

The Benefits of Outer Retina-Choroid (ORC™) Imaging Over FAF for Endpoint Assessment in Dry AMD Clinical Trials

A MERIT White Paper on Structural Imaging Endpoints in Geographic Atrophy

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OBJECTIVE

This white paper examines why the outer retina-choroid (ORC™) en face optical coherence tomography (OCT) image may offer advantages over the fundus autofluorescence (FAF) image as a structural endpoint for dry age-related macular degeneration (AMD) clinical trials, with particular relevance to designs that pair structural imaging with functional testing.

1 FAF's Limitations as an Endpoint Substrate

FAF has served as the primary imaging modality used for total lesion area assessment in geographic atrophy (GA) trials since the 2006 NEI/FDA Symposium on Ophthalmic Clinical Trial Design and Endpoints. Slowing of progression in total lesion area as assessed with FAF is now a validated primary efficacy endpoint that was underpinned by the pivotal OAKS, DERBY, and GATHER programs that led to the first FDA approvals for GA in 2023.¹⁻³ Nonetheless, FAF is a single en face signal: it collapses the outer retina and choroid into one two-dimensional hypoautofluorescence map, discards depth information, and cannot indicate which retinal layer is affected at a given point. Blue-light FAF signal is further confounded by macular pigment — which can limit identification of foveal architecture and cataract, and FAF-based classification cannot separate distinct anatomic states — such as incomplete versus complete RPE and outer retinal atrophy (iRORA/cRORA) or macular fibrosis — that can produce overlapping autofluorescence signatures.^{4,5} In eyes with a thin choroid, background fluorescence from the underlying sclera further reduces the contrast between areas where the RPE is present and absent, compounding the limitations above. More fundamentally, FAF signal reflects primarily RPE fluorophore content rather than the full biology of atrophy, and is relatively insensitive to disease preceding established atrophy. These constraints bear directly on the endpoint problem exposed by the first approved GA therapies: FDA accepted anatomic lesion-growth slowing as a basis for approval, but the EMA issued a negative opinion on pegcetacoplan, concluding that the anatomic effect did not demonstrate clinically meaningful benefit.⁶

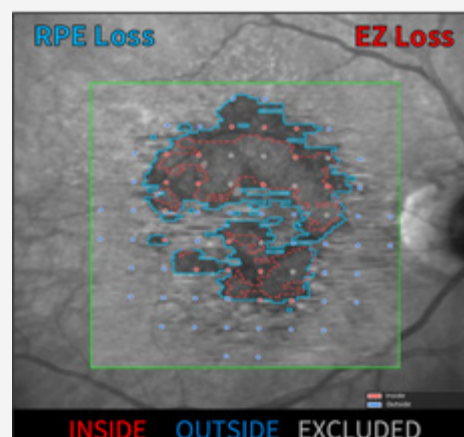
2 ORC: A Structurally Richer Alternative

ORC generates an en face image by summing the posterior OCT signal band — spanning the outer retina and choroid — from a DICOMized volumetric scan processed with a vendor-agnostic noise-reduction algorithm.⁷⁻⁹ Because it is derived from registered B-scans rather than a collapsed 2-D

signal, ORC retains layer-level structural information that FAF cannot provide. In a 29-eye cohort at Retina Consultants of Texas, ORC and FAF produced comparable total lesion area, with a cohort mean $\text{mm}^2 = 7.00$ (range 0.55- 19.61) vs 7.08 (range 0.50-18.28) mm^2 , respectively; but ORC additionally resolved anatomic distinctions — iRORA versus cRORA versus macular fibrosis — that were indistinguishable on FAF, and avoided artifact from macular pigment that affected FAF grading in the same eyes.⁷ A subsequent reproducibility analysis of 27 eyes presented at EU Retina 2026 found ORC outperformed FAF-based RegionFinder grading on every reliability metric: intraclass correlation coefficient 0.985 vs. 0.949, coefficient of variation 5.52% vs. 14.3%, and repeatability coefficient 0.75 vs. 2.42 mm^2 .⁸ That same 27-eye analysis also found a statistically significant difference in absolute lesion area between the two methods (Wilcoxon signed-rank test, $p = 0.00016$): Bland-Altman analysis showed a mean bias of 0.657 mm^2 (95% limits of agreement -0.88 to 2.19 mm^2), with ORC systematically yielding higher values than FAF and a percentage error of 20.8%, indicating moderate rather than complete agreement. Neither ORC nor FAF constitutes a validated gold standard regarding histopathology for lesion area, so the reproducibility advantage described above reflects grader agreement within each method, not absolute agreement between methods. ORC and FAF are therefore correlated but not fully interchangeable at the individual participant level when measured on their respective software platforms. As an investigational morphologic endpoint, this distinction points to a specific test for ORC's biological relevance: whether regions that are ORC-positive but FAF-negative already show significantly reduced retinal sensitivity on microperimetry, and whether those regions subsequently convert to FAF-defined GA. Measurement precision of this magnitude could translate into greater statistical power to detect a treatment effect, potentially supporting smaller sample sizes or shorter follow-up; confirming that potential advantage for trial design would require a formal power analysis.

