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Highlights

- Microperimetry increases eligibility in RPGR gene therapy trials
- LLVA underestimates treatment response across disease stages
- Microperimetry detects more responders than LLVA at Month 12
- Central 16-point grid performs comparably to full 68-point testing but must be utilized with caution
- Endpoint choice substantially alters detection of trial efficacy

Microperimetry as an Outcome Measure Improves Patient Eligibility and Efficacy Detection in RPGR Gene Therapy Trials

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Short title: Outcome measures in *RPGR* clinical trials and patient involvement

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Abstract

Purpose:

To evaluate how primary endpoint selection influences patient eligibility, enrolment, and detection of treatment efficacy in *RPGR* gene therapy trials, comparing low luminance visual acuity (LLVA) with microperimetry-based outcome measures.

Design:

Retrospective analysis of a phase 1/2–3 interventional clinical trial.

Subjects:

Fifteen patients were included in this study. Each was administered with gene therapy in one with the other eye serving as control.

Methods:

Month 12 data from patients with *RPGR*-associated retinopathy enrolled at a single centre in the XIRIUS trial (NCT03116113) were retrospectively analysed. FDA-aligned low-luminance visual acuity (LLVA) responder criteria (≥15-letter gain) and EMA-aligned significant change from baseline in microperimetry mean sensitivity, were applied. Microperimetry outcomes were evaluated across the full 68-point MAIA grid and within a central 16-point subset. Minimal baseline inclusion thresholds were used. The proportion of gene therapy–treated patients meeting FDA- and EMA-aligned (≥2.5 dB improvement in mean sensitivity) responder criteria was determined.

Main outcome measures:

Proportion of patients meeting the responder criteria in either microperimetry or LLVA.

Results:

At baseline, LLVA excluded more patients from study inclusion due to floor effects than microperimetry. At month 12, 2 of 10 patients (20%) met LLVA responder criteria. In contrast, 5 of 11 patients (45%) met EMA-aligned whole-grid microperimetry responder criteria,

including all LLVA responders and three additional patients with clear functional improvement not captured by LLVA. Restricting analysis to the central 16 microperimetry points further increased responder detection, identifying 7 of 11 patients (64%). Improvements in microperimetry mean sensitivity of at least 2.5 dB, exceeding expected test–retest variability. No responders were identified for any endpoint in untreated fellow eyes.

Conclusions:

Primary endpoint choice substantially affects efficacy detection and patient inclusion in *RPGR* gene therapy trials. LLVA demonstrated limited sensitivity and restricted eligibility to a narrow disease window, risking underestimation of treatment benefit. Microperimetry mean sensitivity, particularly when spatially aligned with the treated retinal area, detected functional improvement in a substantially larger proportion of patients and supports broader enrolment. Microperimetry-based endpoints provide a more sensitive and inclusive primary outcome measure for *RPGR* gene therapy trials.

Introduction

Retinitis pigmentosa (RP) encompasses a broad spectrum of genetically heterogeneous disorders characterized by progressive retinal degeneration primarily affecting rod and cone photoreceptors [1]. The disease typically manifests with night blindness and peripheral visual field loss, eventually progressing to severe central vision impairment or complete blindness [2,3]. X-linked RP, primarily caused by mutations in the Retinitis Pigmentosa GTPase Regulator (*RPGR*) gene, represents one of the most severe and common forms. *RPGR* encodes a protein localized to the photoreceptor connecting cilium, where it plays a critical role in protein trafficking between the inner and outer segments of photoreceptors and helps support the delivery of phototransduction-related cargo that is essential for outer segment maintenance and normal photoreceptor survival [4,5].

Two recent phase 3 gene therapy clinical trials have now concluded, and both have failed to meet their primary endpoint. MeiraGTx/Janssen R&D (NCT04671433) failed to meet its primary endpoint on demonstrating improvement on vision-guided mobility of patients compared with an uninjected control group. Similarly, cotoretigene toliparvovec (XIRIUS, NCT03116113) from Biogen also failed to meet its primary endpoint in the number of participants meeting the predefined microperimetry responder criteria (7dB improvement at 5 of 16 central loci), largely due to COVID-related recruitment issues. A third clinical trial (VISTA, NCT04850118) delivering a codon-optimized full length $RPGR^{ORF15}$ sequence is currently underway at sites within the USA, UK and Australia, with 12-month outcomes expected by the end of 2026. There is discrepancy in the agreement of an acceptable primary outcome measures across worldwide regulatory agencies. For the current VISTA trial, the primary outcome measure approved in the United States by the Food and Drug Administration (FDA) is the proportion of participants with a ≥15 letter improvement at month 12 in low luminance visual acuity (LLVA) compared to an untreated control group, whereas, in Europe, the European Medicines Agency (EMA) has approved a significant change,

compared to controls, from baseline to month 12 in mean sensitivity across the whole grid, as measured by MAIA microperimetry.

