PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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, multi-center, randomized, double-masked, and sham-controlled design (ePICO trial)
AUTHORS	Miura, Gen; Ozawa, Yoshihito; Shiko, Yuki; Kawasaki, Yohei; Iwase, Takayuki; Fujiwara, Tadami; Baba, Takayuki; Hanaoka, Hideki; Yamamoto, Shuichi

VERSION 1 – REVIEW

REVIEWER	Perin, Cecilia University of Milan–Bicocca
REVIEW RETURNED	04-Dec-2021

GENERAL COMMENTS	Dear Authors, thank you very much for the very interesting article. I think that the topic is relevant and appropriate for this periodic journal. I saw that the general construction of the article is good. The study design is sufficiently clear and the CONSORT checklist for randomized trials is respected. I outline only some criticism : In the abstract, the introduction should start with a general statement about the use of the TdES for the retinitis pigmentosa. In the introduction section, at line 71, it is important to report some recent reviews concerning this topic (eg Non-invasive current stimulation in vision recovery: a review of the literature-Restorative Neurology and Neuroscience 38 (2020) 239–250) as reference In table 1 at lines 22-23- 38, the significance of the circles is not explained. at line 355, please justify the statement ‘rare occurrence of the RP ‘ with some statistical reference (eg prevalence, incidence, etc.). I suggest accepting the article after minor revisions.

REVIEWER	Jackson, Timothy King's College London, Ophthalmology
REVIEW RETURNED	05-Dec-2021

GENERAL COMMENTS	The authors describe the protocol for a small RCT of 50 participants with retinitis pigmentosa, comparing sham versus transdermal electrical stimulation. A treatment for RP would be a big step forward, and this trial explores a promising new technology. If proven effective this technology would have real impact.

	My key issue is that such a small study should not really be presented as a 'phase 3' (pivotal) trial. However, it remains important if it helps inform a subsequent pivotal trial. Other issues relate mainly to lack of clarity or detail, but I expect most could be addressed with suitable revisions. Other points Title: Minor point but some prefer the use of masked instead of blinded for eye trials (applies elsewhere in paper/abstract) Abstract and summary Primary outcome is change in logMAR VA at week 24, and the top listed secondary is comparison of logMAR at week 24. I realise these are different, but I wasn't sure why two outcomes that are so similar are needed (if the outcome was final VA it would be common to adjust for differences in baseline VA). Authors describe aim as verifying 'maintenance and improvement effect' but this is rather vague; for example it might be better to describe maintenance or improvement in best-corrected visual acuity (applies also in summary pg 4) A sample size of 50 is described as the optimal size of study, but this is a very small study to establish safety/efficacy. The authors justify the small size due to RP being rare, which might be fair depending on definition, but it is the most common inherited retinal dystrophy and larger trials are deliverable. Introduction Please include the number of participants in the phase 2 study in the introduction (we find out it is 10 in the discussion, but this info should come sooner). This begs the question of whether or not there was a phase 1 study - if so please detail. Please provide more information about the phase 2 (± phase 1) study including design/intervention/specific outcomes etc). There is a bit more info in the discussion but it would help to understand what the current study adds earlier on, and help set the context of the current trial. I would question if a trial of 50 can really be considered phase III. I suspect the phase 2 was actually best described as phase 1 and this is phase 2 (as an aside the phase 1/2/3 terminology is usually reserved for drugs, whereas a phase III device trial is usually called a pivotal trial). I suggest a bit more info on other reported means of electrical stimulation for RP including the Ocustim's clinical RCT, and the clinical trial of quantum dots. I think it would also be helpful to amplify that fact this is an important disease with few treatment options, to make clear the significant unmet need that this technology addresses. The authors describe that the study was conducted at three hospitals, but it then says the local PI conducted the study at two of these. I think they mean that Chiba hosted the Chief investigator but also recruited, and the other two hospitals had a PI and

