FSYX™ OCULAR PRESSURE ADJUSTING PUMP (OPAP)

SPONSOR BRIEFING DOCUMENT

OPHTHALMIC DEVICES PANEL

MEETING DATE: 21 MARCH 2024

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List of Abbreviations

Abbreviation	Definition
AE	adverse event
BCDVA	best-corrected distance visual acuity
CI	confidence interval
CSF	cerebrospinal fluid
CSFp	cerebrospinal fluid pressure
DBP	diastolic blood pressure
GAT	Goldmann applanation tonometry
GEE	general estimating equation
IOP	intraocular pressure
ITT	Intent-to-Treat
LC	lamina cribrosa
LGN	lateral geniculate nucleus
MD	mean deviation
MIGS	minimally invasive glaucoma surgery
mITT	modified Intent-to-Treat
NCS	non-clinically significant
NP	negative pressure
NTG	normal-tension glaucoma
OAG	open-angle glaucoma
OCT	optical coherence tomography
OCT-A	optical coherence tomography angiography
OD	oculus dexter (right eye)
OHT	ocular hypertension
OHTN	ocular hypotension
ONH	optic nerve head
OPAP	Ocular Pressure Adjusting Pump
OPP	ocular perfusion pressure
OS	oculus sinister (left eye)
POAG	primary open-angle glaucoma
PP	Per-Protocol
PVD	posterior vitreous detachment
RG	retinal ganglion
RNFL	retinal nerve fiber layer
SAE	serious adverse event
SD	standard deviation
SEM	standard error of the mean
SLT	selective laser trabeculoplasty
UADE	unanticipated adverse device effect
VF	visual field
VFRC	Visual Field Reading Center (at University of Iowa)

1 EXECUTIVE SUMMARY

1.1 Introduction

Glaucoma is a pressure-related disease of the optic nerve and remains the leading cause of irreversible blindness in the US. Most currently available medical and surgical therapies are limited in their ability to either address nocturnal intraocular pressure (IOP) elevations or provide a clinically significant IOP reduction in glaucoma patients with daytime IOP ≤ 21 mmHg (Section 2.1.2). Elevated IOP, generally defined as IOP > 21 mmHg, is a major risk factor for glaucoma onset and progression. However, not all individuals with increased eye pressure will develop glaucoma, and many people with normal IOP (≤ 21 mmHg) still develop the condition. Glaucoma with IOP ≤ 21 mmHg is typically categorized as normal tension- glaucoma (NTG). Additionally, elevations in nocturnal IOP often accelerate disease progression, even when patients are adherent to currently available glaucoma treatment options (De Moraes et al. 2016; Yang et al. 2021; Dubey et al. 2020; Agnifili et al. 2015). Reducing IOP remains the only proven strategy for slowing glaucomatous progression (Section 2.2.3). Despite many proven therapies for patients with glaucoma (e.g., eye drops and surgeries), reducing IOP in glaucoma patients with normal pressure (i.e., IOP ≤ 21 mmHg) poses unique challenges. There are no treatments that specifically address nighttime IOP elevations.

The FSYX™ Ocular Pressure Adjusting Pump (OPAP) was developed to provide an adjunctive treatment option for nocturnal IOP reduction for adults with open-angle glaucoma (OAG) and IOP of ≤ 21 mmHg (Section 3.1). The OPAP System consists of a pair of airtight goggles that are connected to a small programmable bedside pressure pump, which applies a mild, physician-specified negative pressure (NP) to the region over the eye during sleep, reducing nocturnal IOP during use (Section 3.2.3).

1.2 Unmet Need

Glaucoma is the leading cause of irreversible blindness in the US and around the world (Downs et al. 2022). An estimated 3-to-5 million US adults are living with open-angle glaucoma, about 120,000 of whom have developed permanent blindness and about 30-40% of whom have IOP ≤ 21 mmHg. The prevalence of open angle glaucoma is projected to increase to 7.3 million US adults by 2050 (Sheybani et al. 2020) (Section 2.1.1).

The only proven treatment for managing glaucoma is IOP lowering, which includes ocular hypotensive medications (i.e., eye drops), laser procedures, minimally invasive tissue excision or stent implantation, and subconjunctival filtering surgery (Section 2.2.1). While these therapies are generally effective during daytime, most patients with progressive disease still have elevated IOP at night (Dubey et al. 2020), when most established treatments exert diminished efficacy, highlighting the need for additional strategies to manage nocturnal IOP (Section 2.1.3). Multiple long-term studies have confirmed the relationship between total IOP burden and disease progression (Heijl et al. 2002; AGIS 2000). Even a 1 mmHg reduction in IOP can lead to a 10% reduction in glaucomatous disease progression (Heijl et al. 2002). A thorough review of the importance of lowering nocturnal IOP by experts in the field is provided in Appendix 9.5.

Importantly, patients with IOP in the normal range (≤ 21 mmHg) can still experience continued glaucomatous disease progression. Because the IOP-lowering effectiveness of ocular hypotensive medication, laser procedures, and minimally invasive glaucoma surgery is

generally lessened in these patients, they are at particular risk for disease progression (Section 2.2.2).

In short, patients with OAG and daytime IOP ≤ 21 mmHg need adjunctive treatments that safely and effectively lower nocturnal IOP (Section 2.2.3).