Microperimetry has emerged as a valuable tool for quantifying macular retinal function through precise threshold sensitivity measurements correlated with specific retinal locations [6,7]. Unlike conventional perimetry, microperimetry incorporates fundus-tracking technology, enabling precise spatial correlation between anatomical features and functional sensitivity, making it particularly valuable for monitoring macular function in progressive retinal conditions [8]. Previous work by the authors have demonstrated the relative sensitivity of both LLVA and microperimetry mean sensitivity (and their correlation) as outcome measures, with LLVA being sensitive only over a narrow range in those patients where LLVA is impaired by central foveal encroachment of the disease, but not yet extinguished [9-11]. This narrow subset of patients that could demonstrate a functional improvement limits patient recruitment from the already small pool of available patients and risks excluding patients due to insensitivity of the endpoint.

Here, we explore the relative sensitivity and suitability of endpoints by applying the VISTA trial's EMA-accepted microperimetry-based endpoint criteria and the FDA-accepted LLVA endpoint criteria in a post hoc analysis of month 12 results from the phase 2/3 XIRIUS trial. This focus was chosen because, in gene therapy trials, endpoint selection is not only methodological but also regulatory, directly influencing patient eligibility, efficacy assessment, and ultimately whether a therapy may gain approval. Selection of appropriate outcome measures was identified as a priority research topic by the Monaciano Symposium, a global gathering of scientists and physicians focused on accelerating research and developing treatments for Inherited Retinal Dystrophies [12]. Comparing LLVA to microperimetry based outcome measures therefore addresses a clinically and translationally important question: whether currently relevant regulatory frameworks capture meaningful functional benefit in RPGR-associated retinopathy. We further explore the potential of a central 16-point microperimetry endpoint, in keeping with previous FDA-mandated

microperimetry outcomes based on a 7-dB improvement at 5 of 16 central loci, and reflecting the need to align endpoint design with the spatial distribution of treatment effect.

Methods

This retrospective analysis included data from patients diagnosed with *RPGR*-related retinopathy enrolled on XIRIUS (Clinicaltrials.gov NCT03116113); part 1 (phase 1 dose escalation) and part 2 (phase 2/3 masked dose expansion) who were administered with a single subretinal injection of cotoretigene toliparvovec. Whilst the XIRIUS trial was a multicentre study, this post-hoc analysis only includes patients enrolled at the Oxford Eye Hospital. The study adhered to the tenets of the Declaration of Helsinki and written informed consent was obtained from all participants. Ethics Committee approval was obtained prior to study initiation.

Low luminance VA was assessed, following a refraction, using a retro-illuminated early treatment diabetic retinopathy study (ETDRS) chart, placed at 4 meters, with all room lights switched off and a 2.0 neutral density filter added in front of the testing eye (background luminance 1.6cd/m2).

Retinal sensitivity was measured using the MAIA microperimeter (CenterVue, Padova, Italy). The standardized testing protocol employed a 4-2 threshold strategy with a Goldmann III stimulus size, presented for 200ms against a background luminance of 1.27 cd/m². A standard 68-point grid pattern was utilized, henceforth termed “whole-grid”, covering approximately a 10° radius (central 20°) around the central retina with a consistent 2° spacing between stimulus loci. Tests with poor reliability as defined in the protocol (fixation losses >30%) were excluded from the analysis as per standard protocol.

Two key metrics were then extracted and considered for post-hoc analysis, specifically evaluating which patients would have achieved the LLVA and microperimetry-based outcome measures. These are:

1) FDA-aligned endpoint: proportion of participants with a ≥15 letter improvement from baseline to month 12 in low luminance visual acuity (LLVA) [13]
2) EMA-aligned endpoint: proportion of participants with a significant change from baseline to month 12 in mean sensitivity across the whole grid, as measured by MAIA microperimetry [14]
3) Exploratory endpoint: proportion of participants with a significant change from baseline to month 12 in mean sensitivity across only the central 16 points, as measured by MAIA microperimetry

Here, a significant change in microperimetry mean sensitivity is defined in this study as ≥2.5 decibels, which is approximately double the test-retest repeatability [7] and considered functionally significant in the context of *RPGR-associated retinopathy* [9]. This may differ in other studies with different entrance and testing parameters.

A comprehensive description of methods, demographics and results have previously been published [15]. A set of post-hoc inclusion criteria were applied to ensure the inclusion of the broadest range of patients but with minimal compromise on potential detection of treatment efficacy. As such the inclusion criteria at baseline for those included in this analysis were:

1) LLVA > 0 letters &
2) Microperimetry (whole grid) mean sensitivity (MP) > 0 dB

The lower limits of LLVA and microperimetry were set to ensure elimination of patients whose visual function was too poor to be registered at baseline reaching the floor effects of each test. No other bounds were applied ensuring the widest possible inclusion with the above exceptions. Analysis was performed on both the treated and untreated fellow eyes of each patient.

Statistical analysis

All analyses and figure plotting were performed using R software version 4.1.0 [16]. Due to the small sample sizes and research question revolving around proportion of responders using different endpoints, no hypothesis testing was employed in this work and instead we have provided descriptive analyses only.

