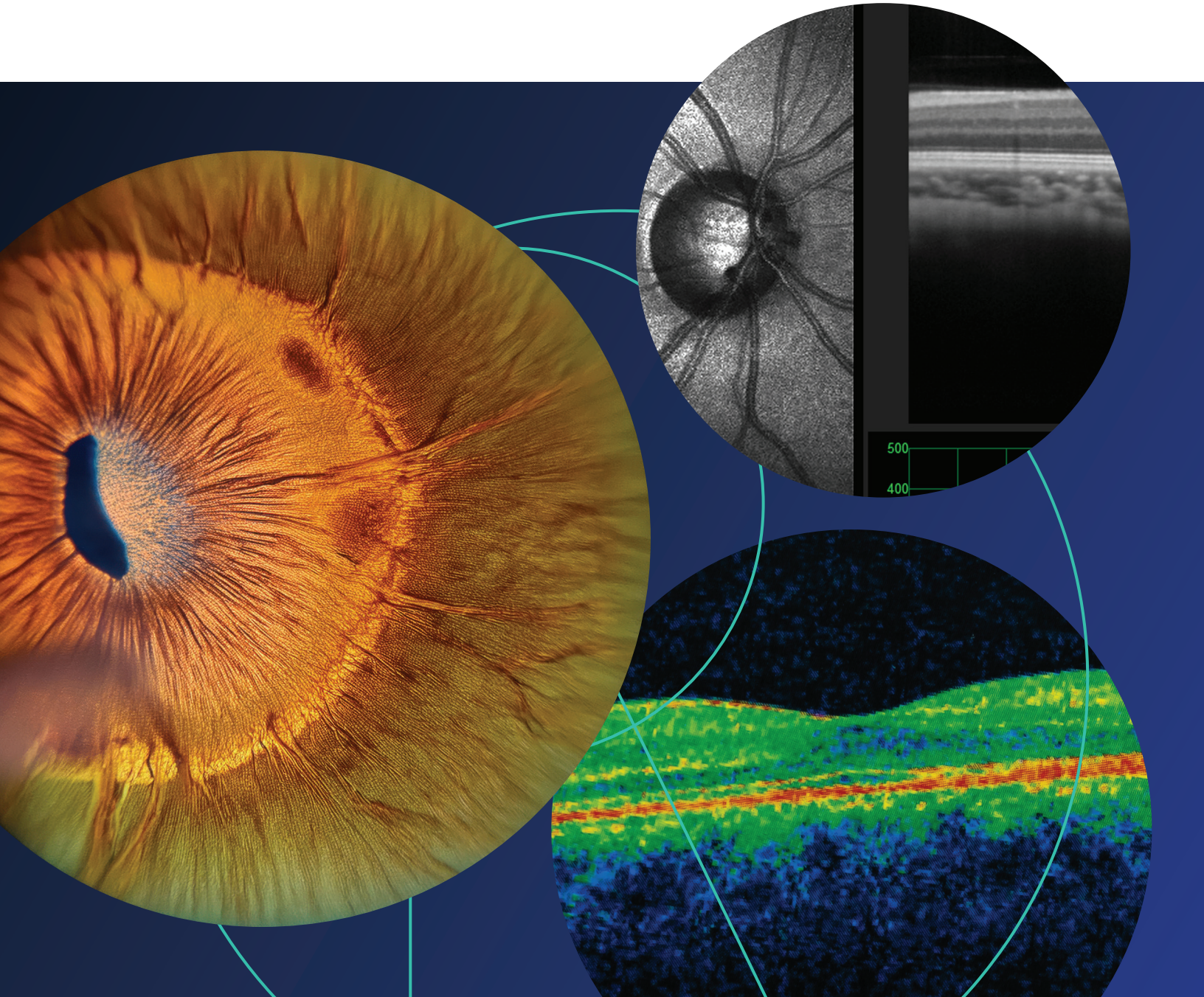
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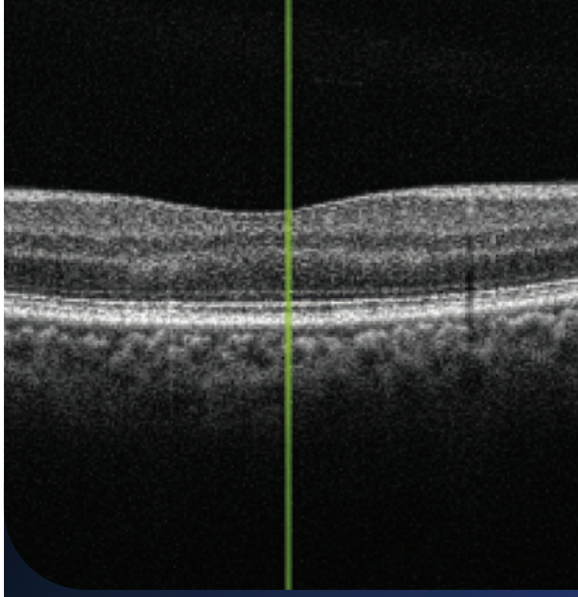
FROM OUR PERSPECTIVE