1.3 Product Overview

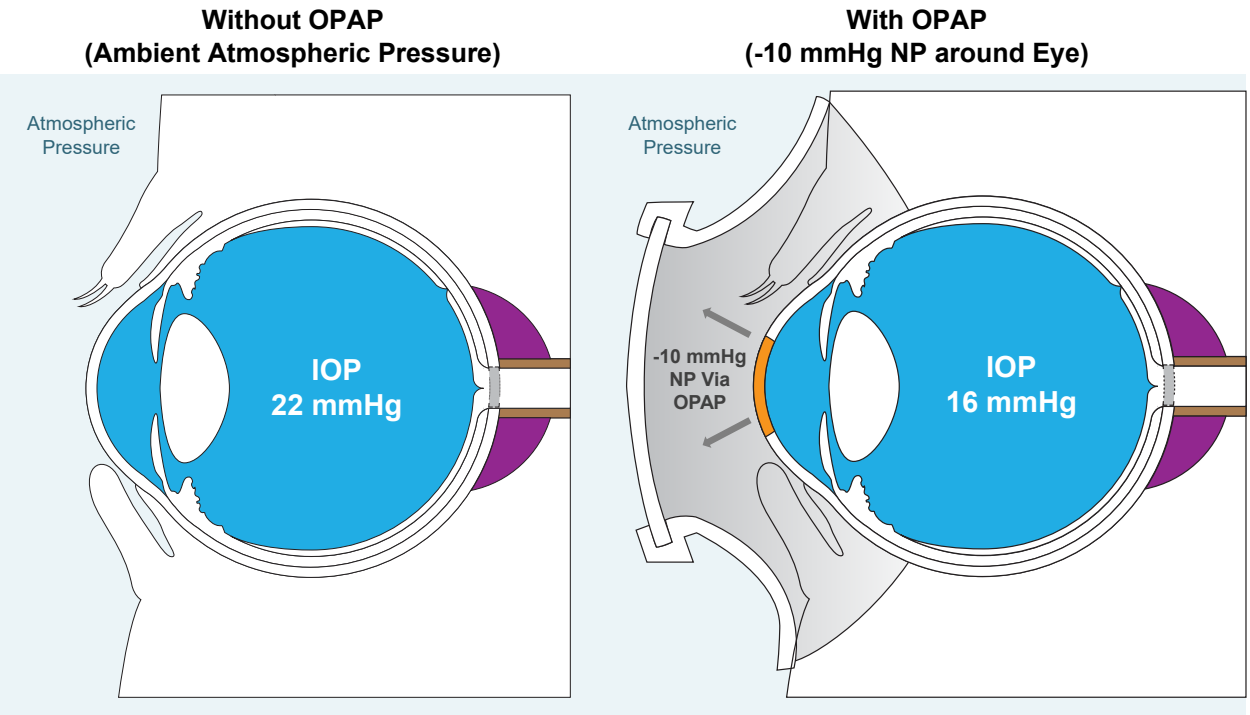
The OPAP consists of a noninvasive programmable pump, connected via pneumatic tubing to a pair of goggles, which patients wear during sleep (Figure 1; Section 3.2.1). The goggles are available in small, medium, and large sizes with an adjustable head strap and adjustable nose bridge. The pump includes software designed to sense and deliver customizable NP over the treatment eye(s), and each goggle can be programmed independently. The OPAP comes pre-programmed with physician-specified parameters, based on each eye's IOP. Trained healthcare professionals can subsequently adjust and manage OPAP pressure using a proprietary application that resides on a dedicated computer in the provider's office. Patients cannot independently modify pressure settings, and NP cannot be changed or monitored remotely because the device has no internet connectivity.

Figure 1: Image of OPAP Goggles, Connected to Programmable Pressure Pump

OPAP=Ocular Pressure Adjusting Pump.

Fundamentally, OPAP leverages fluid mechanics and Pascal's law, which states that pressure changes to a confined fluid at rest are transmitted equally and undiminished to all points in all directions throughout the fluid (Figure 2). In the case of the OPAP System, this means that reducing pressure on the front of the eye reduces pressure inside the eye.

Figure 2: OPAP Mechanism of Action — Intra-Goggle Pressure Is Lower than Atmospheric Pressure and Reduces IOP



IOP=intraocular pressure; NP=negative pressure; OPAP=Ocular Pressure Adjusting Pump.Note: OPAP reduces IOP by approximately 40% – 60% of applied negative pressure. (See Section 3.2.3). In the above example, application of -10 mmHg NP has reduced baseline IOP from 22 mmHg (left panel) by 6 mmHg, to 16 mmHg (right panel).

The most widely used methodology for measurement of IOP is Goldmann applanation tonometry, which involves application of an external force to flatten a fixed area on the corneal surface to determine the transcorneal pressure difference (TCPD) relative to atmospheric pressure. IOP is then estimated by observing the amount of force necessary to achieve the required flattening. The use of Goldmann applanation methodology to determine the IOP -lowering effect of the FSYX OPAP during NP application, however, is complicated by the need to preserve the vacuum inside the goggles. A measurement methodology utilizing access ports in the goggle lenses, called “Excursion Tonometry,” was thus developed and validated by Balance Ophthalmics. (See Figure 17; Section 5.1.1.6.) This measurement method involves insertion of a Reichert Model 30™ pneumatonometer probe through the goggle port to applanate the cornea and measure TCPD referenced to atmospheric pressure, thus approximating Goldmann applanation tonometry. Importantly, experts in the field (Huang, Ethier, Herndon, Samuelson, Weinreb, et al.) in 2021 performed a detailed review of IOP definitions, citing atmospheric pressure surrounding the body as the proper reference point for IOP. Their report, “Review of the Pressure Relationships Created by the Multi-Pressure Dial,” is provided in Appendix 9.4 and was submitted to FDA on 03 January 2021 in a pre-submission meeting request (QXXXXX8) and also in DENXXXXX2/OBJ.

Multiple published clinical studies of OPAP have shown that IOP, as measured by Excursion Tonometry, consistently decreases by 40% – 60% of the applied NP (e.g., -10 mmHg of NP results in an IOP reduction of 4 – 6 mmHg), which would reduce the strain experienced by the

optic nerve by half according to computational models (Section 3.2.3). To further clarify the mechanism of action and the physiological effect of the OPAP, a research study (Confirm Study CP-X24), was conducted in eyes preparing to undergo cataract surgery. IOP measurements during the study were obtained via manometry, the gold standard modality of IOP measurement, which provides direct measurements in reference to atmospheric pressure. In this study, application of NP with the OPAP led to a dose-dependent reduction in IOP of 33% with the application of -10 mmHg of NP and a 51% IOP reduction with -20 mmHg of NP. The IOP reduction observed in this study with direct manometry was consistent with previously published clinical data with Excursion Tonometry. A summary of the study is presented in Section 3.2.3.2.

1.4 Regulatory and Development Program Overview

OPAP is a noninvasive, medium-risk, novel removable device with no predicate upon which to base approval (Section 4.1). Therefore, Balance Ophthalmics (the Sponsor) has requested OPAP be approved as a Class II device using the *de novo* pathway. Because IOP reduction is the only proven method for slowing glaucomatous progression, FDA has prioritized reduction of mean diurnal IOP by ≥ 20% as the primary effectiveness endpoint in studies supporting FDA approval of implantable glaucoma surgical devices (Section 4.2). Because there is no specific FDA guidance for assessing non-implantable glaucoma devices, the sponsor established the ≥ 20% IOP reduction during device use as OPAP's primary effectiveness endpoint.

Balance Ophthalmics, Inc. was founded as Equinox Ophthalmic, Inc. in 2014 by an ophthalmologist to develop a safe way to help lower IOP in some of the most difficult to treat glaucoma patients (Section 4.3). Initial discussions with FDA began in 2017, and a 3-month pivotal study (Apollo Study; Section 4.4.2.1) was submitted as the basis for a *de novo* application in 2020. Although the Apollo Study achieved its primary and secondary effectiveness endpoints with no serious device-related safety events reported, FDA denied the application, and requested a study with at 12 months follow-up.