Results

Fifteen male patients with *RPGR*-associated retinopathy who received a single subretinal injection of cotoretigene toliparvovec in one eye as part of the XIRIUS (part 1 and 2) clinical trial were included in this retrospective analysis. Application of the predefined post-hoc baseline inclusion criteria resulted in the exclusion of five patients from the LLVA analysis due to zero baseline LLVA letter scores and four patients from the microperimetry analysis due to zero baseline mean sensitivity. Consequently, baseline and month 12 LLVA data were available for 10 patients, while baseline and month 12 microperimetry data were available for 11 patients.

All included microperimetry tests met predefined reliability criteria, with fixation losses ≤30%. A summary of demographic and baseline clinical characteristics has been previously reported [15].

Low luminance visual acuity outcomes

Individual LLVA letter scores at baseline and month 12 for all included patients are shown in Figure 1. At month 12, two of the 10 patients (20%) demonstrated an improvement of ≥15 letters from baseline, meeting the FDA-aligned threshold for clinically meaningful change. The remaining eight patients demonstrated either smaller improvements, no change, or a decline in LLVA that did not meet responder criteria. Of the three patients that showed evidence of LLVA declines from baseline to M12 (pt 8, 9 &10 with 10, 5 & 6 letter decrease,

respectively), all were less than the 15 letter change criteria which would be considered clinically significant.

Patients who achieved the LLVA responder threshold exhibited low baseline LLVA values (pt.1=55 letters and pt.2=54 letters), consistent with partial central foveal disease involvement. No patients with higher baseline LLVA achieved a ≥15-letter gain, consistent with a ceiling effect limiting detectable improvement in this subgroup.

Whole-grid microperimetry mean sensitivity outcomes

Mean retinal sensitivity across the full 68-point MAIA grid at baseline and month 12 is shown in Figure 2. Of the 11 patients included in this analysis, five (45%) demonstrated an improvement in mean sensitivity of ≥2.5 dB at month 12, meeting the defined EMA-aligned threshold for clinically meaningful change.

These five responders included the two patients who met LLVA responder criteria, as well as three additional patients who did not achieve a ≥15-letter LLVA improvement despite demonstrating clear increases in retinal sensitivity (see microperimetry heatmaps in figure 2). Across responders, improvements in whole-grid mean sensitivity ranged from approximately 2.5 dB to over 7dB. Non-responders demonstrated minimal change or modest decline in mean sensitivity over the same period. In addition, one patient (pt 10 - see figure 2) demonstrated a clinically significant decline of 5.3 dB in mean sensitivity. This is in stark contrast to this patient's small decline in LLVA (6 letters) which ordinarily would not be considered clinically significant in isolation. On further inspection this patient was administered with a high dose, suggesting possible toxicity effects.

Central 16-point microperimetry analysis

When analysis was restricted to the central 16 loci of the MAIA grid, sensitivity to detect treatment-related functional changes increased further (Figure 3). Seven of the 11 patients (64%) demonstrated an improvement of ≥2.5 dB in central 16-point mean sensitivity at month 12.

This group included all five patients who met whole-grid responder criteria, as well as two additional patients whose improvements were spatially concentrated within the central macula and therefore diluted when averaged across the full grid. The two patients meeting LLVA responder criteria were also identified as responders using the whole grid and central-16 microperimetry mean sensitivity endpoints. Additionally, three patients demonstrated a decrease of ≥2.5 dB in central 16-point mean sensitivity at month 12. These are pt 8, 9 &10 (see figure 3). Patient 10 was previously identified from the whole-grid analysis, however, patients 8 & 9 were not identified in either using LLVA or the whole-grid analysis. Similarly to patient 10, patient 8 was also administered with a high dose suggesting possible toxicity. Patient 9 (low dose) demonstrated a small decrease in the central 16 points but a small increase in the remaining 52 points representing the parafoveal regions. This resulted in a very small overall increase in whole-grid mean sensitivity at M12. This suggests a reorganisation of the retinal sensitivity map rather than any definitive gains or declines.

