

The Balancing Act of a Single Pivotal Trial in Ophthalmology

The US (United States) Food and Drug Administration's (FDA) long-standing mission is to protect and promote public health. In fact, the approval of a drug by the US FDA typically signals to the world that a drug is safe and effective.¹ The FDA's mandate includes both rigorous oversight of regulated products to ensure their safety and effectiveness as well as employing regulatory flexibility to respond to innovation and promote timely access to new treatments.

The US regulatory environment has evolved substantially since the federal government first started to regulating food production and drug development. The initial regulatory policy enacted by the US dates to 1906 with the Pure Food and Drug Act, which was spurred on by Upton Sinclair's book *The Jungle*. The *Jungle* created an intense focus on the quality of food after Sinclair's book highlighted the shortcomings of the meatpacking industry in Chicago, IL, US. While the Pure Food and Drug Act was the first step toward pushing manufactures to create safe and effective products, the Act only required manufactures to accurately list product ingredients.² The 1938 Food, Drug and Cosmetic Act later required drugs to be non-toxic and the 1962 Kefauver-Harris Drug Amendments required drugs to be efficacious.²

The guidance around producing a safe and efficacious drug has continued to evolve over the years, though the FDA's default stance for demonstrating safety and efficacy has been two pivotal clinical trials since the 1962 Kefauver-Harris Amendments.² One could define a pivotal trial as a trial that serves as the basis of approval for a new drug or an existing drug for a new indication.^{1,3} The requirement for two pivotal trials stems from the policies requirement for 'an adequate and well-controlled clinical investigation.'^{3,4} Yet, legislation was passed in 1997 that allowed for drug approval with a single pivotal trial to help bring drugs to market faster, especially for those who are suffering from debilitating disease without treatments.⁵ The FDA has since (2023) provided draft guidance on how to conduct a single pivotal trial.⁶

Statistically speaking, with the two-trial requirement, Sponsors are required to demonstrate that a new drug is effective more than once, thus reducing the likelihood of a false positive result, potentially leading to an incorrect conclusion that a drug is efficacious.

Certain kinds of products in development, especially those aiming to treat diseases with high unmet need and no available therapies, such as rare diseases and oncology indications in particular, faced significant challenges in conducting two standalone trials. Recruiting participants from very small and typically heterogenous disease populations for two trials is often not feasible. Further, the use of placebo controls in diseases that are rapidly progressing, severely debilitating and/or fatal is not ethical. Thus, fulfillment of a two

adequate and well controlled trial mandate was often not possible in these circumstances.²⁻⁴

Flexibility in regulatory decision-making advanced with the emergence of innovative and disease targeted treatments ranging from therapeutic biologics (antibodies, enzymes, proteins, etc.) in the 1990s and more recently to individualised gene therapy/gene editing/T-cell immunology and Chimeric Antigen Receptor T-cell (CART) therapeutic products.² Much of this flexibility has been facilitated by FDA designations/processes such as Orphan, Fast-Track, Breakthrough Therapy, Accelerated Approval, or Priority Review, which again are aimed at bringing treatments to market faster for those who are in need of rehabilitative or life-saving treatments.⁷

The FDA's acceptance of one trial for approval has become more common. This is highlighted by work from Zhang *et al.* who found that 19.4% of approvals between 1995–1997, 39.7% of approvals between 2005 and 2007 and 47.2% of approvals between 2015 and 2017 were supported by single pivotal trial.³ Zhang *et al.* found that using an accelerated pathway programme was not required for a single pivotal trial approval.³ The caveat with the single trial approval approach is the expectation for Sponsors to provide confirmatory evidence of a product's safety and efficacy, from related indications, animal models, class effects and real-world evidence.⁵

In FDA's accelerated approval pathway, which allows product approval with some limitations based on evidence from a single arm trial, a confirmatory trial may be required to be underway at the time the accelerated approval is granted. Products approved through the one trial regulatory process have benefited millions of patients globally.

This year, senior FDA officials announced in a New England Journal of Medicine article, a shift in policy indicating that the FDA's new default is a single pivotal trial.⁵ Confirmatory evidence is still expected, but reviewers are now to focus on the robustness of a single clinical trial namely trial quality, including magnitude of effect, appropriateness of control arms, endpoint selection, statistical power, masking, handling of missing data, biological plausibility (mechanistic or pharmacodynamic data, confirmation of target engagement) and exposure-response on biomarkers and clinical outcomes, among others. Like so many of the FDA's initiatives, time will tell how the impact of this policy shift will unfold.

With all of this in mind, the authors would like to highlight a theoretical framework for the approval of a drug aimed at treating dry eye disease (DED), which is an indication that has typically required two or more pivotal trials to achieve FDA approval. While the proposed framework is just theoretical, it can help Sponsors develop a plan to seek FDA feedback for their own path towards a single pivotal trial in their indication of interest.

