NCX 470, a Nitric Oxide Donating Bimatoprost Compared with Latanoprost - Adaptive Design Period Results from the Phase 3 Mont Blanc Clinical Trial

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INTRODUCTION

Glaucoma is a leading cause of blindness worldwide (Jonas, 2017). Intraocular pressure (IOP) is the primary risk factor for glaucoma, and lowering IOP to prevent optic nerve injury is currently the only proven effective treatment (Jonas, 2017). Topical prostaglandin analogs (PGAs) are the most common first-line therapies used to lower IOP in glaucoma patients.

Nicox is developing NCX 470, a nitric oxide (NO)-donating bimatoprost prostaglandin analog, as a new therapy for lowering of IOP in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT).

Nitric oxide increases outflow of the aqueous humor through the trabecular meshwork (Gabelt, 2011; Heyne, 2013; Cavet, 2014). In addition, NCX 470's bimatoprost moiety increases outflow of aqueous humor through the uveoscleral pathway (Krauss, 2004).

Results of a first-in-man Phase 2 trial, Dolomites, demonstrated a dose dependent linear IOP-lowering effect of NCX 0.021%, 0.042%, and 0.065% QD but failed to identify the optimum concentration for development.

The Phase 3, Mont Blanc, trial provided a unique opportunity to evaluate a higher dose than 0.065% in an adaptive dose selection design with pre-planned interim analysis to allow selection for further development. The results of the subset of patients which were the basis for the decision to proceed with NCX 470 0.1% are presented here.

AIM

To use an adaptive dose selection design to choose the NCX 470 concentration for further development in Phase 3 trials.

METHOD

Mont Blanc was a randomized, double-masked, multi-center, parallel group trial conducted at 56 sites in United States and one site in China. It included a preplanned adaptive dose selection phase, which concluded when at least 30 subjects randomized into each of the three treatment arms (NCX 470 0.065%, NCX 470 0.1%, and latanoprost 0.005%) completed their Week 2 visit. Subjects were randomized to NCX 470 (0.065% or 0.1%) or latanoprost 0.005% once daily in the evening. IOP was measured at 8AM, 10AM and 4PM.

Efficacy in the adaptive phase portion of this study was based on change from baseline in mean diurnal IOP reduction at the 8AM, 10AM and 4PM timepoints at Week 2.

The primary objective of the Phase 3 trial was to demonstrate non-inferiority to latanoprost. The results of this adaptive phase determined the dose to be used for the Phase 3 Mont Blanc trial.

RESULTS

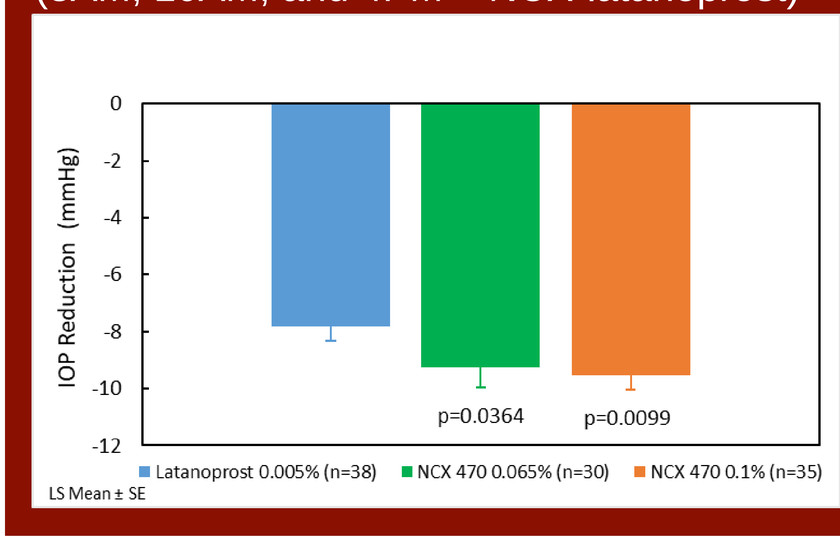
During the 2-week adaptive dose selection phase of this study, 30 subjects were randomized to NCX 470 0.065%, 35 subjects to NCX 470 0.1% and 38 to latanoprost 0.005%. At the Week 2 timepoint, NCX 470 0.065% demonstrated 1.37 mmHg greater mean diurnal IOP reduction from baseline than latanoprost and NCX 0.1% demonstrated 1.73 mmHg greater mean diurnal IOP reduction from baseline than latanoprost.