Intermediate AMD Endpoints

The shift toward structural biomarkers and hypertransmission defects



Intermediate AMD
A critical window for therapeutic intervention



Intermediate age-related macular degeneration (iAMD) has emerged as one of the most active areas of retinal drug development, driven by the promise of intervening before irreversible vision loss occurs. Yet iAMD presents a unique challenge for clinical development. Unlike geographic atrophy (GA) or neovascular AMD, patients often maintain relatively preserved best-corrected visual acuity (BCVA) despite ongoing structural degeneration within the retina. As a result, traditional visual acuity endpoints may lack the sensitivity required to detect treatment effects during this critical stage of disease.

This challenge is particularly relevant as the therapeutic landscape expands beyond prevention of late-stage disease to include approaches aimed at preserving retinal integrity, slowing disease progression, and potentially restoring retinal function. Because the biological changes associated with iAMD frequently precede measurable losses in visual acuity by years, investigators and regulators are increasingly focused on imaging biomarkers capable of quantifying disease progression before substantial functional decline becomes apparent.

OCT-derived structural biomarkers are becoming central to modern iAMD trial design, enabling sponsors to evaluate whether investigational therapies meaningfully alter the trajectory of disease progression.

The growing importance of structural endpoints

Historically, BCVA has served as the cornerstone endpoint in retinal clinical trials. However, its utility is limited in iAMD, where patients can demonstrate substantial anatomical progression without clinically meaningful changes in vision. Consequently, there is growing consensus that efficacy assessment in iAMD should focus on biomarkers that reflect the underlying disease process rather than relying exclusively on visual acuity outcomes.

Recent discussions among retinal experts, including leaders from the Bascom Palmer Eye Institute and the Ryan Initiative for Macular Research, emphasize that successful iAMD development programs will likely require endpoints capable of demonstrating a slowing in the rate of disease progression, rather than simply measuring the occurrence of a late-stage disease event such as conversion to GA or neovascular AMD.

This evolution reflects broader regulatory thinking. FDA discussions highlighted by retinal key opinion leaders have increasingly focused on continuous measures of progression that can demonstrate disease modification over time rather than binary event-based outcomes alone.

Hypertransmission Defects
An Emerging Consensus Endpoint

Among the various structural biomarkers under investigation, persistent choroidal hypertransmission defects (hyperTDs) have emerged as the leading endpoint for iAMD clinical development.

Research led by Philip J. Rosenfeld and colleagues demonstrated that hyperTDs can be detected and quantified using en face OCT imaging, allowing both the onset and enlargement of lesions to be measured longitudinally. Importantly, these lesions represent an earlier stage of atrophic progression, developing before the appearance of clinically recognizable GA.

