United States Subgroup of the Denali Trial: A Randomized Trial Comparing NCX 470 0.1%, a Nitric Oxide-Donating Bimatoprost, and Latanoprost 0.005% for Open-Angle Glaucoma or Ocular Hypertension

Bacharach, J(1) and Hubatsch, D(2) on behalf of the Denali investigators

1 Glaucoma Service Dept. of Ophthalmology, California Pacific Medical Center; Pacific Vision Eye Institute 2 Nicox Ophthalmics. Inc.

INTRODUCTION

Glaucoma is the leading cause of irreversible blindness worldwide, and lowering intraocular pressure (IOP) remains the only proven strategy to slow disease progression. Topical prostaglandin analogues (PGAs), such as bimatoprost, latanoprost, and travoprost, are first-line therapy; however, additional IOP lowering through complementary outflow pathways remains a clinically meaningful goal.

NCX 470 is a nitric oxide (NO)-donating bimatoprost PGA, in development for the treatment of open-angle glaucoma (OAG) and ocular hypertension (OHT). Following esterase cleavage in the eye, NCX 470 releases bimatoprost and nitric oxide. Bimatoprost primarily increases uveoscleral outflow, while nitric oxide relaxes the trabecular meshwork and enhances conventional aqueous humor outflow.

The clinical relevance of NO-donation in glaucoma therapy is further supported by the US Food and Drug Administration approval of VYZULTA® (latanoprostene bunod ophthalmic solution, 0.024%), an NO-donating PGA for IOP reduction in patients with OAG or OHT.

In the first Phase 3 trial (MONT BLANC), NCX 470 0.1% demonstrated robust and consistent IOP lowering, with mean reductions from baseline from 8.0 to 9.7 mmHg compared with 7.1 to 9.4 mmHg with latanoprost 0.005% across all 6 evaluated timepoints (1).

The Phase 3 DENALI trial was subsequently conducted as a second, independent evaluation of NCX 470 compared to latanoprost.

PURPOSE

To evaluate IOP reduction with NCX 470 0.1%, a nitric oxide-donating bimatoprost, compared with latanoprost 0.005% in subjects with OAG or OHT enrolled at US sites in the Phase 3 DENALI trial, a multicenter study conducted in the US and China.

MATERIALS AND METHODS

DENALI was a randomized, double-masked, active-controlled, parallel-group Phase 3 trial conducted at 65 sites in the US and 25 sites in China.

Eligible participants met the following **Inclusion/Exclusion** criteria:

Key Inclusion Criteria

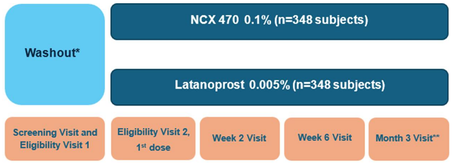
- Diagnosis of OAG or OHT in both eyes
- Untreated IOP following washout of prior IOP-lowering therapy:
  - IOP ≥ 26 mmHg at 8AM, ≥ 24 mmHg at 10AM, and ≥ 22 mmHg at 4PM in the study eye
  - IOP ≤ 36 mmHg in both eyes
- BCVA of +0.7 logMAR or better

Key Exclusion Criteria

- Advanced glaucoma or cup/disc ratio > 0.8
- Narrow or closed angles, congenital glaucoma, or a history of angle closure
- Central corneal endothelial cell density < 2000 cells/mm^2
- Prior glaucoma or angle surgery or laser trabeculoplasty (SLT, YAG, ALT or MLT) within 6 months of screening

Subjects were randomized 1:1 to once-daily treatment in both eyes with NCX 470 0.1% or latanoprost 0.005% for up to 12 months. The primary endpoint was noninferiority of mean IOP reduction from time-matched baseline at 8AM and 4PM at Weeks 2 and 6 and Month 3 in the intent-to-treat population. The design and scope were similar to the other Phase 3 MONT BLANC trial (1).

Figure 1: *Study design for the US subgroup of the Phase 3 DENALI trial. Primary efficacy endpoints were assessed at Weeks 2 and 6 and Month 3*



*Washout applied to subjects receiving IOP-lowering medications at screening.

All subjects were followed through Month 6; a subset continued through Month 12 for safety.

RESULTS

A total of 549 subjects were randomized at US sites (NCX 470, n=272; latanoprost, n=277). Baseline demographics and ocular characteristics were well balanced between treatment groups (**Table 1**). Mean baseline diurnal IOP was 26.7 mmHg in the NCX 470 group and 26.8 mmHg in the latanoprost group.