SUPPORTING FIGURE

Correlate Foci + Multiple Layers. Al-kherson, Wykoff, et al. Microperimetric Sensitivity and RPE and Photoreceptor Outer Segment Loss by En Face OCT Analysis Using Outer Retina Choroid (ORC) in Eyes with GA. *ARVO 2027 Abstract submission in press.*



3 Why This Is Decisive for Structure-Function Analyses

The unresolved question in GA drug development is not whether a therapy slows anatomic lesion growth, but whether that anatomic effect corresponds to preserved visual function — the discordance that has separated FDA and EMA conclusions to date.^{6,10} Answering that question requires structural data that can be spatially registered, point by point, against functional testing such as microperimetry. A single collapsed FAF signal cannot support this: it carries no layer-specific information at a given locus, so a change in FAF intensity cannot be attributed specifically to photoreceptor loss, RPE loss, or choroidal change, and it cannot be reliably co-registered to a functional testing grid. ORC's B-scan-derived, layer-resolved structure is built for exactly this correspondence. This is why MERIT's imaging scientists and collaborating retina specialists have identified the quantified OCT-based ORC biomarker paired with microperimetry as an analysis with the potential to help connect anatomic change to functional benefit — an association that regulators, including the EMA, have identified as critical to demonstrating clinical meaningfulness. Layer-specific structural measures are expected to correlate more directly with functional outcomes than lesion area alone, and establishing that relationship is expected to be an important component of multi-national regulatory strategy for new GA therapies.

4 Regulatory Precedent for OCT-Based Structural Endpoints Analyses

ORC is not the first OCT-derived structural measure to seek a role once reserved for FAF-based endpoints, and the regulatory record for its predecessors is instructive. Ellipsoid zone (EZ) attenuation moved from an exploratory secondary measure in the ReCLAIM-2 phase 2 trial of elamipretide to an FDA-confirmed approvable primary endpoint in 2023, on the strength of a 43% reduction in total EZ attenuation and 47% reduction in partial EZ attenuation at 48 weeks relative to placebo — despite that trial missing its prespecified anatomic and visual acuity endpoints.¹¹ That confirmation now underpins the phase 3 ReNEW elamipretide program, which uses OCT-based EZ mapping as its primary endpoint. OCT-based EZ mapping is not without its own limitations — boundary definition can be affected by interobserver variability and image quality — but FDA's acceptance of it as a primary endpoint nonetheless establishes precedent for OCT-derived structural measures. Separately, a CAM Study Group consensus has identified choroidal hypertransmission defect growth, the same hypertransmission signal ORC measures across the full posterior slab, as one of the OCT features suitable for use as a continuous-variable endpoint in intermediate AMD trials.¹² Neither precedent qualifies ORC by extension, but both demonstrate that FDA has already accepted OCT-derived, layer- or signal-specific structural measures as primary endpoints where FAF could not reach, establishing a qualification pathway that ORC's ongoing validation program is designed to follow.

5 From Quantification to Structure-Function Validation

Regulatory acceptance of an anatomic endpoint is necessary but not sufficient; MERIT's retina KOL working group has emphasized that imaging biomarkers must be reliably quantified before they can support endpoint definitions, inclusion criteria, or enrichment strategies, and that quantification is what ultimately allows an anatomic signal to be paired credibly with a functional endpoint. Because these are the same features required for regulatory acceptance, the more direct framing leads with the need for the measure to be reliably reproducible and independently validated, which in turn enables that regulatory acceptance: reproducible, reliable quantification is what facilitates the topographic structure-function correspondence needed to demonstrate responsiveness and to enable validation across disease states and severity. ORC's layer-resolved, B-scan-registered output is being extended toward systematic quantification of additional structural features — including hyperreflective foci and outer retinal layer loss — using the same vendor-agnostic processing pipeline validated for lesion-area measurement. Pairing this quantified continuous structural endpoint with microperimetry at matched retinal loci is, in the view of MERIT's collaborating investigators, the analysis best positioned to demonstrate that a structural treatment effect corresponds to a measurable functional one, directly addressing the concern that shaped the EMA's review of the first approved GA therapies.

6 Outlook: Extending the Approach to Intermediate AMD

The limitations of FAF described in Section 1 are, if anything, more consequential earlier in disease. FAF is largely insensitive to the OCT-defined precursor changes — incomplete RPE and outer retinal atrophy (iRORA), nascent GA, and choroidal hypertransmission defects — that mark the transition from intermediate AMD to established GA, which limits its utility for trials targeting the stage at which intervention may be most effective. A comparison of ORC against Layer Loss Analysis for iRORA detection across 37 eyes with intermediate AMD and GA found high agreement between the two OCT-based methods (94.6% by eye, 88.6% by locus), including hypertransmission defects at the GA border and in the perilesional zone that were not well seen on FAF.¹³ MERIT and its collaborating retina specialists are pursuing longitudinal cohorts in intermediate AMD, imaged at approximately six-month intervals alongside microperimetry, to characterize progression risk and further validate ORC's biomarker utility ahead of established GA. This extension is the subject of continued investigation and a planned subsequent white paper.