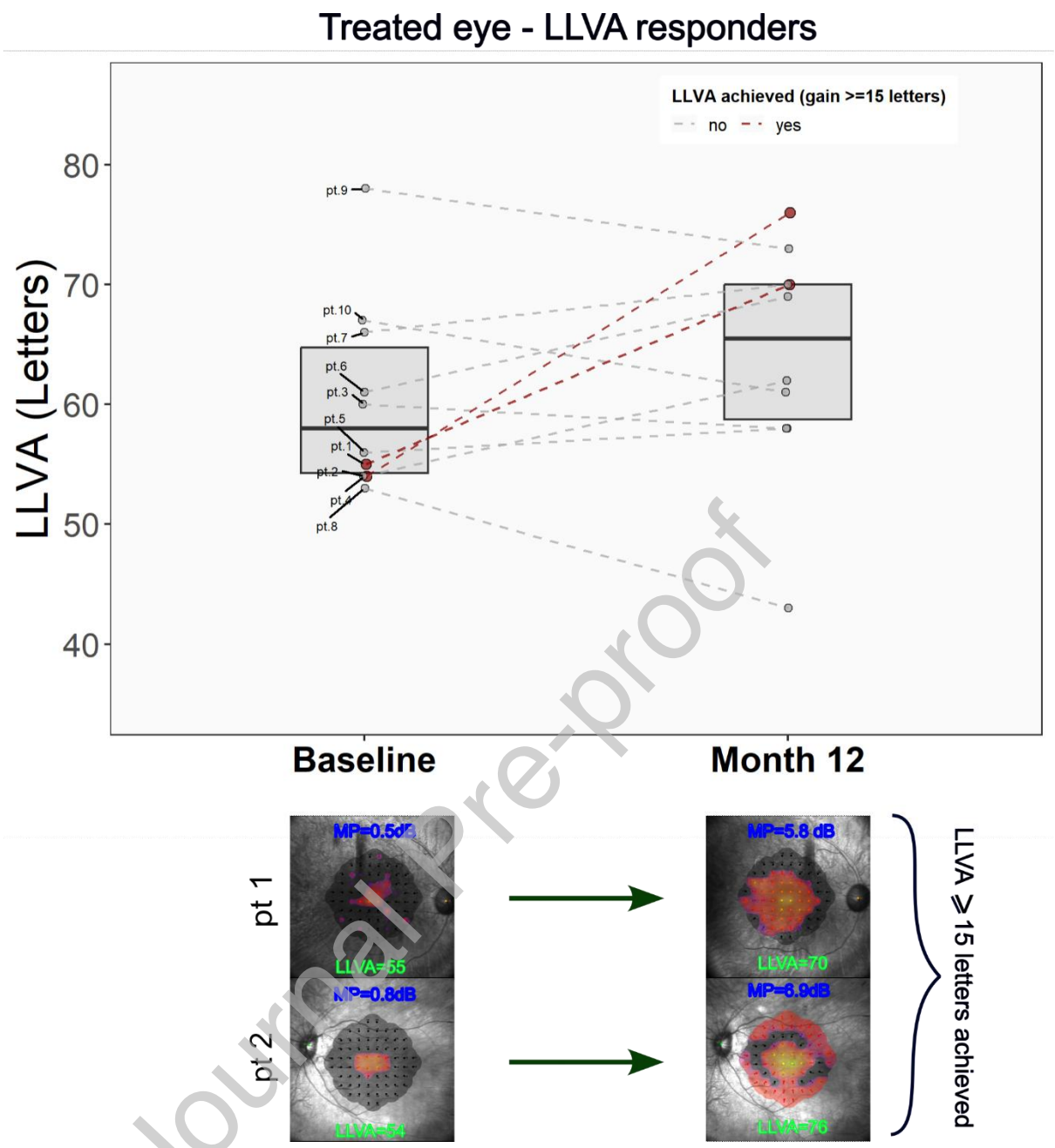
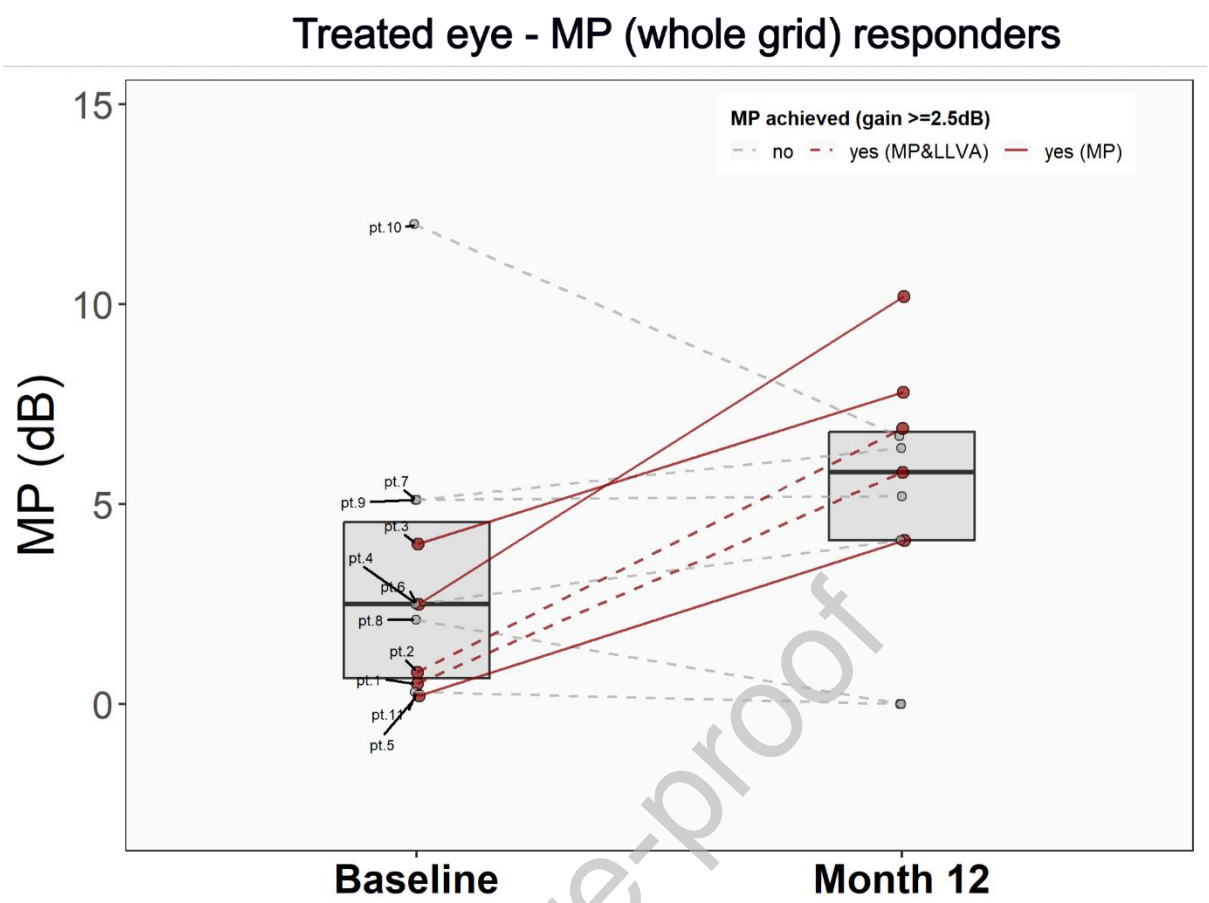


