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Clinical trials submissions to The Ocular Surface


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### Authors

Novack, Gary D
de Paiva, Cintia S



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BYLINE: GARY D. NOVACK, PHD[1,2] and CINTIA S. DE PAIVA, MD, PhD[3]

FOOTNOTES
From [1]Department of Ophthalmology & Visual Sciences, University of California, Davis, [2]PharmaLogic Development Inc., San Rafael CA and [3]Department of Ophthalmology, Baylor College of Medicine, Houston, TX.

Disclosure:
Gary D. Novack PhD consults with numerous pharmaceutical and medical device firms.
Cintia de Paiva, MD, PhD reports a relationship with Spring Discovery that includes: consulting or advisory; with F Hoffmann-La Roche Ltd that includes: funding grants; with Aries Pharmaceuticals that includes: funding grants; with BioAegis that includes funding grants and Serpass Biologicals that includes funding grants.

Since its inception in 2003 by Michael Lemp, M.D. and Susan Erickson, the journal has been a scientific journal dedicated to researchers and clinicians interested in the ocular surface. Initially limited to review articles, in approximately 2014, the journal expanded to publish original research reports. In the period, we have received a large number of manuscripts, and published many quality articles of therapeutic trials, epidemiology and basic science.

However, in review of The Ocular Surface, as well as other ophthalmology journals, we find variability in the nature of reporting of clinical trials of new pharmacological agents in particular. This variability is seen in terms of the relationship of a priori efficacy outcomes, results, and conclusions. Given the multiple signs and symptoms evaluated in clinical trials in patients with ocular surface disease, it is key to respect statistical hierarchy or appropriate adjustments for multiplicity. That is, if you ask the question of "$p \leq 0.05$" (which is 1/20) for twenty different measures, at least one is going to be found statistically significant by pure chance.

In reviewing the literature, we looked at the relationship between results and conclusions. In some cases, we found a negative relationship. For example, a study which was of relatively poor design – retrospective, non-comparative, open-label, authors concluded that the treatment was safe and effective. On the other hand, a vehicle-controlled, dose-response double-masked, parallel study which found efficacy in secondary measures (albeit not primary) had no conclusions about efficacy.

In particular, the phrase "safe and effective" is a "protected phrase". It stems from a ground breaking 1962 law (Kefauver-Harris amendment) stating that for approval, new drugs have to provide "substantial evidence of safety and efficacy". The FDA and other regulatory agencies feel that this is their remit to decide. Nearly 20 years ago, the editors of the top ophthalmology journals, together with Wiley Chambers, M.D. of the FDA, warned against use of this term in publications – especially those which did not meet the standards for 'well controlled studies".[1]

Pharmacotherapies for dry eye hold a special place in FDA approvals. For many years, and as recently codified in an FDA guidance (December 2020; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/dry-eye-developing-drugs-treatment-guidance-industry), the Sponsor has to provide evidence that the new drug is more effective than a negative control in both a sign and a symptom in two studies. Note that a Sponsor might also be able to show equivalence (technically non-inferiority) to an approved product – but none has successfully done that yet. There are many reasons for this – first is the need for a much larger sample size (in excess of 500 subjects per group), as well as issues of different efficacy measures for different classes of molecules (e.g., corneal staining versus Schirmer), and double-masking.[2]

Of the five FDA-approved pharmacotherapies for dry eye approved through 2022, none met the standard for superiority over vehicle, prospectively, in a sign and a symptom in one trial. In the guidance and precedent, the Sponsor can conduct up to 4 trials (two each for sign and two each for symptom). Some of the more recently approved products took 3 and 4 trials to show the required efficacy. Thus technically, some of the early trials would be judged as failures. One cyclosporine product reached approval only on a post hoc, subset analysis. One reached approval in a post hoc analysis of a Phase 2 trials, changing the endpoint. In both of these products, the primary outcome measure was changed (from a continuous analysis of corneal staining to a categorical analysis of Schirmer score).

Thus, unlike treatments for lowering elevated intraocular pressure in glaucoma or for visual acuity in wet age-related macular degeneration, treatments for dry eye have a lot of flexibility – especially in early stage trials. Stated differently, unless there is an obvious safety issue, it is challenging to know from a Phase 2 study of a novel pharmacotherapy for dry eye whether it will eventually become an approved therapy.

*The Ocular Surface* welcomes clinical study reports at all stages of development, Going forward, we plan to standardize characteristics of manuscripts for therapeutic trials of novel pharmacotherapies for the treatment of ocular surface disease. These include:

- Preference is given to adequate and well-controlled studies (see 21 CFR 314.126).[3]
- Studies must be registered with a website such as clinicaltrials.gov.
- The primary and secondary outcomes must be clearly stated, as well as statistical measures to adjust for multiplicity (e.g., hierarchical approach, Bonferroni correction, etc.).
- Results for all measures may be presented for consideration by reviewers.
- Authors are cautioned to restrict use the statement “safe and effective”, especially for early stage or inadequately controlled studies.[1]
- Given the variability seen in clinical signs and symptoms, we ask for individual data to be plotted along with means and/or medians.

We look forward to your submissions, and support as we move toward what we hope is a more consistent process for publishing high quality reports of clinical trials of new therapies for our patients.

Appendix:
News from pharmaceutical and medical device companies related to the ocular surface

- Aldeyra announced results from its phase 3 INVIGORATE-2 clinical trial of 0.25% reproxalap ophthalmic solution in patients with allergic conjunctivitis (June 2023).
- Aldeyra announced that the U.S. FDA accepted for review its New Drug Application (NDA) for topical ocular reproxalap for the treatment of the signs and symptoms of dry eye disease (February 2023).
- Bausch + Lomb acquired the rights to Xiidra® (lifitegrast ophthalmic solution) from Novartis (June 2023).
- Bausch + Lomb and Novaliq received U.S. FDA approval for its Miebo™ (perfluorohexyloctane ophthalmic solution, NOV03), for the treatment of the signs and symptoms of DED (May 2023). Senju has licensed the Japanese rights to this product (June 2023).
- Novaliq received approval for its Vevye® (cyclosporine ophthalmic solution). The firm licensed US and Canadian rights to Harrow (July 2023).
- Senju and Mochida started Phase 3 clinical trials in Japan for SJP-0132 for the treatment of Dry Eye Disease (March 2023).
- Senju and Mochida started Phase 3 clinical trials in Japan for SJP-0132 for the treatment of Dry Eye Disease (March 2023).
- Versea Ophthalmics is marketing its "T-POC Total IgE" immunoassay kits in the U.S (July 2023).
- YuYu announced results of its ICECAP Phase 1 /2 trial of YP-P10 in dry eye disease (June 2023).
- The U.S. FDA:
    - Issued a warning against the unproven safety and efficacy of amniotic fluid eyedrops (April 2023).
    - Together with the U.S. Centers for Disease Control provide continued updates on the infections related to unpreserved, multi-dose over-the-counter tears from Delsum and Ezricare (June 2023).

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