	recruited. I think the information is there but could be misread (when I read it first time I wondered where the third hospital had gone, but on re-reading it did make sense). It is not necessary to note that the CI/PI is assisted by research nurses/coordinators. Please justify the dosing regimen (biphasic, frequency etc) based on earlier dose finding studies or scientific rationale. Line 106 notes the patients (participants) were randomised but please detail how that was done - I since see this information is provided later so maybe just add '(details below)' as other readers may have the same question at this juncture. Line 110 typo (conent) Line 113 describes follow up to 48 weeks but the abstract notes 2 years. Please clarify and ensure they are consistent. Primary outcome is listed as superiority of logMAR VA but I think the outcome is change from baseline, and that is tested for superiority ie the methods of analysis (superiority) should be listed in the stats/analysis section but superiority it isn't an outcome per se. Please clarify if this is mean? Line 228 it would be nice to have a picture of the device in use. Re the sham group, how was treatment simulated? Did the operator somehow simulate live treatment eg with instructions, device audio cues etc? I think it is assumed, but please state that the sham treatment was administered at same interval as the live treatment. Is see authors are also reporting ETDRS VA -why do two measures? Please justify/provide rationale. Please provide more details about the secondary outcomes, for example, rather than saying VFQ-25 score, it would help to specify, mean change in composite score compared to baseline, or whatever it might be. Please do this for each secondary, where possible/applicable. Please give units of measure eg dB. The safety section lists a number of conditions of special interest, but it does not note that all adverse events will be recorded and how these will be coded / presented (eg medDRA/ proportions by group etc). Some of this info comes later but should be given here. Please detail how VAs were converted to logMAR or provide a suitable reference. It is not necessary to note that FDA accept the ETDRS chart but the testing protocol does need to be detailed for each chart (eg full refraction for each visit etc). Were staff and equipment certified? Please provide reference for the testing protocol if it followed a specific standard operating procedure. It is possible this info is in the Japanese language supplements but please clarify for those who do not speak Japanese. Please detail how the VFQ25 was administered eg self-administered. Also, some more information on other measures would help. Please provide detail on when and how refraction was done. If it was not, please state this for readers.

	Please provide more info on masking (operator/participant/statistician) Inclusion criteria: the decimal VA from .1 to .7 I assume is as tested during screening? Please make this clear as it appears the visual field criterion used historic information. Criterion 6 is unclear- I think the authors mean the participant was thought able to comply with the study protocol including regular visits every 2 weeks… Exclusion criterion 15 is hard to understand; can it be clarified? Line 254: is this severe AE or serious AE (applies later also)? May well be correct as given but I just want to check, as a severe AE is usually defined as an AE of high intensity, but it may not meet the criteria that usually define a 'serious adverse event'. Please note if the DMC members were all independent. Statistics I wasn't clear what is meant by 'a similar methods was applied to the secondary efficacy of the change score'? I thought the secondary BCVA was not change but final VA. As noted earlier it is not clear if some variables are comparing an individual's change from baseline or final mean/median score. Please clarify if the primary outcome was the only protected comparison or if that applied to any of the secondary outcomes (eg were they unprotected/hypothesis generating/hierarchical testing etc) Line 303-307 I wasn't clear why the value changed from positive (0.032) to negative (-0.008). If this is an improvement is it a placebo or learning effect? However, presumably one would expect a reduction due to natural history/disease progression? In limitations section please expand on the small size of the study, and that a larger trial will be needed to better establish both safety (especially rare events) and efficacy. If there isn't much underpinning the chosen dose please also explain that the ideal dose/regimen of treatment is not yet known. Reporting checklist There are a few items that have just been listed as NA that do seem to apply. For example, if there is no plan to make the data available publicly that can be stated in the paper, and the the role of sponsor can be added (I wonder if the authors think sponsor relates to an external commercial sponsor?). Some of the items on this checklist were not really fully described in the paper – if the authors went through this list carefully and provided more details as needed I think that would address most of my queries above.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer #1

1. In the abstract, the introduction should start with a general statement about the use of the TdES for the retinitis pigmentosa.
In the introduction section, at line 71, it is important to report some recent reviews concerning this topic (eg Non-invasive current stimulation in vision recovery: a review of the literature-Restorative Neurology and Neuroscience 38 (2020) 239–250) as reference

Answer:
We appreciate your precise review comments very much.
We added to the introductory section page 5 the general status of the use of TdES for retinitis pigmentosa, adding the literature you mentioned, line74.

2. In table 1 at lines 22-23- 38, the significance of the circles is not explained.

Answer:
Black circles are items that must be performed. White circles are items to be performed only when the investigator deems it necessary. We added the explanation about them, line129.

3. at line 355, please justify the statement ‘rare occurrence of the RP ‘ with some statistical reference (eg prevalence, incidence, etc.).

Answer:
We added the reference about the prevalence of retinitis pigmentosa, line 406.

Response to Reviewer #2

1. My key issue is that such a small study should not really be presented as a ‘phase 3’ (pivotal) trial. However, it remains important if it helps inform a subsequent pivotal trial.

