

Assessing Novel Efficacy Endpoints in Ophthalmologic Rare Disease Drug and Biologics Development

Hybrid Meeting | National Press Club

September 17, 2025 9:30 am-2:30 pm ET

Discussion Guide

Background and Event Objectives

Millions of Americans live with severe vision loss or blindness, which can immensely hinder quality-of-life and daily functions. Clinical trials for ophthalmologic products to treat these conditions face fundamental design challenges because traditionally accepted endpoints may be infeasible for those living with severe vision loss. Clinical trials for treatments for rare diseases that cause severe vision loss often involve small, heterogeneous patient populations and therefore require sensitive efficacy endpoints that capture meaningful quality-of-life improvements for those with limited visual function.

This meeting, convened by the Duke-Margolis Institute for Health Policy under a cooperative agreement with the U.S. Food and Drug Administration (FDA), will focus on novel efficacy endpoints used in interventional clinical trials for drugs and biological products intended for patients with severe vision loss to support regulatory decision-making. The meeting will include insights from patient advocates, clinicians and researchers, and representatives from the FDA.

Presently, ophthalmologists most commonly use best corrected visual acuity (BCVA) as the gold standard metric for assessing a patient's vision. The measure assesses the eye's ability to discern the shape and details of an object at a given distance using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, widely adopted for its ease of use and cost-effectiveness. Historically, a three-line or fifteen-letter improvement in the ETDRS chart has been considered a clinically meaningful change for the purposes of regulatory decision-making. BCVA and its corresponding visual acuity tests are often infeasible for people with severe vision loss or an ophthalmologic disease affecting areas outside of the macula. A person with severe vision loss may not be able to see any of the letters on the ETDRS chart, and a three-line improvement on the chart may be an unreasonable target. Furthermore, when targeting disease progression as the primary efficacy outcome in the setting of a slowly progressive disease, BCVA may not be sensitive to detect an early benefit on disease stabilization or change over the 1-to-2 year study duration.

Novel endpoints can help mitigate some of the limitations of traditionally accepted endpoints but, in order to constitute the primary evidence used to support regulatory decision-making, they must demonstrate clinical meaningfulness for people living with vision loss – measuring an improvement in how they feel, function, or survive. This meeting will consider full-field stimulus threshold testing (FST) and ellipsoid zone data (EZ), two novel ophthalmologic outcome assessments of interest to clinicians, researchers, and regulators alike. Panelists will discuss the opportunities and limitations associated with each tool, and the meeting will culminate in a discussion of future priorities and key takeaways for these

tools to potentially serve as endpoints in regulatory decision-making for interventional ophthalmologic rare disease trials where severe vision loss precludes reliable assessment with traditional efficacy endpoints such as BCVA.

Session I: Role of Full-Field Stimulus Threshold in Ophthalmologic Therapeutic Drug and Biologics Development

Background

Full-field stimulus threshold testing measures rod-, cone-, or mixed-mediated changes using different colored stimuli. FST measures the level of intensity needed for patients to see the stimuli fifty percent of the time, and improvements in FST indicate detection of dimmer light stimuli. Some evidence exists to correlate FST measurements with other assessments of visual function for patients with certain ophthalmologic conditions.^{1,2} Research also suggests that FST is a more sensitive measure than BCVA and does not experience similar floor effects (i.e., it can produce a usable measurement for patients with severe vision loss whose vision would be “off the chart” in BCVA tests), making the endpoint more suitable for patients already experiencing severe vision loss. Additional research into the validity and clinical meaningfulness of FST is underway, particularly related to establishing a threshold for a clinically meaningful change in FST measurements, as well as its utility and applicability for different ophthalmologic conditions and patient populations.

Discussion Questions

1. What is the clinical meaningfulness of FST to patients’ experience with the disease, such that it can inform how patients feel and function in their daily lives?
 - a. What is a clinically significant change in FST? If this is not yet determined, how can clinicians and researchers go about determining an appropriate value?
 - b. What data exist to demonstrate that FST correlates with clinical outcomes?
2. What are the considerations regarding how to measure and assess FST in pediatric populations?
3. What are the methodological considerations regarding assessment of FST to support regulatory decision making?
 - a. What is an appropriate correlation coefficient?
 - b. What data exists to support the sensitivity and specificity of an FST based endpoint?
 - c. What are the considerations regarding instrument to measure FST to ensure the data is reliable and reproducible?