Primary evidence of effectiveness and safety for the current application comes from the 12-month, randomized, controlled, assessor- and patient-masked Artemis Study comprising 186 eyes of 93 patients with NTG and baseline unmedicated IOP between 12 – 21 mmHg, inclusive (Section 5.1).

Supportive evidence of IOP lowering and/or safety has been generated by a total of 12 clinical investigations of 634 eyes in 378 patients across the OPAP clinical development program (Table 36, Appendix 9.3).

1.5 Effectiveness Findings

The pivotal Artemis Clinical Study met its primary and secondary endpoints, showing clinically meaningful and statistically significant reductions in IOP during device use, which were consistent across all measurement time points in all analysis populations. As consistently reported in the peer-reviewed literature, elevations in nocturnal IOP are a reliable predictor of glaucoma progression and an important target for adjunctive treatments (De Moraes et al. 2016; Yang et al. 2021; Kim et al. 2020; Dubey et al. 2020; Agnifili et al. 2015; Mansouri, Weinreb, and Liu 2015).

1.5.1 Pivotal Study Design — Artemis Study

Artemis Study Overview

Artemis was a 12-month prospective, multicenter, randomized, controlled trial that included 186 eyes of 93 patients with NTG (Figure 16; Section 5.1.1) with baseline daytime unmedicated IOP between 12 – 21 mmHg, inclusive. Study enrollment was initiated on January 21, 2020; the last subject exited the study on October 20, 2022, amidst the COVID-19 pandemic. The study included patients who had previously undergone laser trabeculoplasty or minimally invasive glaucoma surgery but excluded patients with a history of trabeculectomy or tube-shunt filtering surgery. After completing a 14-day run-in period to confirm willingness and ability to comply with nightly wear of OPAP, patients were randomly assigned to receive NP application via the OPAP goggles over one eye and no NP in the contralateral control eye. Both patients and staff performing effectiveness assessments were masked to randomization assignments, and IOP was measured in a masked fashion: one staff member applied the tonometer probe to the eye while another independently read and recorded the measurement. Patients were asked to use the OPAP for approximately 6 hours per night for at least 5 nights per week for the entire 1-year study duration.

Patients using ocular hypotensive medication at the time of initial screening underwent a minimum 30-day washout period before randomization to confirm they met the daytime unmedicated IOP criteria of $\leq$ 21 mmHg. Thereafter, patients resumed use of their prescribed ocular hypotensive medication throughout the study period.

IOP assessments while using OPAP were taken with the patient in a seated position during in clinic- visits at Day 0 and Weeks 26 and 52 (Section 5.1.1.2). Additional IOP assessments during OPAP use were taken at night in the supine position during two Sleep Lab Visits: the first Sleep Lab Visit was scheduled within 3 weeks of initial randomization; the second Sleep Lab Visit occurred shortly before the final Week 52 in-clinic visit.

Measurement Techniques

As noted in Section 1.3, traditionally available applanation methodologies cannot be used to determine the IOP -lowering effect of the FSYX OPAP during NP application because of the need to preserve the vacuum inside the goggles. Instead, “Excursion Tonometry,” (Figure 17) was used. This procedure utilizes access ports in the goggle lenses, which contain a loose latex membrane that is positioned onto the corneal surface and allows applanation with a tonometer. Using these “Excursion Goggles,” IOP is measured while preserving the vacuum inside the goggles. To perform the procedure, a Reichert Model 30™ pneumatonometer probe is inserted through the goggle port to applanate the cornea and measure TCPD referenced to atmospheric pressure. The Reichert Model 30™ pneumatonometer (not to be confused with “air puff” or pneumotonometry) was selected for its flexibility in accommodating measurements both seated in the clinic and supine in the sleep lab (Section 5.1.1.6).

Excursion Tonometry was previously validated and published in the literature (Ferguson et al. 2020; Brambilla et al. 2022), and has been confirmed by FDA as an acceptable methodology for assessing these endpoints (Section 5.1.1.6).

Effectiveness Endpoints

Assessment of primary and secondary effectiveness endpoints was performed on the modified Intent-to-Treat Population (mITT Population), which included all patients who had at least one full NP application following randomization (Section 5.1.1.7.4).

- **Primary effectiveness endpoint** was the proportion of study eyes with Week 52 in clinic- IOP reduction ≥ 20% during NP application in comparison with Baseline IOP (measured seated prior to NP application that day).
- **Secondary effectiveness endpoint** was the proportion of study eyes with Week 52 sleep lab mean IOP reduction ≥ 20% during application of NP as compared with Baseline IOP (measured supine prior to NP application that evening).

Multiple sensitivity analyses were performed on the primary endpoint, including: (1) proportion of study eyes that achieved Week 52 in clinic- IOP reduction ≥ 20% in the population of patients who completed both sleep lab visits with no major protocol deviations (Per-Protocol Population; Section 5.1.1.7.4) and (2) a tipping-point analysis of patients in the mITT Population with missing data (Figure 23; Section 5.1.2.4.3). A detailed summary of statistical analyses and considerations is provided in Section 5.1.1.7.

1.5.2 Pivotal Study Results — Artemis Study

Patient Disposition, Demographics, and Baseline Characteristics

A total of 165 patients enrolled in the study. Of the enrolled patients, 93 were randomized and included in the mITT Population for primary analysis (Figure 19; Section 5.1.2.2). A total of 71 (43.0%) patients exited the study before randomization. Most patients who discontinued during screening (before randomization) failed to meet study eligibility criteria (67/165 [40.6%]); The primary reasons for failure to meet criteria were: did not have NTG criteria or unmedicated IOP ≤ 21 mmHg in both eyes (34/165 [20.6%]), unwillingness to commit to study procedures, including OPAP home use (25/165 [15.2%]), and unwillingness to commit to study duration (8/165 [4.8%]) (Table 7). Four additional patients discontinued before randomization due to concerns about participation in the sleep lab during the COVID-19 pandemic. One additional patient, who was randomized but determined ineligible because of a historical IOP > 21 mmHg that was identified shortly after randomization, was discontinued from the study at the randomization visit and did not initiate treatment; therefore, this patient was excluded from the mITT Population for primary analysis.

Patient demographics and baseline medical characteristics were largely consistent with the US population of patients with OAG (Table 9 [demographics]; Table 10 [baseline characteristics]; Section 5.1.2.2).