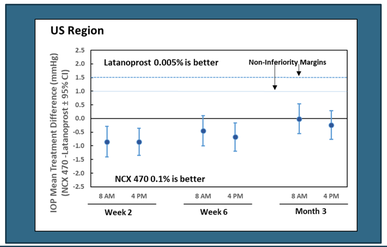
Table 1: *Baseline demographics and ocular characteristics of the US subjects*

		NCX 470 0.1%	Latanoprost 0.005%
Age	**Mean (SD)**	64.8 (11.1)	63.8 (10.2)
Sex	**N (%) Female**	143 (52.6%)	147 (53.1 %)
Race	**N (%)**		
	White	180 (66.2%)	196 (70.8%)
	Asian	8 (2.9%)	11 (4.0%)
	Black or African American	82 (30.1%)	68 (24.5%)
	Other	2 (0.7%)	2 (0.7%)
Completed the Study	**N (%)**	242 (89.0%)	257(92.8%)
Baseline Time Matched IOP (mmHg)			
	8 AM Mean (SD)	28.1 (2.0599)	28.1 (1.9742)
	10 AM Mean (SD)	26.8 (2.2797)	26.9 (2.2333)
	4 PM Mean (SD)	25.3 (2.3708)	25.5 (2.5601)
Mean Diurnal IOP	**N (SD)**	26.7 (1.9787)	26.8 (2.0581)

IOP reduction with NCX 470 was evident by Week 2 and was maintained across all 6 evaluated timepoints through Month 3.

The primary objective of the Phase 3 DENALI trial was met, with NCX 470 0.1% demonstrating noninferior IOP reduction compared with latanoprost. Noninferiority was prespecified such that the upper bound of the 95% confidence interval was required to be ≤ 1.5 mmHg at all 6 timepoints and ≤ 1.0 mmHg for at least 4 timepoints. These criteria were met at all 6 timepoints **(Figure 2).**

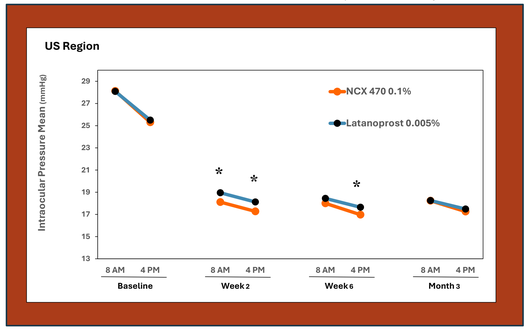
Figure 2: *Mean difference in IOP reduction (NCX 470 – latanoprost) with 95% confidence intervals at Weeks 2 and 6 and Month 3. Values below zero favor NCX 470*



RESULTS (continued)

Mean IOP reductions ranged from 8.1 to 10.1 mmHg with NCX 470 and 7.3 to 9.9 mmHg with latanoprost across all 6 timepoints. Mean IOP reduction favored NCX 470 at multiple timepoints, with statistically significant differences observed at Week 2 (8AM and 4PM) and Week 6 (4PM), reaching differences of up to 0.9 mmHg (**Figure 3**).

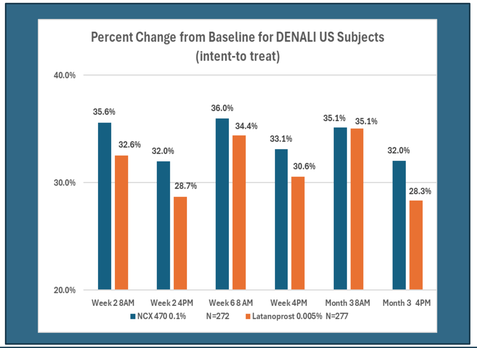
Figure 3: *Mean IOP over time with NCX 470 0.1% and latanoprost in US subjects*



* indicates statistically significant differences between treatment groups (p<0.05)

Percent IOP reduction from baseline ranged from 32.0% to 36.0% with NCX 470 and 28.3% to 35.1% with latanoprost, demonstrating consistent IOP lowering across all timepoints (**Figure 4**).

Figure 4: *Percent change from baseline in IOP over time with NCX 470 0.1% and latanoprost 0.005% in US subjects*



RESULTS (continued)

The most common adverse events over the 12-month study period included conjunctival hyperemia (14.9% NCX 470, 6.9% latanoprost, punctate keratitis (5.9% vs. 3.2%) and eyelash growth (5.6% vs 0.4%). No treatment-related serious ocular adverse event occurred. Discontinuation of subjects from the study due to adverse events (1.1% vs 0.4%) or lack of efficacy (2.2% vs 1.4%) were uncommon.

DISCUSSION

The US subgroup results from DENALI are consistent with the proposed benefit of dual outflow pathway modulation, combining prostaglandin-mediated uveoscleral outflow with nitric oxide-mediated enhancement of conventional aqueous humor outflow. The early onset and consistency of IOP lowering observed with NCX 470 suggest that NO donation may contribute meaningfully to treatment response when added to a prostaglandin analogue. These findings extend prior Phase 3 results and provide additional evidence supporting NCX 470 as a differentiated therapeutic approach for patients with OAG or OHT.

CONCLUSION

In the US subgroup of the Phase 3 DENALI trial, NCX 470 0.1% demonstrated robust IOP lowering in patients with OAG or OHT. NCX 470 met the prespecified noninferiority criteria compared with latanoprost 0.005% and achieved statistically greater IOP reductions at 3 of 6 evaluated timepoints. NCX 470 was safe and well tolerated, with no treatment-related serious adverse and low, similar discontinuation rates between treatment groups

REFERENCE

1. Fechtner, R. et al, *Am J Ophthalmol* 2024;264: 66–74