CONCLUSION

ORC remains at the proof-of-concept stage and has not yet been formally validated as a clinical trial endpoint; longitudinal validation and formal biomarker qualification with FDA, and EMA Scientific Advice for global programs, remain outstanding. But the evidence to date — lesion-area quantification correlated with FAF though not fully interchangeable at the individual participant level, superior reproducibility, and preservation of layer-specific structural information — positions ORC as the more capable substrate for the structure-function analyses that next-generation dry AMD trials, and the regulators evaluating them, increasingly require. MERIT recommends that sponsors evaluating structural endpoints for dry AMD trials, particularly those pairing imaging with functional testing, incorporate ORC alongside FAF as a complementary or exploratory structural measure. Further studies are needed to differentiate how the ORC image correlates with photoreceptor dysfunction, iRORA, and established RPE loss, so that this imaging modality can ultimately help categorize disease into biologically meaningful compartments.

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SUPPORTING FIGURES

Representative ORC and FAF images from the ARVO 2025 proof-of-concept cohort (Figure 2 and 3 of Reference 7) and from the ARVO 2026 27-eye cohort from participants with high-risk Dry AMD (Fig 2 of Reference 13) illustrating the anatomic distinctions described in Sections 2 and 3

Figures: proof-of-concept cohort

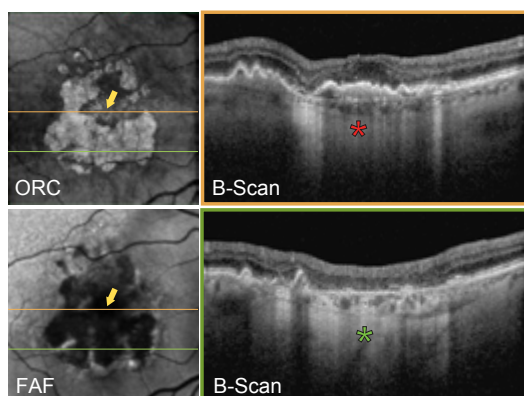


Figure 2. ORC (top left) and FAF (bottom left) images of the same lesion show similar boundaries, but FAF displays a presumed macular-pigment artifact (yellow arrow) that is absent on ORC; matched B-scans at right.⁷

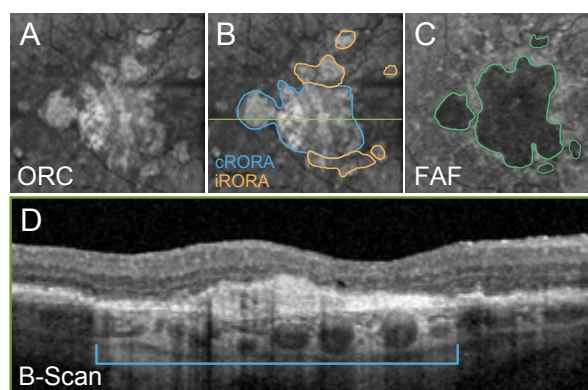


Figure 3. ORC (A) resolves complete (cRORA, blue) and incomplete (iRORA, orange) atrophy within one lesion (B) that appears as a single confluent area on FAF (C); the corresponding B-scan (D) shows fibrosis not distinguishable from atrophy on FAF alone.⁷

Figure: 27-eye cohort

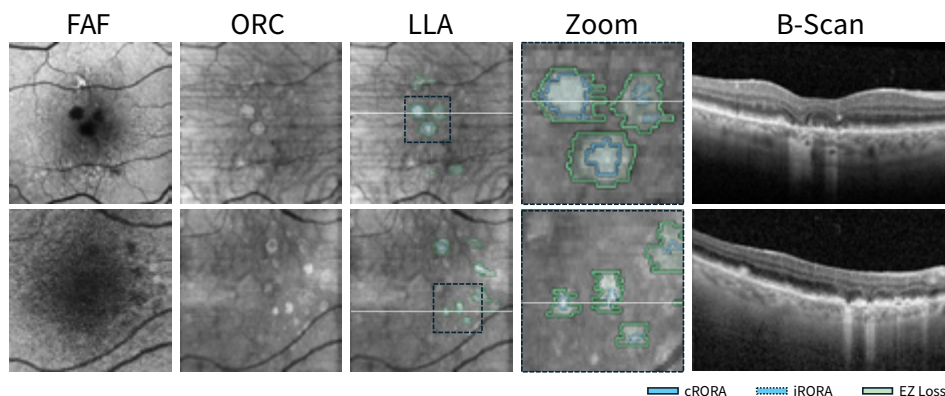


Figure 2. Top row, an eye with multiple loci of abnormality on both FAF and ORC. Three regions of interest are shown from the LLA analysis with a representative B-scan that passes through an area of cRORA and iRORA (top right). The LLA and Zoom images show 1) areas of EZ defect outlined in green, and 2) areas of RPE defect outlined in blue. Lesions meeting the size criteria for iRORA are shown with dashed lines while those larger have solid lines. Bottom row, a second eye with multiple loci of iRORA on FAF and more notably on ORC™ and LLA. The representative B-scan passes through two regions of iRORA.