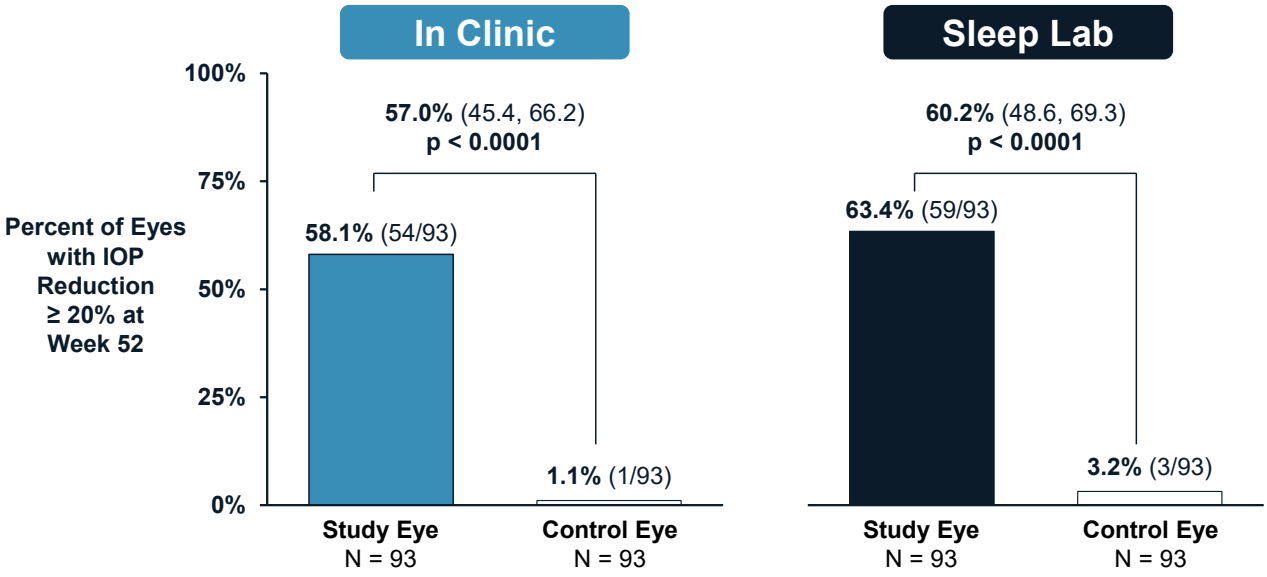
Effectiveness Findings

OPAP achieved its primary effectiveness endpoint: 54/93 (58.1%) treated eyes vs 1/93 (1.1%) control eye in the mITT Population had IOP reduced by ≥ 20% from baseline during NP application at Week 52, as measured while seated in the clinic ($p < 0.0001$; Figure 3 [left panel]; Table 12; Section 5.1.2.4.1).

OPAP also achieved its secondary endpoint: 59/93 (63.4%) study eyes vs 3/93 (3.2%) control eyes achieved mean (of the 11 pm, 2 am, and 5 am) IOP reduction ≥ 20% from baseline during

NP application at Week 52, as measured in the supine position in the sleep lab (p < 0.0001; Figure 3 [right panel]; Table 14; Section 5.1.2.5).

Figure 3: Effectiveness Endpoints Results, Proportion of Eyes with IOP Reduction ≥ 20% during Negative Pressure Application at Week 52, Measured while Seated In Clinic- (Primary) and Supine in Sleep Lab (Secondary) (mITT Population)



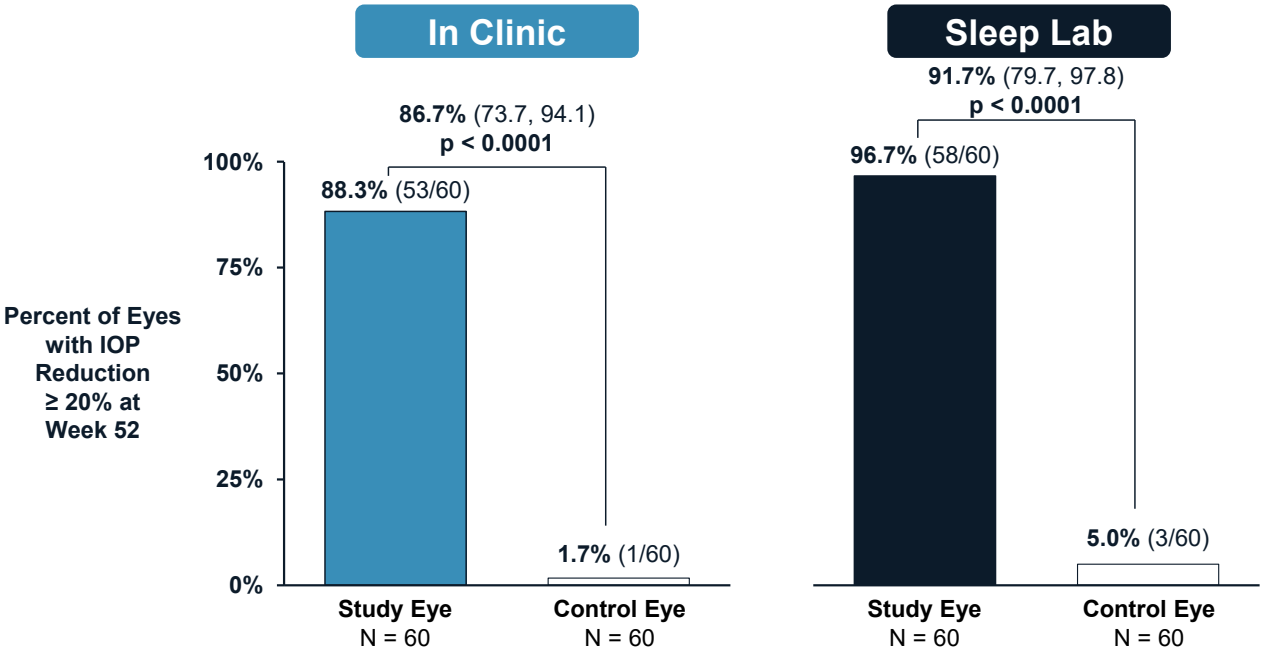
IOP=intraocular pressure; mITT=modified Intent-to-Treat; NP=negative pressure.
Note: Missing data/dropouts imputed as failure; Sleep Lab data represent the mean IOP reduction of three overnight measurements, taken at 11:00 p.m., 2:00 a.m., and 5:00 a.m.; IOP comparisons performed by Excursion Tonometry during and prior to NP application.

Results were consistent in the Per Protocol Population (N=60), which consisted of all patients who returned for 52-week follow-up and had no major protocol deviations. While the mITT analysis treated patients with missing data as non-responders, the Per-Protocol analysis was performed as a sensitivity analysis to the primary endpoint to estimate OPAP performance among patients who had not discontinued using the device.

In the Per Protocol Population, 53/60 (88.3%) study eyes vs 1/60 (1.7%) control eye achieved IOP reduction ≥ 20% at Week 52, as measured while seated in the clinic (p < 0.001; Figure 4 [left panel]; Table 13; Section 5.1.2.4.2). All patients in the Per-Protocol Population had a reduction in IOP during NP application (Figure 22).