Figure 1. LLVA responders results from baseline to month 12 for all 10 analysis eligible patients. Of these, only 2 patients (20%) achieved an LLVA gain of 15 or more letters that would be considered clinically significant according to guidance from the FDA.



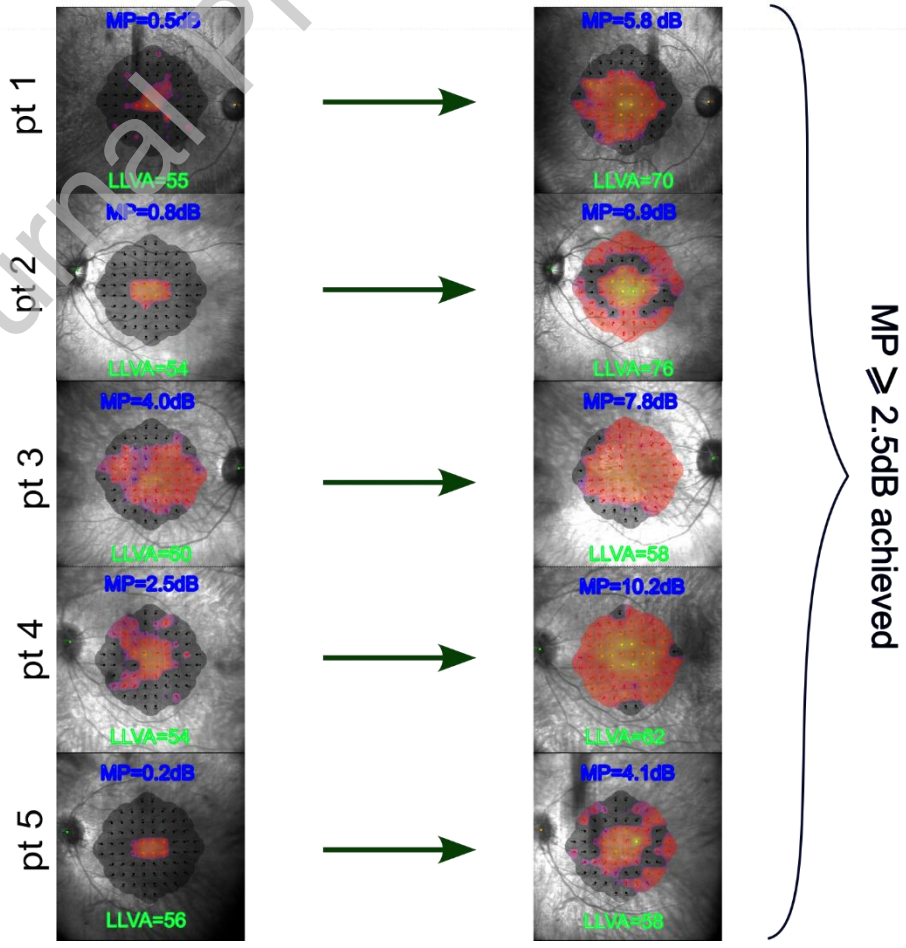


Figure 2. Mean sensitivity responder results (of the entire 68-point grid) from baseline to month 12 for all 11 analysis eligible patients. Here, 5 patients achieved a microperimetry gain of 2.5 decibels or more that would be considered clinically significant according to guidance from the EMA.

