Glaucoma Candidate BOL-303259-X Meets Primary Endpoint in Phase 2b Study

A phase 2b study of BOL-303259-X met its primary efficacy endpoint and showed positive results on a number of secondary endpoints, according to Bausch + Lomb and NicOx SA. BOL-303259-X (previously NCX 116) was licensed by NicOx to Bausch + Lomb in March 2010. According to a news release, Bausch + Lomb will pay a $10 million milestone payment to NicOx and will initiate a global phase 3 development program for BOL-303259-X.

BOL-303259-X is a novel nitric oxide-donating prostaglandin F2-α analogue for use in patients with open-angle glaucoma or ocular hypertension.

Bausch + Lomb initiated the randomized, investigator-masked, phase 2b study in November 2010 to identify the most efficacious and safe dose of BOL-303259-X for the reduction of IOP. The study enrolled 413 patients across 23 sites in the United States and Europe. Patients were randomized to receive either BOL-303259-X (various concentrations) or latanoprost ophthalmic solution 0.005% (Xalatan; Pfizer, Inc.) once a day in the evening for 28 days.

The primary efficacy endpoint was the reduction in mean IOP on day 28. According to a news release, BOL-303259-X consistently lowered the IOP in a dose-dependent manner. Two of the four doses tested showed a greater reduction in IOP compared with latanoprost, with differences of more than 1 mm Hg between the two treatments ($P < .01$).

“We know from several studies that every mm Hg of IOP reduction is important, as it reduces the risk of developing glaucoma and progression of glaucoma,” Robert N. Weinreb, MD, distinguished professor and chairman of ophthalmology, University of California San Diego, said in a new release. “A safe and well-tolerated therapy that can better lower IOP compared to current prostaglandin therapies would be welcomed by both clinicians and patients.”

The most efficacious dose of BOL-303259-X also reportedly showed positive results on a number of secondary endpoints, including consistently better control of IOP over 24 hours on day 28 as well as a statistically significantly greater percentage of responders (patients achieving an IOP of 18 mm Hg or less) versus latanoprost. The responder rate was 68.7% for the most efficacious dose of BOL-303259-X compared with 47.5% for latanoprost ($P = .006$).

The safety of BOL-303259-X was comparable to that of latanoprost, according to the news release. The most common adverse event was ocular hyperemia, which occurred at a similar rate across all treatment groups.

Zioptan Approved for Treatment of Elevated IOP in Patients With Open-angle Glaucoma

The FDA approved Zioptan (tafluprost ophthalmic solution 0.0015%; Merck & Co., Inc.) for reducing elevated IOP in patients with open-angle glaucoma or ocular hypertension.

The FDA’s approval was based on efficacy and safety results from five controlled clinical studies of up to 2 years in 905 patients, according to a company news release. Both preservative-containing and preservative-free formulations of tafluprost were used in these clinical studies. Tafluprost, dosed once daily in the evening, lowered IOP from a baseline pressure ranging from 23 to 26 mm Hg by 6 to 8 mm Hg at 3 months and by 5 to 8 mm Hg at 6 months.

According to the company, the drug may gradually change eyelashes and vellus hair in the treated eye. In addition to altering the color, thickness, shape, and number of lashes, tafluprost may increase their length.

“The major difference between tafluprost and [prostaglandin analogues] previously available is this is the first time that there is really a truly preservative-free option available in that class,” David Michelson, MD, vice president, neurology and ophthalmic therapeutic area, Merck Research Laboratories, said in an interview with Glaucoma Today.
Dr. Michelson said there are several reasons a preservative-free formulation may be desirable, including sensitivity concerns for select patients with other prostaglandins.

Tafluprost became available in the United States in March.

**Mobius Therapeutics Receives Final FDA Approval for Mitosol**

The drug delivery platform Mitosol (Mobius Therapeutics, LLC) received approval from the FDA for use in glaucoma surgery, according to a company news release.

Mitosol reportedly delivers a precise dose of its active ingredient, mitomycin C. According to the company, use of the drug delivery system does not require ophthalmologists to change their current surgical technique.

"The approval of Mitosol for use in glaucoma surgery represents the culmination of more than 5 years of work on the part of Mobius Therapeutics," Ed Timm, president of the company, said in a news release. "It will provide surgeons, hospitals, and patients with enhanced convenience, safety, and consistency in the surgical treatment of glaucoma."