As measured in the supine position in the sleep lab, 58/60 (96.7%) study eyes vs 3/60 (5.0%) control eyes achieved IOP reduction ≥ 20% at Week 52 (p < 0.0001; Figure 4 [right panel]).

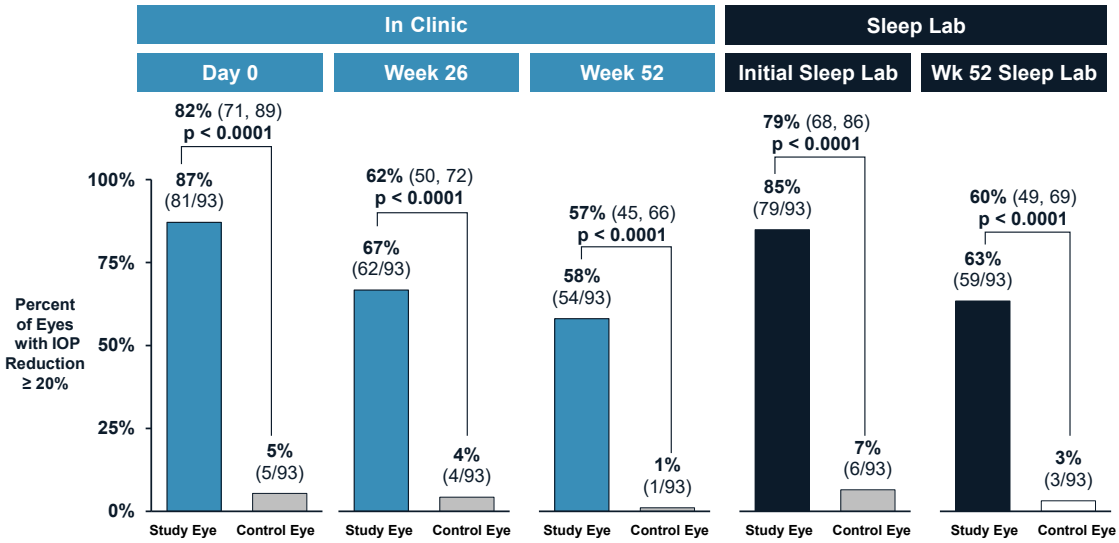
Figure 4: Sensitivity Analyses of Primary and Secondary Effectiveness Endpoints, Proportion of Eyes with IOP Reduction ≥ 20% during Negative Pressure Application at Week 52 (PP Population)



IOP=intraocular pressure; NP=negative pressure; PP=Per-Protocol.
Note: Sleep Lab data represent the mean IOP reduction of three overnight measurements, taken at 11:00 p.m., 2:00 a.m., and 5:00 a.m.; IOP comparisons performed by Excursion Tonometry during and prior to NP application.

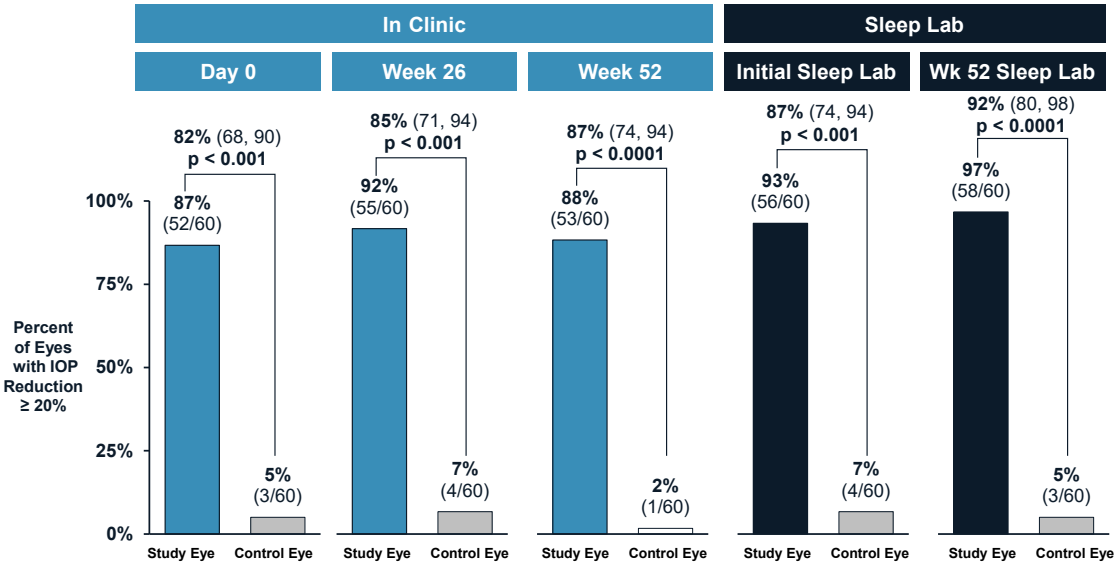
IOP reduction was also consistent at each measurement timepoint, with a significant treatment effect at all measured timepoints through Week 52, both in-clinic and in the sleep lab. Figure 5 shows results for the mITT Population where missing data and discontinuations were treated as non-responders, and Figure 6 provides results for the Per-Protocol Population. In the Per-Protocol Population, the proportion of subjects achieving the primary and secondary endpoints is unchanged at each measurement timepoint.

Figure 5: Secondary Analysis of Effectiveness (mITT Population)



IOP=intraocular pressure; mITT=modified Intent-to-Treat; NP=negative pressure; Wk=week.
Note: Missing data/dropouts imputed as failure; Sleep Lab data represent the mean IOP reduction of three overnight measurements, taken at 11:00 p.m., 2:00 a.m., and 5:00 a.m.; IOP comparisons performed by Excursion Tonometry during and prior to NP application. This chart presents tabular data previously presented to FDA in the CP-X19 CSR; the chart was prepared for Expert Panel consideration and has not been reviewed by FDA. P-values/confidence intervals at Day 0 and Week 26 not pre-specified, not adjusted for multiple comparisons.

Figure 6: Secondary Analysis of Effectiveness (PP Population)



IOP=intraocular pressure; NP=negative pressure; PP=Per-Protocol; Wk=week.
Note: Sleep Lab data represent the mean IOP reduction of three overnight measurements, taken at 11:00 p.m., 2:00 a.m., and 5:00 a.m.; IOP comparisons performed by Excursion Tonometry during and prior to NP application. This chart presents tabular data from Week 52 previously presented to FDA in the CP-X19 CSR, with additional data from Day 0 and Week 26 In-Clinic and the Initial Sleep Lab, which have not been reviewed by FDA; the chart was prepared for Expert Panel consideration and has not been reviewed by FDA. P-values/confidence intervals at Day 0 and Week 26 not pre-specified, not adjusted for multiple comparisons.