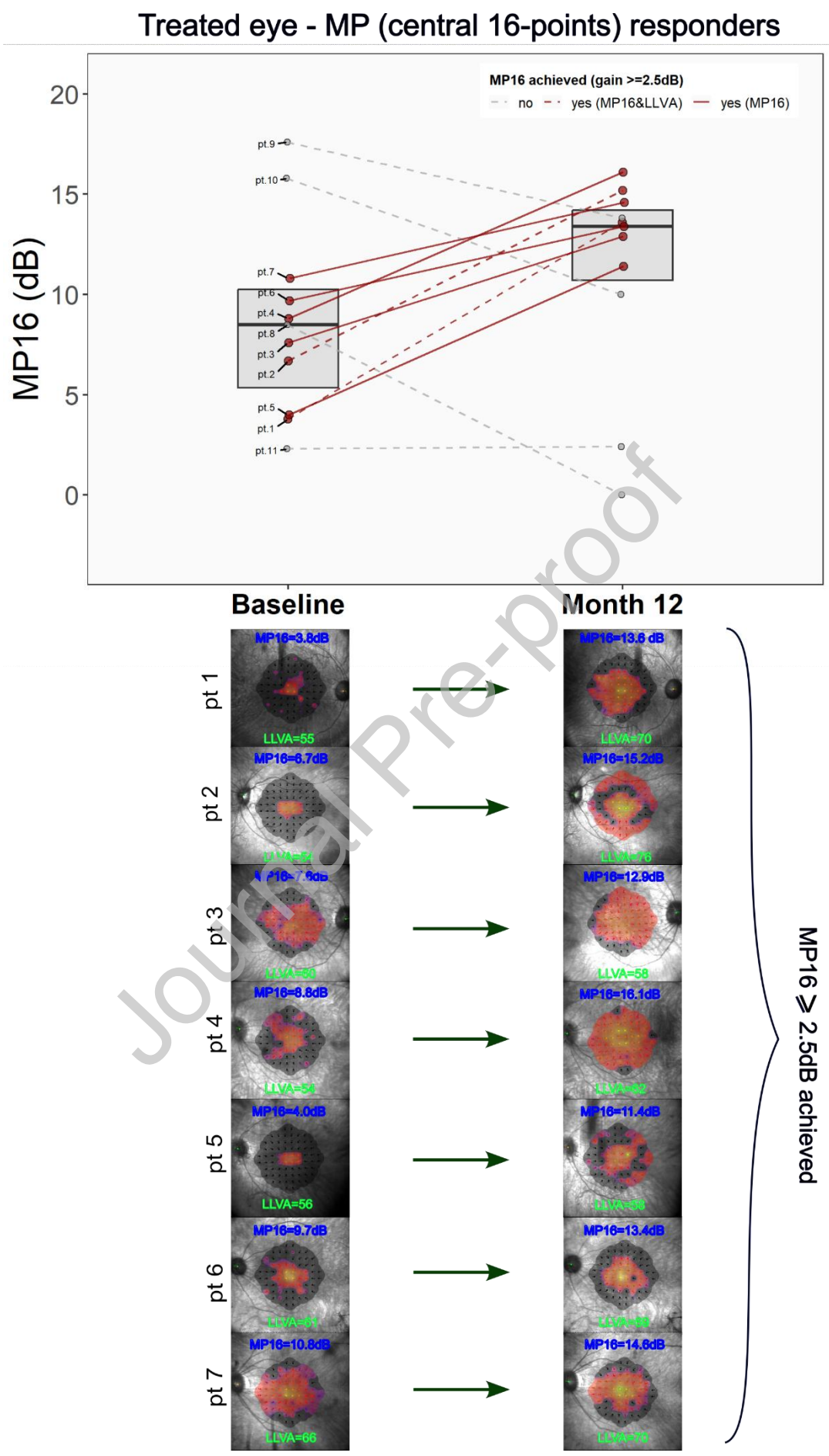


Figure 3. Mean sensitivity responder results (of the central 16-points) from baseline to month 12 for all 11 analysis eligible patients. Here, 7 patients successfully achieved the ≥2.5 decibel gain criteria, which would be a suggested improvement on the previous regulatory authority criteria, namely, microperimetry pointwise changes of 5-points exhibiting a 7-decibel or greater gain. In addition, 3 patients exhibited clinically significant declines (> 2.5 dB) in the central 16-points with all 3 demonstrating only small, clinically insignificant declines in LLVA.

Untreated fellow eye responder analysis

Of the fifteen male patients with *RPGR*-associated retinopathy, application of the predefined post-hoc baseline inclusion criteria on the untreated fellow eyes resulted in the exclusion of four patients from the LLVA analysis due to zero baseline LLVA letter scores and three patients from the microperimetry analysis due to zero baseline mean sensitivity. Consequently, LLVA data were available for 11 patients, while microperimetry data were available for 12 patients.

For the fellow untreated eyes, there were no responders in either the LLVA, whole-grid MP or central 16-point MP endpoints (Figure 4).