Example Theoretical Path to a Single Pivotal Trial

DED 'is a multifactorial, symptomatic disease characterised by a loss of homeostasis of the tear film and/or ocular surface, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage and neurosensory abnormalities are etiological factors.⁸ With DED, it is one of the most common indications in the ophthalmology sector,⁹ so there is a plethora of data on this topic and there is even an FDA draft guidance document for bringing a DED drug to market (Table 1). Evaluating these sources can likewise help a Sponsor understand what primary endpoints may be most suitable for developing a drug. While established endpoints are typically most reliable, novel endpoints are of interest and may provide a drug with market differentiation. Novel endpoints should be discussed with the FDA prior to implementation and are typically included as exploratory outcomes in pre-pivotal trials.

Endpoint selection should always be aimed at evaluating the underlying etiological factors promoting the condition. With the most recent Tear Film and Ocular Surface (TFOS) report on DED, three primary DED subtypes were identified (tear film deficiencies, eyelid abnormalities and ocular surface abnormalities). Each have different underlying deficiencies that can be evaluated with different, established endpoints.⁸ Table 2 lists the most common endpoints, which should be selected for a clinical trial based upon the novel drug's underlying mechanism of action and pre-clinical data.

With DED, the FDA draft guidance indicates a need for assessment of two primary outcomes (one sign and one symptom pertinent to the condition) unless evaluating a specific primary outcome (Table 2). In considering the clinical development of a new DED treatment, it is highly recommended to fully evaluate the clinical trial designs and outcome measures that have been utilised previously. This process could start by evaluating public sources of clinical trial information such as ClinicalTrials.gov and the peer-reviewed literature.⁹ With our theoretical trial, we will start with a Phase II trial based upon developing a topical, small molecule drug and a well-established pathway for DED. Starting with a Phase II trial to establish initial safety and efficacy of our drug is well supported by the literature. This is highlighted by Pucker et al. who determined that there have been 346 DED clinical trials conducted as of 2024 with only 4 of these trials being pure Phase I trials.⁹ The authors likewise found that the typical Phase II trial (n = 42) enrolls a median of 207 participants, which can provide a basis for a starting sample size given that first in human studies often do not have a fully powered sample size.⁹ Our drug has a mechanism of action and pre-clinical data suggesting that it has the potential to improve tear volume and tear stability.

Participant Instructions: Please rate how your eyes feel by placing a single, vertical mark that represents how your "Eye Dryness" symptom feels at this moment.



Participant Instructions: Please rate how your eyes feel by placing a single, vertical mark that represents how your "Ocular Discomfort" symptom feels at this moment.



Participant Instructions: Please rate how your eyes feel by placing a single, vertical mark that represents how your "Drop Tolerability" symptom feels at this moment.



Figure 1: Example Image of Schirmer Test, Image created with AI by Andrew D. Pucker, OD, PhD.

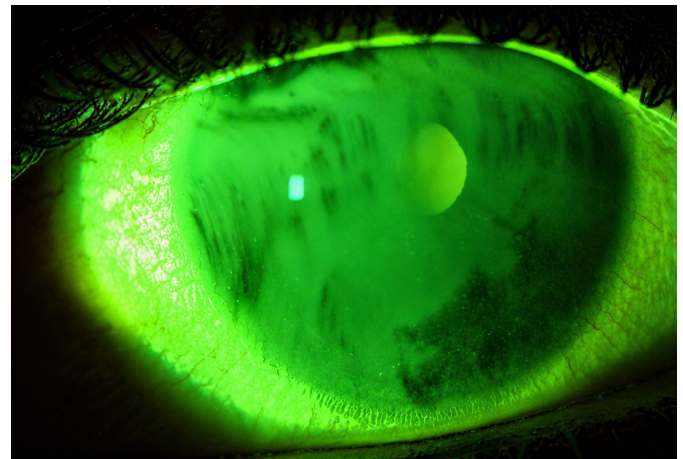


Figure 2: Example Image of Tear Break Up Time: Note that dark spots over the cornea are regions of tear break up. Image captured by Andrew D. Pucker, OD, PhD.