Longitudinal imaging studies have shown that hyperTDs emerge in eyes with iAMD, enlarge over time, and eventually coalesce into larger atrophic regions characteristic of established GA. This progression provides a unique opportunity to measure disease activity before traditional late-stage endpoints become apparent.

Recent consensus recommendations further strengthened the role of hyperTDs by identifying the onset and enlargement of hyperTDs measured with en face OCT imaging as the only currently validated OCT-based endpoint for quantifying disease progression in iAMD clinical trials.

As a result, many sponsors are increasingly evaluating

- Incidence of new hyperTD formation
- Change in hyperTD area from baseline
- Rate of hyperTD growth over time
- Overall slowing of hyperTD progression relative to control

Recent clinical trial design recommendations

In 2024, a consensus framework for iAMD clinical trials was presented by Philip J. Rosenfeld and collaborators from the Ryan Initiative for Macular Research and the Classification of Atrophy Meeting (CAM) group. Key recommendations included:

- Design studies around slowing disease progression rather than preventing a single event.
- Utilize OCT-derived structural endpoints capable of continuous measurement.
- Enrich study populations with high-risk patients most likely to demonstrate progression within the study period.
- Plan studies with sufficient duration, typically 18 to 24 months, to characterize changes in disease trajectory.
- Structure Phase 2b studies so they may contribute directly toward pivotal development programs.

The consensus group also recommended enrolling eyes at elevated risk of progression, including those with:

- Central drusen volume ≥0.22 mm^3
- Presence of hyperreflective foci
- No evidence of existing persistent hyperTDs at baseline

These enrichment strategies are intended to maximize the likelihood of observing meaningful anatomical progression within a clinically practical study duration.

Recommended endpoint strategy for iAMD studies

For many iAMD programs, efficacy assessments are expected to focus on changes from baseline through study completion, typically over 18 to 24 months.

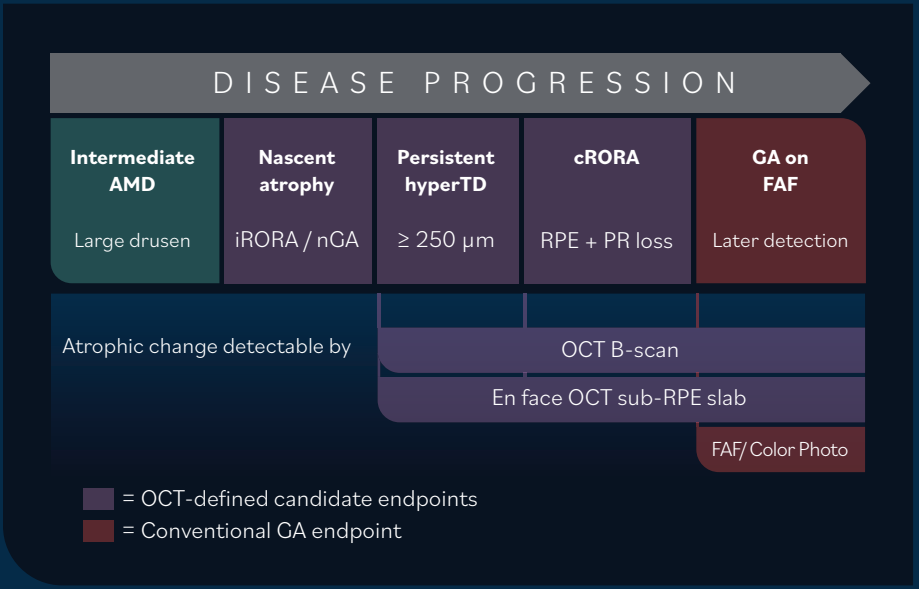
Leading OCT based endpoint under evaluation for clinical trials

Persistent Choroidal Hypertransmission Defects (hyperTDs)

Potential primary analyses include:

- HyperTD incidence
- HyperTD area growth
- Rate of hyperTD enlargement
- Change from baseline to end of study
- Slowing of hyperTD progression versus control

Because hyperTDs occur before clinically recognized GA, they provide a means of evaluating therapeutic impact earlier in the disease continuum.