A summary of mean and percent changes in IOP during NP application at Day 0 and Week 52 is provided in Table 1. (Detailed findings are provided in Section 5.1.2.8.1 for in clinic- measurements and Section 5.1.2.8.2 for sleep lab measurements.)

Table 1: Summary of IOP Changes before and during Negative Pressure Application, Measured In Clinic- and in Sleep Lab, at Day 0 and Week 52 (mITT Population)

	Initial Visit (Day 0)		Final Visit (Week 52)	
Mean IOP change:	**Study**	**Control**	**Study[1]**	**Control[1]**
In-Clinic Change	N=93	N=93	N=61	N=61
Mean Baseline IOP	16.8 mmHg	16.8 mmHg	18.0 mmHg	17.4 mmHg
Mean IOP change	-6.1 mmHg	-0.8 mmHg	-6.6 mmHg	-0.6 mmHg
Mean percent change	-35.9%	-4.4%	-36.0%	-3.4%
Sleep Lab Change	N=80	N=80	N=61	N=61
Mean Baseline IOP	20.1 mmHg	18.6 mmHg	20.4 mmHg	19.4 mmHg
Mean IOP change	-7.6 mmHg	-1.8 mmHg	-8.0 mmHg	-1.6 mmHg
Mean percent change	-37.5%	-9.4%	-39.1%	-8.4%

IOP=intraocular pressure; mITT=modified Intent-to-Treat; NP=negative pressure.
Note: IOP assessed during and prior to NP application.
1. Measurement could not be obtained for one patient who was uncooperative.

Device usage is directly recorded by the OPAP, and patients generally complied well with the requested device use parameters. Over the course of the 1-year study, patients used OPAP an average of about 5.5 hours per night on > 78% of nights between office visits — i.e., at least 5 nights per week (Table 11; Section 5.1.2.3).

Effectiveness results from the pivotal Artemis Study are supported by findings from 9 additional clinical studies that measured IOP lowering, for a total of 584 eyes of 340 participants. For completeness, these are summarized in Table 35, Appendix 9.3. Results from these studies showed similar lowering of IOP in comparison to the pivotal Artemis Study.

(Appendix 9.3 includes detailed summaries of previous investigations: an overview of all clinical studies [Table 34], IOP changes in clinical studies that applied NP to participant eyes [Table 35], and device-related AEs in all participants [Table 36] and in patients with IOP ≤ 21 mmHg [Table 37].)

1.6 Safety Findings

No serious device-related adverse events (AEs) occurred, and there were no AEs reflective of damage to the structure and function of the optic nerve or anterior segment. None of the safety assessments reflected a worsening in clinical outcomes or unanticipated adverse device effects (UADE), and all device-related AEs resolved without sequelae.

The primary assessment of safety for this application comes from the pivotal Artemis Study (Section 5.1), in which 93 study eyes in 93 patients with NTG and baseline IOP between 12 and

21 mmHg (inclusive) received approximately 5.5 hours of NP application per night, 5 nights a week, for up to a year. The contralateral eye served as control for each patient.

Summary of Ocular and Periorbital Adverse Events

Ocular and periorbital AEs, respectively, were reported in 26.9% and 18.3% of study eyes vs 14.0% and 7.5% of control eyes (Table 2):

- Ocular AEs reported in > 5% of study eyes included: transient lid edema, generally mild-to-moderate in severity (11 [11.8%] study vs 1 [1.1%] control eyes), and mild symptoms of dry eye (5 [5.4%] study vs 5 [5.5%] control eyes; Section 6.2.2).
- Periorbital AEs reported in > 5% of study eyes included only transient mild-to-moderate periorbital edema (12 [12.9%] study vs 1 [1.1%] control eyes; Section 6.2.3).

All ocular and periorbital AEs were mild or moderate, except one case of patient-reported lid edema which the patient considered to be severe. This occurred approximately 4 months into treatment and resolved without sequelae within a week of discontinuing OPAP use. No ocular or periorbital AE was considered serious, and all resolved without sequelae before study completion. No device-related serious AEs (SAEs) were reported.

Table 2: Ocular and Periorbital Adverse Events in ≥ 3% of Study Eyes (Safety Population)

	Study Eyes (N=93)			Control Eyes (N=93)		
Ocular or Periorbital Adverse Event:	# of Reports	# of Eyes	% of Eyes	# of Reports	# of Eyes	% of Eyes
Any ocular AE	39	25	26.9%	17	13	14.0%
Lid edema	12	11	11.8%	1	1	1.1%
Symptoms and signs of dry eye	6	5	5.4%	5	5	5.4%
Conjunctival hyperemia	4	4	4.3%	2	2	2.2%
Eye pain	4	3	3.2%	0	0	-
Any periorbital AE	20	17	18.3%	7	7	7.5%
Periorbital edema	12	12	12.9%	1	1	1.1%
Periorbital contact dermatitis	4	4	4.3%	3	3	3.2%

AE=adverse event; BCDVA=best-corrected distance visual acuity.

As expected, rates of device-related AEs were similar to rates of ocular and periorbital events: 32 (34.4%) study eyes vs 10 (10.8%) control eyes had an AE reported as possibly, probably, or definitely related to device use (Table 21; Section 6.2.5).

All device-related AEs resolved without sequelae after treatment modification (e.g., reduced NP settings, temporary suspended use) or discontinuation.

(Additional clinical details of device-related ocular and periorbital AEs are provided in Appendices 9.2.2 and 9.2.3, respectively. A summary of ocular and periorbital AEs reported during the 7-day run-in period is provided in Table 32 in Appendix 9.2.1.)

For completeness, safety results from the pivotal Artemis Study are similar to findings from an additional 11 clinical studies performed using the OPAP. Altogether, 634 eyes of 378 participants were assessed for safety throughout the clinical development program (Table 36). In those studies, no serious device-related- AEs occurred, and there were no AEs reflective of damage to the structure and function of the optic nerve or anterior segment. None of the safety assessments reflected a worsening in clinical outcomes or unanticipated adverse device effects (UADEs), and all AEs considered device related- resolved without sequelae in all studies conducted in the development program.

Summary of Adverse Events Leading to Discontinuation

During the year-long Artemis Study, 3 (3.2%) patients had an AE that led to discontinuation, 2 (2.2%) of which were considered as possibly, probably, or definitely device-related, and both of which resolved without sequelae (Section 6.4). These were 2 cases of periorbital contact dermatitis, which the investigator considered as potentially a reaction to the OPAP goggles, and the patients therefore discontinued. The remaining discontinuation was a patient who was diagnosed with Stage 4 pancreatic cancer, which was unrelated to the study device.