Tear volume is typically evaluated with a Schirmer's test (Figure 1; Table 2), and tear stability is typically evaluated with tear break up time (TBUT; Figure 2; Table 2). Since the primary goal for the Phase II trial is to establish initial safety and efficacy, safety measures are selected as the primary outcomes and Schirmer's test and TBUT are selected as secondary outcomes. Including multiple secondary outcomes can allow for a proof of concept to provide guidance for the selection of the primary efficacy outcome in a planned pivotal trial. While not always required, the optimal dose is likely unclear for your novel drug, so the FDA typically requires a dose finding aspect to your Phase II trial. Pre-clinical data suggests that concentrations A, B and C could be safe and effective in patients. DED treatments tend to have a high placebo effect and published data clearly indicate that treatments as simple as topical saline have a positive effect on the signs and symptoms of DED;¹⁰ thus, you should consider designing a randomised trial where participants are allocated in a 1:1:1:1 manner to concentrations A, B and C or vehicle. Likewise, with the placebo effect being a major potential confounding factor, all participants in your trial should complete a two-week run-in phase with vehicle to help ensure that your eligible participants still have symptoms while on vehicle and that the enrolled participants can demonstrate reasonable treatment compliance. Controlling for treatment compliance is also a major factor in chronic disease trials like DED, because the longer a participant uses a drug, the less likely they are to take it on schedule and could subsequently diminish the chances of observing a treatment effect.^{11,12} You also conduct an unpowered trial with a sample size of 200 participants (50/participants group), so you can gain an initial understanding of your drug's pharmacologic



Figure 3: Example of Dry Eye Visual Analog Scales

Trial Design	Traditional Histology-Based Trial Design
	Parallel, randomised, double-masked trails should be conducted.
Comparator	If evaluating efficacy, a natural exposure/environmental trials should be at least 2-weeks in duration and if evaluating safety, trials should be least 6 weeks in duration if efficacy trials are shorter.
Trial Population	Drug should demonstrate a clinically meaningful and a significant improvement over vehicle control.
	Symptomatic dry eye disease participants should be enrolled.
	Inclusion criteria should include both signs and symptoms of dry eye disease.
Efficacy Considerations	A representative sample of dry eye disease participants should be enrolled.
	Safety and efficacy should be demonstrated in at least two well-controlled, multi-center trials (Note – now possibly only one very robust trial).
	A significant between-group difference should be demonstrated for at least one dry eye disease sign and symptom, or
	A significant between-group difference in complete resolution of corneal staining, or
Safety Considerations	A significant between-group difference in participants having a ≥10 mm increase in Schirmer’s test.
	At least 400 participants treated with the drug at a concentration at least as high as that of the intended marked use.
Clinical Evaluations	At least 300 participants should have completed at least 6 weeks of follow up and at least 100 participants should have at least 1 year of follow up (International Council for Harmonisation [ICH] requirement).
	Distance best corrected visual acuity should be conducted at every visit.
	Ocular comfort should be evaluated before and after drug application at every visit.
	Ocular health should be adequality evaluated with a slit-lamp.
	Program should include a trial that evaluates the following safety outcomes over at least 3 months: systemic laboratory evaluation, corneal endothelial cell counts, and dilated fundus examination.

Table 1: Summary of Key Food and Drug Administration (FDA) Draft Dry Eye Disease Guidance

activity and have the data needed for sample size planning for your upcoming pivotal trial. Planning a 6-week treatment phase post-run in to collect sufficient initial safety data is optimal because your drug’s mechanism of action suggests that the treatment effect will improve with time.

Optimally, after completing your Phase II trial you find that your drug is safe and that there is a clear trend towards improvement in TBUT at 4 and 6 weeks. You also find that concentration C provided the largest numerical improvement compared to vehicle at both 4 and 6 weeks. Therefore, after consulting with the FDA, you select TBUT as the primary sign outcome for your pivotal trial and you select the Eye Dryness VAS as your primary symptom outcome for your pivotal trial because it also showed an improvement during Phase II testing and because the Eye Dryness VAS is the most common symptoms questionnaire used in the DED space (Figure 3).¹³ Since you are gearing up to complete a single pivotal trial, you elect to enroll 800 participants, so you can ensure that at least 400 participants are treated with the drug at the marketed use concentration (overall count includes participants from Phase II trial to help account for attrition provided there are no substantive formulation changes and the pivotal trial test material is comparable to earlier trial material). The sample size is large to help demonstrate safety and is much more than the projected sample size for finding between group differences for TBUT. This trial randomises participants in a 1:1 manner to concentration C or vehicle after they complete a 2-week run-in phase. Additionally, one year of safety data is needed for at least 100 treated participants. Since it is more challenging to enroll participants for a one-year trial and since you do not need all 800 participants to complete a one-year trial, you randomise the first 300

participants in your trial to the one-year segment of your trial. The authors’ experience has found that the US FDA typically requires corneal endothelial cell counts data over one year, so the entire first group of participants complete this outcome at baseline, 12 weeks and 52 weeks. After 300 participants are enrolled, the remaining 500 participants are only asked to complete 12 weeks of follow up to help ensure sufficient follow up to demonstrate durable efficacy. Your pivotal trial likewise includes safety laboratory data on all participants and you include pharmacokinetic (PK) testing at two of your clinical sites, so sufficient PK data is collected from about 20 treated participants to understand systemic drug exposure from a topical ocularly administered drug. You conduct this trial with 40 clinical trial sites that are well-trusted across the US and potentially key European countries that you also hope to gain approval in to help ensure the DED population is representative and that the trial is enrolled within your 8-month target timeline.^{9,14} If enrolling in non-US countries, different regulatory standards likely apply and they should also be incorporated into the trial design.