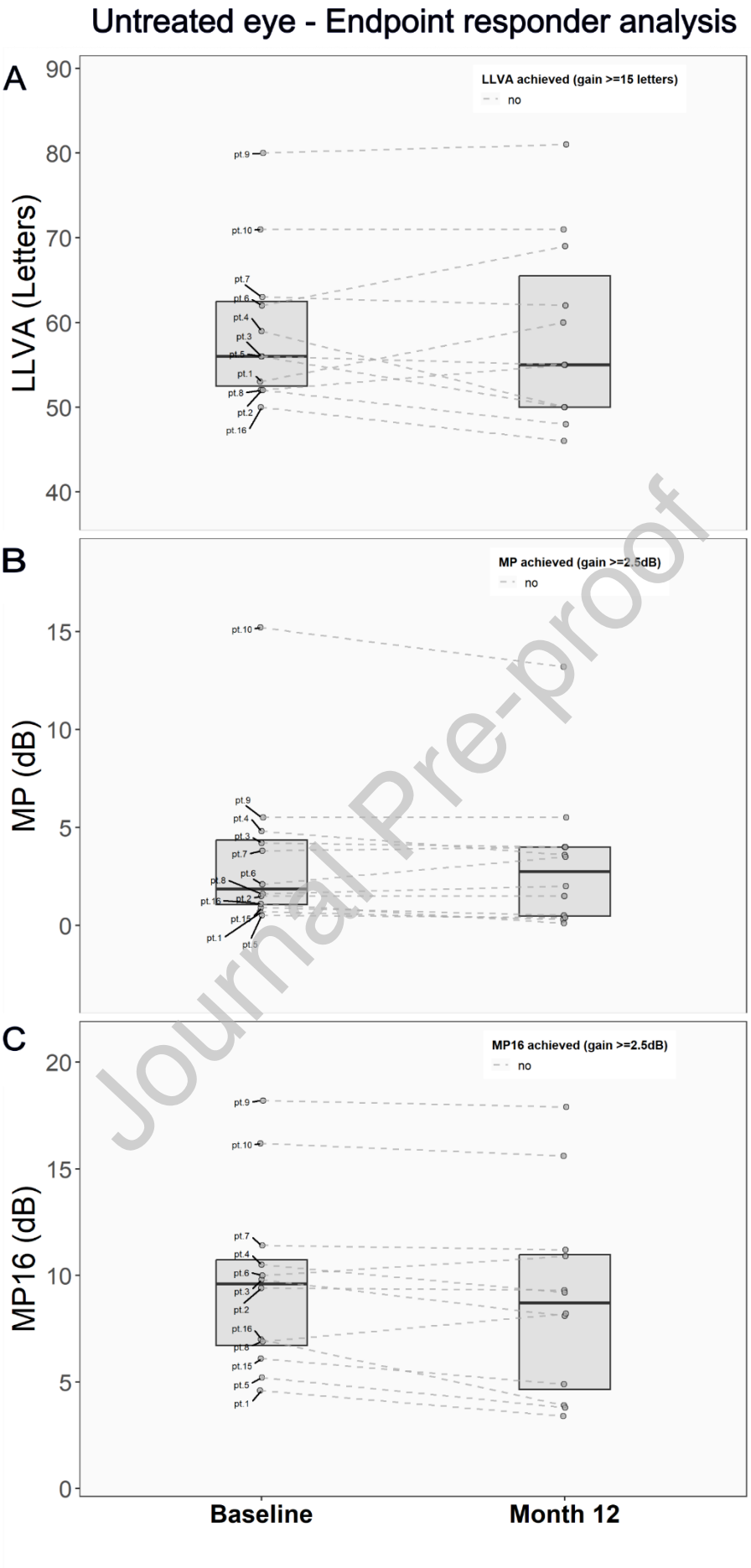


Figure 4. Untreated fellow eye responder analysis. A) LLVA results at baseline and month 12 for all 11 included patients. B) Mean sensitivity results (of the entire 68-point grid) at baseline and month 12 for all 12 included patients. C) Mean sensitivity results (of the central 16-points) at baseline and month 12 for all 12 included patients.

Discussion

This post-hoc analysis demonstrates that primary endpoint selection substantially influences the detection of treatment efficacy and potential dose related toxicity in *RPGR* gene therapy trials. When regulatory responder criteria are retrospectively applied to the XIRIUS datasets, microperimetry-based endpoints identify treatment benefit in substantially more patients than low luminance visual acuity. These findings highlight that LLVA, while simple to perform and intuitive for both clinician and patient, did not capture as many responders as microperimetry based outcomes during the XIRIUS trial. This may not be fully reflective of results in other studies, such as current VISTA trial, where eligible patients, chosen with a moderate preservation of LLVA may show more significant gains.

LLVA has gained interest as a functional outcome reflecting visual performance under mesopic stress [11]. However, its utility in *RPGR*-associated retinopathy is constrained by a narrow dynamic range. As previously shown, LLVA is informative only when disease has partially involved central foveal function. Patients with preserved foveal structure often exhibit near-normal LLVA at baseline, resulting in ceiling effects, while those with advanced central disease frequently reach floor effects below which LLVA is unrecordable [17].

This limitation was evident in the present analysis. Despite clear improvements in retinal sensitivity detected by microperimetry, only two patients met the FDA-aligned ≥15-letter LLVA improvement threshold. Notably, these individuals also demonstrated some of the largest microperimetry gains, suggesting that LLVA responsiveness reflects a specific central

disease location rather than providing a broadly sensitive measure of treatment effect across the treated retinal area. Consequently, reliance on LLVA as a primary endpoint may favour only a small subset of patients. Importantly, the additional responders identified by microperimetry did not demonstrate corresponding LLVA gains, underscoring LLVA's relative insensitivity in this context. Observed microperimetry mean sensitivity improvements of 3–10 decibels represent substantial functional gains exceeding expected learning effects, or test-retest variability (~1.3 decibels [7,18]).

