estimated using the Clopper-Pearson exact CI. All comparisons were planned, and all p values were two sided. The statistical significance has been set at $p < 0.05$. All statistical analyses will be performed using SAS software (V.9.4; SAS).

Missing values

In principle, the missing values are not supplemented. On supplementing as necessary, we made the following considerations:

Consider conducting an analysis using a mixed-effects model repeated measures for missing values because of discontinuation or the omission of efficacy evaluation items.

In the sensitivity analysis, the stability of the result was confirmed by analysing the observing case, last observation carried forward, and multiple imputation. However, the Markov chain Monte-Carlo method was used in the MI analysis, and the number of utterances was set to 100. The supplementary method and the results of the sensitivity analysis are reported in the analysis report.

Sample size estimation

The primary objective of the present study was to compare the change in logMAR visual acuity between the treatment and sham groups from week 0 to week 24. The null hypothesis was that there would be no significant between-group differences in the change in logMAR visual acuity. The results of our previous study (Study No. K29001) demonstrated an improvement in the logMAR visual acuity. Therefore, we assume the mean and SD of the 24-week change from baseline to be 0.1 logMAR and 0.124 logMAR visual acuity, respectively. In contrast, the placebo effect of the sham group was 1.6 characters (0.032 logMAR visual acuity), as reported in a 2-year long clinical trial of neovascular age-related macular degeneration.[18] The placebo effect of the sham group was presumably linear with time, and that during evaluation (week 24) of the primary endpoint was assumed to be −0.008 logMAR visual acuity. Therefore, the difference in the TdES and sham groups from the baseline was 0.1 log MAR and −0.008 log MAR, respectively. Moreover, the common SD of the groups was 0.124 log MAR. Therefore, we calculated the sample size according to the expected change in the logMAR visual acuity from week 0 to week 24 in the treatment and sham groups (0.1 and −0.008, respectively) (SD=0.124). Based on these assumptions, the required sample size was 22 patients per group (two sided, α=0.05, β=0.8, t-test). Considering a 10% drop-out rate, we targeted 25 patients per group. Therefore, the target sample size for the randomised trial was 50.

Interim analysis and monitoring

No interim analysis has been planned.

Patient and public involvement

The patients and general public were not involved in the trial design.

Ethics and dissemination

The protocol was approved by the institutional review board at the Chiba University Hospital and two other institutions, and was registered with the Japan Registry of Clinical Trials on 17 May 2021. The trial will be conducted in accordance with the principles of the Declaration of Helsinki, and is in accordance with Good Clinical Practice standards. We intend to publish results of this ePICO trial in a major journal.

DISCUSSION

Previous studies have reported on improved visual function of eyes with traumatic and ischaemic optic neuropathy,[19] retinal artery occlusion,[20] [21] dry age-related macular dystrophy,[22] [23] glaucoma,[24] Leber hereditary optic neuropathy[25] and RP following TdES with corneal electrodes.

The previously conducted clinical trial demonstrated no AEs caused by electrical stimulation. In addition, the mean BCVA and MD of HFA 10-2 significantly improved after TdES. Currently, there are no approved electrical stimulation devices for ocular diseases in Japan. We planned this trial to approve ocular electrical stimulation therapy devices for patients with RP.

The electrodes of the treatment device used in this trial do not touch the corneal or conjunctival surface, thus preventing dry eye symptoms previously reported using transcorneal electrodes.[11] Moreover, no serious AEs were observed in the previous pilot study.[13] Therefore, our treatment device using skin electrodes has the advantage of being an easier and safer option than one that uses corneal electrodes.

Morimoto *et al* investigated the stimulus conditions (Morimoto2010 Exp Eye Res) that maximised RCG survival rate using optic nerve transected rat. Also, the results of clinical trials in which electrical stimulation was applied to patients with RP (schatz2017, Bittner 2018 Acta, Wagner), optic neuropathy (Fujikado2006 JJO), and CRAO (Inomata Graefe 2007) were reported. We determined the electrical stimulation settings with reference to the results of those previous studies and conducted our exploratory study with 20 eyes of RP patients. Since improvement in visual acuity and visual field sensitivity was obtained in the study, the same stimulation settings were applied in this trial.

In the previous clinical trial, the sample size was as small as 10 and the treatment period was as short as 12 weeks. In addition, we did not set a follow-up period, thus could not evaluate the safety and efficacy post-treatment. Therefore, we decided to set the target number of patients to 50 and the treatment period to 24 weeks. We also set the postobservation period to 36 weeks and 48 weeks to acquire data post-treatment.

This trial has several strengths, in addition to larger sample size and longer treatment duration. This is the first randomised, double-masked and sham-controlled clinical trial of TdES in patients with RP. It is the first step in the clinical application of electrical stimulation therapy for other ocular diseases effectively treated by electrical stimulation. Simultaneously, we are conducting a clinical trial of TdES for central retinal artery occlusion (UMIN000036219) and non-arteritic ischaemic optic neuropathy (UMIN000036220) using a similar treatment device. We intend to apply the findings as a set with the results of the aforementioned and current ePICO trial for an approval of the TdES device.

A limitation of this trial is the small target patient size. This can be attributed to the rare occurrence of RP (approximately 1 in 4000 people).[26] However, further studies are needed in the future to investigate the effects of electrical stimulation on the retina in detail. Second, we determined the electrical stimulation settings with reference to the results of previous studies. However, the ideal dose/regimen of electrical stimulation treatment is not yet known.

In summary, an easier and less invasive treatment method will likely become widespread in patients with RP after confirming the efficacy of TdES in this trial.

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