After completing your trial, you obtain amazing results and you demonstrate a statistically significant and clinically meaningful improvement in both TBUT and Eye Dryness VAS scores. There are also no quality issues either with trial data integrity or inspections in general as they contribute to the quality robustness expected for a one trial approach. You also demonstrate a good safety profile and ultimately, the US FDA approves your drug.

While the above scenario demonstrates that a Sponsor can potentially obtain approval of a DED drug with a single pivotal trial after a well-planned initial safety trial, everything will likely

Ocular Surface/Dry eye Disease Symptoms	
Ocular Surface Disease Index (OSDI)	The OSDI has three question groups (12 total questions) that ask about experiencing ocular symptoms (e.g., blurred vision), having trouble with performing visual tasks (e.g., reading, driving at night), and having trouble with environmental factors (e.g., windy conditions, low humidity environments) over the past week. ¹⁸
Eye Dryness Visual Analog Scale (VAS)	A VAS consists of a horizontal line (continuous scale without numbers) with an anchor on each end; the left-side anchor typically represents the complete absence of symptoms while the right-side anchor typically represents the most extreme presentation of symptoms. ¹⁹⁻²¹ The Eye Dryness VAS typically probes the named symptom at the visit.
Ocular Discomfort Visual Analog Scale (VAS)	The Ocular Discomfort VAS is like the Eye Dryness VAS, but it probes the named symptom at the visit.
Drop Tolerability Visual Analog Scale (VAS)	The Drop Tolerability VAS is like the Eye Dryness VAS, but it probes the named symptom typically at drop application in office. It might also measure this symptom for up to 10 mins post-drop use.
Symptom Assessment in Dry Eye (SANDE)	The SANDE is a standardised and psychometrically tested 2-item VAS used to quantify the frequency (question 1) and severity (question 2) of dry eye and/or ocular irritation symptoms. ²²
Tear Volume	
Schirmer's Test	Schirmer's Test evaluates tear volume with a 5 mm wide piece of standard filter paper that is 35 mm long. It is performed by placing the strip in the conjunctival sac and letting most of the filter paper hang over the edge of the eye for 5 minutes. ^{23,24} Tear volume is determined by the amount of strip wetting.
Tear Film Osmolarity	Tear osmolarity is a key diagnosis test for dry eye because participants with dry eye tend to have higher tear osmolarities due to a lower tear volume and higher tear solute concentrations. ²⁵ It is typically measured with a device called TearLab Osmolarity System.
Ocular Surface Damage/Irritation	
Corneal Fluorescein Staining	Corneal surface damage is typically evaluated with a vital dye called sodium fluorescein, which highlights breaks/damage. ²⁶ Damage is typically quantified with an integer grading card.
Conjunctival Staining	Conjunctival surface damage is typically evaluated with a vital dye called lissamine green, which highlights breaks/damage. ²⁶ Damage is typically quantified with an integer grading card.
Tear Stability	
Tear Break Up Time (TBUT)	TBUT is a measure of tear stability. Sodium fluorescein causes the tear film to be more visible when viewed with a cobalt blue light with and a slit-lamp biomicroscope. ²⁷ During the procedure, the participants are asked to blink, and the amount of time after the blink until the first dark spot is seen in the tear film is timed with a stop watch. ²⁷ Faster TBUTs are considered to be worse because faster times signify worse tear stability. ²⁸

Table 2: Common Endpoints in Dry Eye Disease Trials⁹

need to go according to plan to accomplish this feat. In the case where the pivotal trial demonstrated a clinically meaningful improvement in symptoms, but the primary sign outcome failed to reach significance, an additional pivotal trial may be needed to confirm efficacy. Interestingly, the DED guidance does indicate that demonstrating sign and symptoms efficacy does not need to occur in the same trial, which can be useful if efficacy is not fully proven upon first attempt.¹⁴ Other concerns such as the cost of running and investing in a single pivotal trial with 800 participants or including all of the needed outcomes (laboratory evaluation, corneal endothelial cell counts, PK, adequate participants in the safety database), some of which require one year of follow up, in a single trial may cause Sponsors to opt for the two pivotal trial approach. Therefore, even though the US FDA has indicated that their new default path is a single pivotal trial,⁵ the scientific community is still sceptical and hesitant to embrace this approach.¹⁵⁻¹⁷ It is likewise unclear if a single pivotal trial will be sufficient in non-US markets. As noted earlier, time will tell whether the single trial approach to registering a product for marketing will be acceptable. In any case conducting a well-executed, well-designed trial that is executed robustly will provide the opportunity for the investigational product to become a successful treatment for patients.

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