From a trial design perspective, this poses a major challenge. *RPGR*-associated retinopathy is rare, and endpoints sensitive only within narrow phenotypic windows restrict recruitment, limit detectable efficacy, and increase the risk of false-negative outcomes. LLVA may not adequately capture underlying biological efficacy unless patients are carefully selected during eligibility assessments, potentially reducing the pool of potential patients even further.

Microperimetry offers several advantages by directly mapping central macular sensitivity within the treated retinal area. In this analysis, mean sensitivity across the 68-point grid identified more than twice as many responders as LLVA using EMA-aligned criteria. Restricting analysis to the central 16 points further increased responder detection and, arguably, has greater functional significance for patients since the central 16-points encompasses the fovea and para-foveal regions most crucial for reading, facial recognition and many other aspects of modern life. This region's greater association with functional benefit for patients initially appears to bode well for previous FDA-approved microperimetry outcome measure (7-dB improvement at 5 of 16 central loci), however, consideration of only the central 16-points leads to several significant drawbacks; 1) a greater vulnerability to test–retest variability, 2) unintentional restriction of patient enrolment to only those late-stage patients who have impaired central function and 3) potential type 2 error (false negative) in efficacy detection where peripheral gains exist. Hence, caution is warranted when adopting endpoints based solely on the central 16 points, as this may overlook treatment-related improvements in patients with very early disease affecting more peripheral macular regions

whilst leaving the central 16-points relatively unaffected. Although such phenotypes were not eligible for the XIRIUS trial patients considered here, they may be relevant for future trials. Volumetric retinal sensitivity metrics may therefore offer a promising outcome measure which allows for meaningful measurement of retinal sensitivity across most disease stages [19].

Regulatory agencies increasingly emphasize the importance of clinically, or functionally meaningful and disease-appropriate endpoints in inherited retinal disease trials [20]. However, the divergence between FDA-preferred LLVA criteria and EMA-accepted microperimetry mean sensitivity-based endpoints remains unresolved. Our findings show this divergence has tangible consequences: FDA-aligned LLVA responder criteria suggest limited efficacy detection unless strict eligibility criteria are applied, whereas EMA-aligned microperimetry criteria reveal benefit in a substantially larger proportion of patients. This raises concern that effective therapies may fail due to endpoint selection rather than a lack of true biological efficacy.

A key motivation for this analysis was to assess how endpoint choice affects overall patient inclusion. Applying minimal baseline exclusion thresholds preserved broad eligibility while maintaining sensitivity to change. Even so, LLVA excluded more patients at baseline than microperimetry in this post-hoc study due to floor effects. Analysis of untreated fellow eyes revealed no control responders for any explored endpoints, supporting the adequacy of the selected responder thresholds in minimising false positives.

Endpoints enabling broader enrolment are particularly important in rare disease trials and enhance generalisability, recruitment efficiency, and external validity. Microperimetry's ability to detect functional change in patients with preserved central acuity but declining parafoveal sensitivity is therefore especially valuable and aligns with the therapeutic goal of preserving vision before irreversible foveal loss occurs.

This study has limitations. As a retrospective, post-hoc analysis, findings are exploratory, with small sample size and so results are limited to descriptive analyses. Dose variability represents a latent confounder to assessments of overall treatment efficacy which has not been considered and deemed not relevant to the question of endpoint sensitivity here. Nevertheless, the magnitude and consistency of microperimetry improvements exceed those reported in natural history studies and clearly demonstrate superior detection of treatment efficacy compared with LLVA when retrospectively analysing XIRIUS data.

This analysis demonstrates that microperimetry-based outcome measures identify treatment efficacy and possible treatment-related toxicity in a substantially larger proportion of *RPGR* gene therapy recipients than LLVA-based criteria in this post-hoc analysis of XIRIUS trial patient data. This finding may apply more broadly to future trials, particularly in rare diseases, where maximum inclusion is sought by minimizing the number of patients lost due to ineligibility.

Disclosures

Robert E. MacLaren is listed as an inventor on a patent for RPGR gene therapy owned by the University of Oxford and is a scientific co-founder of Beacon Therapeutics. All other authors declare no conflicts of interest.

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Table of contents statement

Microperimetry-based outcome measures identified treatment efficacy and possible treatment-related toxicity in more patients with retinitis pigmentosa GTPase regulator-associated retinopathy receiving gene therapy than low luminance visual acuity criteria. These findings suggest that microperimetry may improve patient eligibility and efficacy detection in future retinal gene therapy trials, supporting its use as a more sensitive and inclusive clinical trial endpoint.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Robert E. Maclaren has patent issued to Robert E. MacLaren is listed as an inventor on a patent for RPGR gene therapy owned by the University of Oxford. All other authors declare no conflicts of interest. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.