Session II: Role of Ellipsoid Zone Data in Ophthalmologic Therapeutic Drug and Biologics Development

Background

Ellipsoid zone (EZ) related endpoints are anatomical endpoints that measure reduction in EZ band thickness, area, or volume using optical coherence tomography (OCT) imaging. The rate of EZ loss should be measured and the comparison should be made between the baseline and at least two subsequent area images, with intervals of 6 months or more between images.³ The EZ itself is a band of densely clustered photoreceptors that is highly reflective and therefore may be visible in OCT images. The

correlation with visual function is being explored. Though EZ is an anatomical, rather than functional, endpoint, changes to the EZ band are increasingly considered an indicator of photoreceptor integrity and thus disease progression and loss of visual function. For some inherited retinal diseases, changes in EZ area and width are commonly used endpoints, including the upcoming phase 3 oral N-acetylcysteine trial for retinitis pigmentosa.⁴ Research indicates the band's reflectivity may increase the endpoint's sensitivity, resulting in earlier disease detection, relative to other structural measures (i.e., changes to outer nuclear thickness often occur later in disease progression).^{5,6} However, the endpoint is commonly supplemented with functional measures to demonstrate clinical meaningfulness for patients. CBER recently approved ENCELTO, a gene therapy, with change in EZ area loss as the primary outcome measure using OCT imaging and aggregate sensitivity loss of microperimetry as a secondary measure.⁷ Notably, there may not be a direct relationship between EZ and visual function. Segments of the EZ can remain stable in one part of the eye while the band degrades in a separate location. In addition, EZ loss may precede visual function loss and, in some cases, change in EZ can be detected before changes in BCVA or visual field become apparent. Additional considerations for the endpoint include inter-device variation resulting from different imaging technology or varied pupil placement in imaging devices. Ongoing and future EZ research priorities include efforts to standardize imaging practices and OCT grading techniques.

Discussion Questions

1. What is the clinical meaningfulness of EZ to patients' experience with the disease, such that it can inform how patients feel and function in their daily lives?
 - a. How can we assess the clinical significance of different degrees of change in the EZ?
 - b. What data exists to demonstrate that EZ correlates with clinical outcomes?
2. What are the considerations regarding how to measure and assess EZ in pediatric populations?
3. What are the considerations regarding how to measure and assess EZ in different diseases?
4. What are the methodological considerations regarding assessment of EZ to support regulatory decision making?
 - a. What is an appropriate correlation coefficient?
 - b. What data exists to support the sensitivity and specificity of an EZ based endpoint?
5. What steps or approaches may be appropriate to ensure reliable and reproducible measurements of EZ across different reading centers and with different OCT imaging equipment?
 - a. How might these differ across automated, semi-automated, and manual methods?

Session III: Key Takeaways and Next Steps for FST and EZ in Interventional Clinical Trials

Background

Clinical trials for rare diseases often involve challenges unique to these conditions – including small patient populations, variable rates of disease progression, and heterogenous patient experiences. The use of FST, EZ, and any other tools in clinical trials require standardized methodologies and documentation that help reduce inter-site variability in trials and clinical care settings. This may be

particularly critical for clinical trials for rare diseases, where effect sizes and the statistical power of clinical trials may be smaller than in other fields.

Researchers and clinicians are also considering the role of artificial intelligence and semi-automated algorithms in reading imaging data. These technologies require thoughtful consideration and introduce an increased risk of measurement variability. While these technological advancements cannot exist independent of trained clinicians and technicians, they are nonetheless shaping future ophthalmologic clinical trial priorities and capabilities.

Discussion Questions

1. How can patient-reported outcomes or other forms of patient input support the development of thresholds for clinically meaningful difference? How can performance-based tests (e.g., multi-luminance mobility testing) support these efforts?
2. What are ways to make the use of FST and EZ more feasible and standardized, and more accessible for populations with different levels of visual impairment?
3. What are ways to address the limitations of FST and EZ data to support regulatory decision making?
4. What are the most important takeaways for regulators, industry, patients and caregivers, and others in the audience from today's discussions and from the existing clinical research on FST and EZ?

References:

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