NCX 470 0.065% and 0.1% were well tolerated with ocular or conjunctival hyperemia being the most common adverse event.

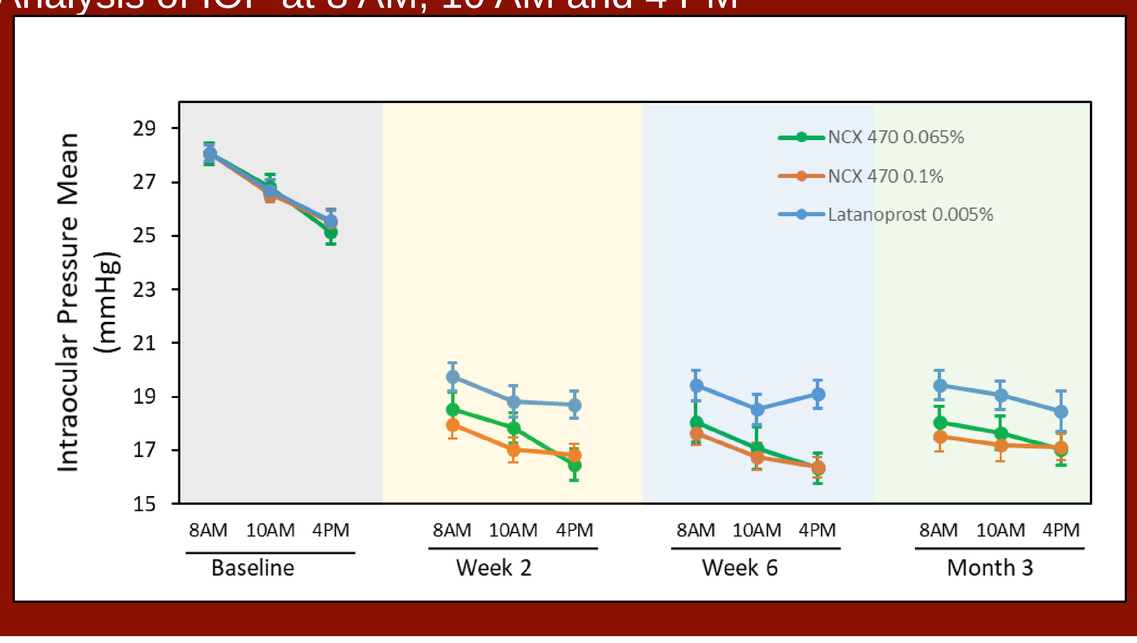
Mont Blanc Adaptive Dose Selection Demographics

	NCX 470 0.065% n = 30	NCX 470 0.1% n = 35	Latanoprost 0.005% n = 38
Age (Years)			
n	30	35	38
Mean (SD)	66.5 (10.87)	65.9 (9.77)	63.2 (11.05)
Age Categories			
≥ 18 to < 65	11 (36.7)	16 (45.7)	23 (60.5)
≥ 65	19 (63.3)	19 (54.3)	15 (39.5)
≥ 75	5 (16.7)	7 (20.0)	5 (13.2)
Sex, n (%)			
Male	13 (43.3)	15 (42.9)	18 (47.4)
Female	17 (56.7)	20 (57.1)	20 (52.6)

Change From Baseline Mean Diurnal IOP (8AM, 10AM, and 4PM – NCX-latanoprost)



Mont Blanc Adaptive Dose Selection Population Analysis of IOP at 8 AM, 10 AM and 4 PM



CONCLUSIONS

This Phase 2, dose-ranging study (Dolomites) may suggest that concentrations of 0.021%, 0.042%, and 0.065% NCX 470 might still be below the top of the dose response curve. To explore this hypothesis and to make a decision on the concentration for further development, a concentration of 0.1% was included in an adaptive dose selection period of the Phase 3 Mont Blanc trial.

Analysis of the results at Week 2 with the ~ 30 patient cohort demonstrated that NCX 470 0.1% had greater mean diurnal IOP reduction than NCX 470 0.065% compared with latanoprost 0.005%. The innovative design allowed selection of an optimum dose while saving time, costs, and exposure of patients to a less effective dose.

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