Answer:
We appreciate your precise review comments very much.
We agree with the reviewer's suggestions.
We changed to pivotal study instead of the term phase 3 and pilot study instead of phase 2.

2. Title: Minor point but some prefer the use of masked instead of blinded for eye trials (applies elsewhere in paper/abstract)

Answer:
We changed all "blinded" in the text to "masked".

3. Primary outcome is change in logMAR VA at week 24, and the top listed secondary is comparison

of logMAR at week 24. I realise these are different, but I wasn't sure why two outcomes that are so similar are needed (if the outcome was final VA it would be common to adjust for differences in baseline VA).

Answer:
Our intention is to evaluate the change from 24 weeks as the primary endpoint and the change from baseline over time from 0 to 24 weeks as the secondary endpoint.
To make it easier for readers, we have changed the secondary endpoint from "at week 24" to "Base line to 24 weeks".

4. Authors describe aim as verifying 'maintenance and improvement effect' but this is rather vague; for example it might be better to describe maintenance or improvement in best-corrected visual acuity (applies also in summary pg 4)

Answer:
We changed to describe maintenance or improvement in best-corrected visual acuity in summary and the main text.

5. A sample size of 50 is described as the optimal size of study, but this is a very small study to establish safety/efficacy. The authors justify the small size due to RP being rare, which might be fair depending on definition, but it is the most common inherited retinal dystrophy and larger trials are deliverable.

Answer:
We agree with the reviewer's suggestions.
We emphasized that larger trials are needed in the future in the limitation part, line 406.

6. Please include the number of participants in the phase 2 study in the introduction (we find out it is 10 in the discussion, but this info should come sooner). This begs the question of whether or not there was a phase 1 study - if so please detail. Please provide more information about the phase 2 (± phase 1) study including design/intervention/specific outcomes etc). There is a bit more info in the discussion but it would help to understand what the current study adds earlier on, and help set the context of the current trial.

Answer:
We added the number of participants in the previous study that we conducted in the introduction part with the reference. We also added the information of design of the previous study to help understanding what the difference between the current and the previous study, line 81.

7. I would question if a trial of 50 can really be considered phase III. I suspect the phase 2 was actually best described as phase 1 and this is phase 2 (as an aside the phase 1/2/3 terminology is usually reserved for drugs, whereas a phase III device trial is usually called a pivotal trial).

Answer:
We agree with the reviewer's suggestions.
We changed to pivotal study instead of the term phase 3 and pilot study instead of phase 2.

8. I suggest a bit more info on other reported means of electrical stimulation for RP including the Ocustim's clinical RCT, and the clinical trial of quantum dots. I think it would also be helpful to amplify that fact this is an important disease with few treatment options, to make clear the significant unmet need that this technology addresses.

Answer:
We added the information of study about the intravitreal quantum dots as the attempt to establish electrical stimulation as a treatment for RP in introduction part with the reference (Intravitreal quantum dots for retinitis pigmentosa: a first-in-human safety study. Jackson TL, Mandava N, Quiroz-Mercado H, Benage M, Garcia-Aguirre G, Morales-Canton V, Wilbur L, Olson J. Nanomedicine (Lond). 2021 Apr;16(8):617-626.), line76.

9. The authors describe that the study was conducted at three hospitals, but it then says the local PI conducted the study at two of these. I think they mean that Chiba hosted the Chief investigator but also recruited, and the other two hospitals had a PI and recruited. I think the information is there but could be misread (when I read it first time I wondered where the third hospital had gone, but on re-reading it did make sense). It is not necessary to note that the CI/PI is assisted by research nurses/coordinators.

Answer:
We deleted "A local principal investigator, supported by other staff members, such as a research nurse or clinical research coordinator, conducted the study at the Kobe and Nagoya City University Hospital." in method part.

10. Please justify the dosing regimen (biphasic, frequency etc) based on earlier dose finding studies or scientific rationale.

Answer:
Morimoto et al. investigated the stimulus conditions (Morimoto2010 Exp Eye Res) that maximized RCG survival rate using optic nerve transected rat.
Also, the results of clinical trials in which electrical stimulation was applied to patients with retinitis pigmentosa (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.
However, as you pointed out, there isn't much underpinning the chosen dose especially for human. We added a description about those facts to the discussion part, line381.

11. Line 106 notes the patients (participants) were randomised but please detail how that was done - I since see this information is provided later so maybe just add '(details below)' as other readers may have the same question at this juncture.

Answer:
We added '(details below)' in Trial design part and detail the way of randomization (Viedoc's dynamic allocation) in Registration and randomization part, line234.