1.7 Benefit-Risk Summary

Glaucoma is a pressure-related disease of the optic nerve and remains the leading cause of irreversible blindness in the US. Most currently available medical and surgical therapies are limited in their ability to either address nocturnal IOP elevations or provide a clinically significant IOP reduction in glaucoma patients with daytime IOP ≤ 21 mmHg. The OPAP has been demonstrated to safely reduce IOP during use in patients with OAG and IOP ≤ 21 mmHg, providing an important adjunctive treatment for controlling the nocturnal IOP elevations that are associated with glaucomatous progression.

In the pivotal 12-month Artemis Study, OPAP met both its primary and secondary endpoints of reducing IOP ≥ 20% during NP application, which is consistent with guidance for minimally invasive glaucoma devices provided by FDA (FDA 2015) for other IOP-lowering medical devices. In the PP population at the Week 52 sleep lab, 96.7% of study eyes achieved a mean IOP reduction of $\geq$ 20% during NP application as compared to 5.0% of control eyes; mean IOP was lowered by 39.1% in study eyes vs 8.4% in the control eyes at night. Compliance was generally high and consistent, with patients wearing the device for approximately 5.5 hours a night, at least 5 nights a week. These effectiveness findings were consistent with previous studies in the clinical development program.

All device-related AEs were mild or moderate in severity, except for one case of patient-reported severe lid edema. All AEs were manageable with standard supportive care and/or modified use parameters (e.g., reduced NP settings, temporary use suspension) or discontinuation. All device-related AEs resolved without sequelae by the end of the study. There were no device-related SAEs. These safety findings were consistent with previous studies in the clinical development program.

Table 3: Summary of Unmet Need and Results of Pivotal Artemis Study

Unmet Need	Effectiveness	Safety
• Glaucoma remains the leading cause of irreversible blindness • Lowering IOP is the only way to slow glaucomatous progression • Lowering nocturnal IOP is difficult, and elevated nocturnal IOP corresponds with disease progression • Lowering IOP in patients with IOP ≤ 21 mmHg is difficult, especially in patients already receiving treatment	• Artemis Trial met all endpoints with clinically meaningful, statistically significant IOP reductions • Consistent reductions in all subgroups • OPAP lowers nocturnal IOP • OPAP lowers IOP in patients whose IOP is ≤ 21 mmHg • OPAP lowers IOP in addition to existing medications and prior surgery	• No serious device-related AEs • All device-related AEs resolved without sequelae • No evidence of device-related damage to structure/function of optic nerve or anterior segment • No evidence of worsening in clinical outcomes

AE=adverse event; IOP=intraocular pressure; NP=negative pressure.

Given the meaningful unmet need, noninvasive treatment with OPAP offers an effective and important adjunct to current therapies for safely lowering IOP during use in OAG patients with daytime IOP ≤ 21 mmHg. Importantly, the patient maintains control over initiating, pausing, and stopping NP application at any time, and physicians can adjust pressure settings to address patient comfort and potential side effects. Accordingly, the likely benefits of the device to both individual patients and public health overall outweigh the likely risks.

2 BACKGROUND ON GLAUCOMA

Summary

- Glaucoma is the leading cause of irreversible blindness in the US
  - Glaucoma is a neurodegenerative disease of the optic nerve that irreversibly damages retinal ganglion cells
  - Approximately 3-5 million US adults are estimated to be living with open-angle glaucoma
  - 120,000 US adults have developed blindness because of glaucoma
  - While 60-70% of patients with open angle glaucoma have IOP >21 mmHg, 30-40% have IOP ≤ 21 mmHg
- A joint paper by the American Glaucoma Society (AGS) and American Society of Cataract and Refractive Surgeons (ASCRS) emphasized two key unmet needs:
  - 24-hour IOP profile, and
  - Noninvasive therapeutics to lower IOP especially “in challenging patients who do not adequately respond to current therapies or those in whom IOP is already within the normal range” (Downs 2020)
- Reducing IOP is the only proven strategy to slow or stop disease progression and preserve vision, even if IOP is ≤ 21 mmHg
  - IOP reduction ≥ 20% is the recommended target for glaucoma management
  - Patients with daytime IOP ≤ 21 mmHg often cannot achieve adequate IOP reduction with current pharmacological and surgical treatments
  - Nocturnal IOP elevations are associated with disease progression and most therapies are less effective at night
  - Patients with daytime IOP of ≤ 21 mmHg often have nocturnal IOP elevations

2.1 Overview of Glaucoma

2.1.1 Epidemiology

Glaucoma, a progressive disease of damage to the optic nerve around the head or disc, is a common disorder and the leading cause of irreversible blindness in the US and around the world (Downs et al. 2022). The most prevalent type of glaucoma is open-angle glaucoma (OAG), which represents more than 80% of cases in the US. The majority of OAG cases have elevated IOP > 21 mmHg; however, 30% – 40% of patients with OAG, including those with normal-tension glaucoma (NTG), have IOP within the normal range of 12 – 21 mmHg. (Varma et al. 2016; Vajaranant et al. 2012; Bonomi et al. 1998; Sales et al. 2014; Sommer et al. 1991; Nemesure et al. 2007). More than 3 million US adults are estimated to have OAG, which is projected to increase to more than 7.3 million cases by 2050 (Sheybani et al. 2020). Approximately 120,000 US adults are legally blind because of glaucoma (Quigley and Broman 2006).

2.1.2 Pathophysiology and Causes of Glaucoma

Although the exact mechanisms of glaucomatous damage are not fully understood, three different but fundamental and potentially interrelated mechanisms are commonly proposed (Sheybani et al. 2020; Weinreb, Aung, and Medeiros 2014; Kingman 2004) (Figure 7, right panel):