Key secondary endpoints

Targeted Microperimetry

Microperimetry provides localized assessments of retinal sensitivity and may detect functional changes before BCVA deterioration. Change from baseline through study completion can help evaluate whether anatomical preservation translates into functional benefit.

Ellipsoid Zone (EZ) Loss

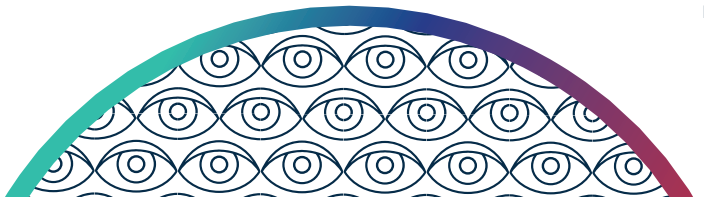
Progressive EZ loss represents an important marker of photoreceptor integrity and retinal degeneration. Alongside hyperTDs, EZ loss is one of the few structural biomarkers that can be measured continuously over time and may serve as an important complementary endpoint.

Contrast Sensitivity

Low-Luminance Quantitative Contrast Sensitivity Function (LL-QCSF) testing can provide a sensitive measure of visual performance and may be useful for detecting clinically meaningful functional change over time.

Low-Luminance Visual Function

Low-luminance visual acuity and related assessments are frequently incorporated into iAMD studies because they may identify subtle visual dysfunction earlier than conventional BCVA testing.



Progression to Late AMD

- Incidence of geographic atrophy
- Incidence of neovascular (wet) AMD

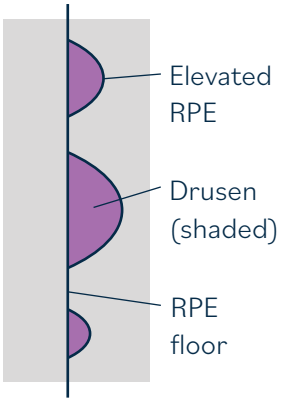
While event-based outcomes remain clinically important, they are generally considered supportive measures rather than the most sensitive indicators of treatment effect in iAMD.

Exploratory Endpoints

Drusen Volume

Drusen volume is increasingly being explored as a quantitative OCT biomarker that may support patient enrichment strategies and provide additional insight into disease activity. OCT-based volumetric analysis enables assessment of the three-dimensional burden of subretinal and sub-retinal pigment epithelium (RPE) deposits and may help identify eyes at greater risk for progression.

Although changes in drusen volume may provide valuable biological information, current evidence suggests its greatest utility may be in identifying high-risk populations and understanding disease behavior rather than serving as a primary efficacy endpoint.



Conclusion

Intermediate AMD is rapidly evolving from a disease defined primarily by risk of progression to one increasingly targeted by therapeutic intervention. As the development landscape expands, endpoint strategies are shifting beyond traditional visual acuity measures toward sensitive structural biomarkers capable of detecting earlier disease modification.

Emerging consensus supports persistent choroidal hypertransmission defects as the leading and currently validated OCT-based endpoint for quantifying disease progression in iAMD. At the same time, complementary measures such as microperimetry, low-luminance visual function, contrast sensitivity, EZ loss, and progression to late AMD can provide a broader understanding of treatment impact.

As with any development program, endpoint selection should ultimately align with the specific mechanism of action, biological target, and anticipated treatment effect of the investigational therapy. Thoughtful integration of structural, functional, and progression-based measures will be critical to demonstrating meaningful clinical benefit and advancing the next generation of therapies for patients with iAMD.

For additional perspective on endpoint selection, imaging biomarkers, and study design considerations for your iAMD program, contact Ora at www.oraclinical.com.

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