12. Line 110 typo (conent)

Answer:
We corrected it to the correct spelling.
Thank you for pointing out.

13. Line 113 describes follow up to 48 weeks but the abstract notes 2 years. Please clarify and ensure they are consistent.

Answer:
We modified to "follow them up for 1 years."

14. Primary outcome is listed as superiority of logMAR VA but I think the outcome is change from baseline, and that is tested for superiority ie the methods of analysis (superiority) should be listed in the stats/analysis section but superiority it isn't an outcome per se. Please clarify if this is mean?

Answer:
Same as the answer to 3, our intention is to evaluate the change from 24 weeks as the primary endpoint and the change from baseline over time from 0 to 24 weeks as the secondary endpoint.
To make it easier for readers, we have changed the secondary endpoint from "at week 24" to "Base line to 24 weeks".
We also added a description about the evaluation items to the statistics part, line 312.

15. Line 228 it would be nice to have a picture of the device in use.

Answer:
We added a picture of the device as Figure 1 and figure legend.

16. Re the sham group, how was treatment simulated? Did the operator somehow simulate live treatment eg with instructions, device audio cues etc? I think it is assumed, but please state that the sham treatment was administered at same interval as the live treatment.

Answer:
We added the statement that the sham treatment was administered at same interval as the live treatment in Treatment method part, line 264.

17. Is see authors are also reporting ETDRS VA -why do two measures? Please justify/provide rationale.

Answer:
In Japan, it is mandatory to hold a several discussion meetings with the national agency called Pharmaceuticals and Medical Devices Agency (PMDA: https://www.pmda.go.jp/english/index.html) before starting a clinical trial, and only protocols approved by PMDA are allowed to conduct. The PMDA has been evaluating ophthalmic clinical trials with the same guidance as the one pointed out here. In other words, the instructions are based on precedent. We set this protocol because the PMDA instructed us to add an ETDRS visual acuity assessment at the protocol evaluation meeting prior to the start of this study. This is a necessary for future application for approval as a treatment device in Japan.

18. Please provide more details about the secondary outcomes, for example, rather than saying VFQ-25 score, it would help to specify, mean change in composite score compared to baseline, or whatever it might be. Please do this for each secondary, where possible/applicable. Please give units of measure eg dB.

Answer:
We provided details about each secondary outcomes including units of measure.

19. The safety section lists a number of conditions of special interest, but it does not note that all adverse events will be recorded and how these will be coded / presented (eg medDRA/ proportions by group etc). Some of this info comes later but should be given here.

Answer:
All adverse events are recorded and coded in MedDRA (vas.6.0).
We added this information to Safety endpoints section, line 289.

20. Please detail how VAs were converted to logMAR or provide a suitable reference. It is not necessary to note that FDA accept the ETDRS chart but the testing protocol does need to be detailed for each chart (eg full refraction for each visit etc). Were staff and equipment certified? Please provide reference for the testing protocol if it followed a specific standard operating procedure. It is possible this info is in the Japanese language supplements but please clarify for those who do not speak Japanese. Please detail how the VFQ25 was administered eg self-administered. Also, some more information on other measures would help. Please provide detail on when and how refraction was done. If it was not, please state this for readers.

Answer:
We added the detail about below.

- How VAs were converted to logMAR with the reference.
- Visual acuity, visual field, and OCT tests were all performed by a certified orthoptist.
- Refraction measurement was done every time visual acuity measurements.
- The treatment device used in this trial is pending a domestic patent.
- VFQ-25 is self-administered and was answered by the patients themselves.

We have created a procedure manual for the provision and management of investigational equipment for this trial, so we provide it as supplementary material.

21. Please provide more info on masking (operator/participant/statistician)

Answer:
Operators are divided into blind and unblind.
The unblinded operator only operates the device to treat the TdES and sham treatment groups.
The blinded operator performs examinations, safety assessment, confirmation of results during trial period. After the trial is completed, they become unblind and perform evaluation of results.
Participants are blind, in which they are not known which group they are in.
The Statistician accesses and analyzes the data after the test is completed.
This means that blind operators statistical analysts remain blinded until the trial is complete, and results are available.
We added information about that, line 246.

22. Inclusion criteria: the decimal VA from .1 to .7 I assume is as tested during screening? Please make this clear as it appears the visual field criterion used historic information.

Answer:
Patients with a decimal visual acuity of 0.1-0.7 on a vision test during screening can attend this trial.
We added this information to Inclusion criteria section, line 186.