Mobius Therapeutics said that it would begin marketing and production efforts immediately. The FDA’s approval of Mitosol is only for glaucoma surgery; the company is reportedly awaiting approval for refractive and corneal surgery.

**Working Group Calls Preservative Toxicity a Disease**

The Working Group on Preservative Toxicity, an advisory panel of glaucoma experts, was recently convened to examine the issue of preservatives in glaucoma medications from an evidence-based perspective. The Working Group, which is chaired by Stephen Obstbaum, MD, of New York University Langone Medical Center, is sponsored by Valeant Ophthalmics.

The Working Group discussed the interface between ocular surface disease and glaucoma, and it reviewed the evidence regarding the effect of preservatives used in glaucoma medications on the ocular surface. The group’s observations included the recommendation that the toxic effects glaucoma patients can experience as a result of preservatives in many glaucoma medications be recognized as a disease.

"The long-term view is to recognize preservative toxicity as a disease that may make glaucoma harder to treat," said Paul Kaufman, MD, of the University of Wisconsin in a news release. "What is required is a complete paradigm shift in how we look at surface toxicity. At the end of the day, preservative toxicity is going to translate into increased medical treatment of the side effects, discontinuation of topical drug therapy, or perhaps even inflammation-induced failure of glaucoma surgery."

Christophe Baudouin, MD, PhD, of the University of Paris summarized his early observations of inflammation in patients with glaucoma, which were published in 2010.1

"I saw a relationship between inflammation and the preservatives of topical glaucoma medications," Dr. Baudouin said in a news release. "First, I observed inflammation in a disease in which there is no reason to observe inflammation at the ocular surface. Second, the inflammation was not related to a specific compound or specific family of eye drops but was a significant finding in patients treated for a long period of time or treated with several drugs, so it seemed logical to consider that there was something common to every treatment."1

Dr. Baudouin also noted the difficulty of recognizing preservative toxicity.

"A toxic reaction accumulating over time in a patient treated with two, three, four drugs is something that is not caught by evidence-based medicine because clinical trials are focusing on a specific population with a specific drug for a specific duration," Dr. Baudouin said.2

Fluctuating and blurred vision was identified as the primary problem for patients with ocular surface disease and is associated with preservatives.

"It’s been recognized for decades that preservatives are detergents," Stephen C. Pflugfelder, MD, of the Baylor College of Medicine said in a news release. "They break the tight junctions in the apical epithelial cells in the cornea and probably the conjunctiva also. They may have some cytotoxic activity themselves and in certain concentrations will cause apoptosis or programmed cell death or necrosis.1 So, from multiple mechanisms, preservatives can impact on the barrier..."
function in the cornea. And as the cells start to be lost from the apical cornea, then the ability of the cornea to hold the tear film diminishes. The tear film becomes more unstable, and then patients complain of blurred and fluctuating vision and reduction in their best corrected visual acuity, in some cases to almost functional blindness.”


**Glaucoma Research Foundation Emphasizes Importance of Collaborative Research**

The Glaucoma Research Foundation (GRF) announced that it will double its Catalyst for a Cure (CFC) research consortium to eight research scientists from prestigious universities across the United States. The Foundation also reported that it has awarded more annual research grants in 2012 to explore new ideas than in any prior year.

CFC was launched in 2002. CFC researchers are engaged in an ongoing partnership; they reportedly spend time in each other’s laboratories, collaborate online, share their results, and work toward a unified understanding of disease progression and therapeutic targets.

According to the GRF, the original team of four investigators has had a significant impact on the field of glaucoma research by redefining glaucomatologists’ understanding of how glaucoma affects sight and creating possibilities for new therapeutic approaches to the disease.

This year, the GRF has assembled a second team of four investigators to collaborate and expand what is known about glaucoma. The research consortium includes David Calkins, PhD, Vanderbilt University; Alfredo Dubra, PhD, Medical College of Wisconsin; Jeffrey Goldberg, MD, PhD, Bascom Palmer Eye Institute; Philip Horner, PhD, University of Washington; Andrew Huberman, PhD, University of California, San Diego; Nicholas Marsh-Armstrong, PhD, Johns Hopkins University; Vivek Srinivasan, PhD, Massachusetts General Hospital; and Monica Vetter, PhD, University of Utah.