23. Criterion 6 is unclear- I think the authors mean the participant was thought able to comply with the study protocol including regular visits every 2 weeks…

Answer:
As you assume, it means a person who can go to the hospital once every two weeks for 6 months.

24. Exclusion criterion 15 is hard to understand; can it be clarified?

Answer:
For example, if the investigator determines that regular visit, treatment or evaluation is not possible for some reason, it is an item that allows the inclusion of the patient to be excluded.
This item is generally included in Japanese clinical trials.

25. Line 254: is this severe AE or serious AE (applies later also)? May well be correct as given but I just want to check, as a severe AE is usually defined as an AE of high intensity, but it may not meet the criteria that usually define a ‘serious adverse event’.

Answer:
This is the serious AE. We have revised the relevant part.

26. Please note if the DMC members were all independent.

Answer:
We clarified that the data monitoring committee members were all independent, line 301.

27. I wasn’t clear what is meant by ‘a similar methods was applied to the secondary efficacy of the change score’? I thought the secondary BCVA was not change but final VA. As noted earlier it is not clear if some variables are comparing an individual’s change from baseline or final mean/median score.

Answer:
We have removed the confusing expression "similar method" and clarified that the amount of change should be analyzed using a mixed effect model.
We added “To supplement the analysis of the primary endpoints, we will analyze 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.” ,line 312.

28. Please clarify if the primary outcome was the only protected comparison or if that applied to any of the secondary outcomes (eg were they unprotected/hypothesis generating/hierarchical testing etc)

Answer:
We have stated that only the primary endpoint is protected.
Multiplicity evaluation is not performed for secondary endpoint items.
We added that to the statistics section, line 176.

29. Line 303-307 I wasn't clear why the value changed from positive (0.032) to negative (-0.008). If this is an improvement is it a placebo or learning effect? However, presumably one would expect a reduction due to natural history/disease progression?

Answer:
-0.0008logMAR visual acuity is a placebo effect as you pointed out.
This reference is presented as an example of specific numerical values for which the placebo effect in an ophthalmic study is linear and used for sample size calculations.

30. In limitations section please expand on the small size of the study, and that a larger trial will be needed to better establish both safety (especially rare events) and efficacy. If there isn't much underpinning the chosen dose please also explain that the ideal dose/regimen of treatment is not yet known.

Answer:
We emphasized on the small size of the study, and that a larger trial will be needed in discussion part.
Also as second limitation, we emphasized that the ideal dose/regimen of treatment is not yet known, line 409.

31. There are a few items that have just been listed as NA that do seem to apply. For example, if there is no plan to make the data available publicly that can be stated in the paper, and the the role of sponsor can be added (I wonder if the authors think sponsor relates to an external commercial sponsor?). Some of the items on this checklist were not really fully described in the paper – if the authors went through this list carefully and provided more details as needed I think that would address most of my queries above.

Answer:
We revisited the items we submitted as NA last time and filled out the pages corresponding to those items.
We appreciate the reviewer for his guidance.

VERSION 2 – REVIEW

REVIEWER	Jackson, Timothy King's College London, Ophthalmology
REVIEW RETURNED	12-Feb-2022

GENERAL COMMENTS	Thanks for the helfpul revision and response. I have only a few outstanding issues

	1. The authors describe this as a pivotal trial. As per my earlier review I do not consider a trial of this size sufficient to really label as pivotal. Please remove this term. 2. The authors have changed blinded to masked in some places, but some new text reverts to use of blinded. Minor point, but suggest change that to masked. 3. There is now a bit more info on sham treatment (authors noting it was done at same interval as active treatment) but please provide info on how the sham wa

VERSION 2 – AUTHOR RESPONSE

Response to Reviewer #2

Reviewer: 2

1. The authors describe this as a pivotal trial. As per my earlier review I do not consider a trial of this size sufficient to really label as pivotal. Please remove this term.

Answer:

We appreciate the reviewer for his repeated evaluations.

We removed the term pivotal.

2. The authors have changed blinded to masked in some places, but some new text reverts to use of blinded. Minor point, but suggest change that to masked.

Answer:

We changed the term blind to mask from line 250.

3. There is now a bit more info on sham treatment (authors noting it was done at same interval as active treatment) but please provide info on how the sham was done, so readers can assess how effective the masking is likely to be.

The electrodes were attached in place similar to the TdES group.

A normally energized 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 energized was 0 μA. When the unmasked operator pressed the start button, 30-minute timer would automatically start, and after 30 minutes 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.

We added the above more details about sham treatment further.