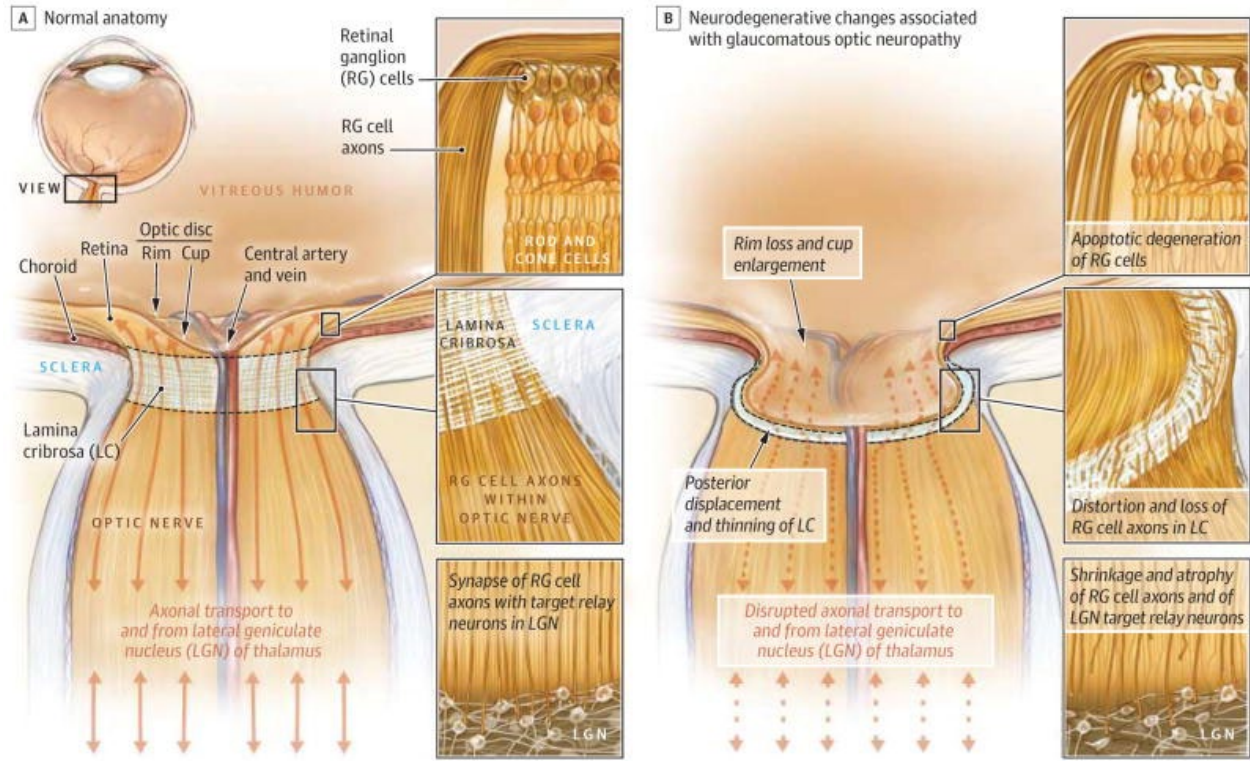
- **Mechanical strain** results from elevated IOP exerting deformation that exceeds the biomechanical capacity of the optic nerve head, leading to damaged ganglion cells.
- **Blood flow** reduction results from a low ocular perfusion pressure (mean arterial pressure minus IOP), which results in damage to the optic nerve.
- **Metabolic stress** occurs when IOP is too high, resulting in a blockade of axonal transport of neurotrophic factors within the retinal ganglion cell axons, which leads to apoptotic degeneration of the retinal ganglion cells.

It is clear that IOP is a critical factor in glaucoma, and lowering IOP decreases mechanical strain, improves blood flow, and improves axonal transport. The result is reduced apoptosis of ganglion cells and, therefore, slowed disease progression (Weinreb, Aung, and Medeiros 2014; Sheybani et al. 2020).

Converging lines of investigation also reveal the importance of other physiological pressures, including blood pressure and cerebrospinal fluid pressure (CSFp), in relation to IOP. The difference between IOP and CSFp can be referred to as the translaminar pressure difference (TLPD), with increases leading to further strain on, and damage to, the optic nerve and structures around the lamina cribrosa (Sigal et al. 2007; Baneke et al. 2020; Leske et al. 2007).

Low CSFp, even in the setting of normal IOP, has been implicated in the pathogenesis and progression of glaucoma (Berdahl and Allingham 2009; Berdahl, Allingham, and Johnson 2008; Berdahl et al. 2008; Ren et al. 2010; Gallina et al. 2023). Similarly low ocular perfusion pressure (OPP), defined as the difference between mean arterial pressure and IOP, has been shown to increase damage to the optic nerve (Weinreb, Liebmann, and Pasquale 2017) and is linked to increased risk of glaucomatous progression (Kwon et al. 2017; De Moraes et al. 2012; Sommer et al. 1991). By some estimates, patients with glaucoma who have a ≥ 20% reduction in nocturnal blood pressure face a greater than 3-fold increase in visual field progression (Kwon et al. 2017).

Figure 7: Schematic Illustration of Normal Anatomy and Neurodegenerative Changes Associated with Glaucomatous Optic Neuropathy

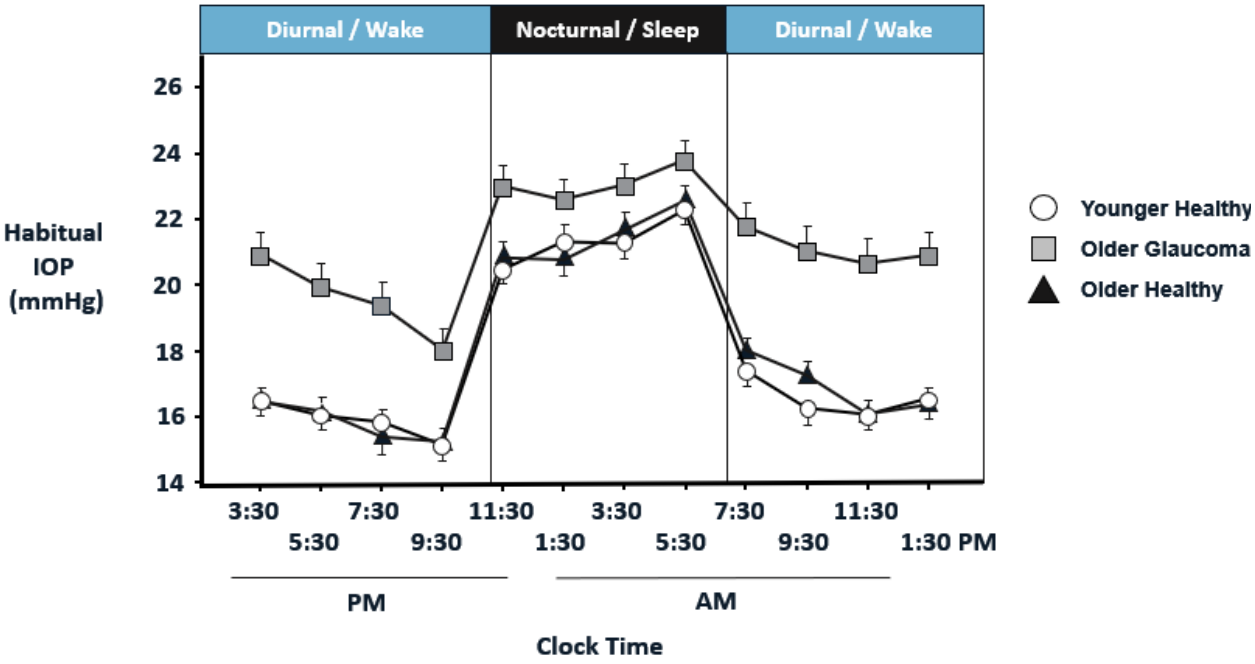


LC=lamina cribrosa; LGN=lateral geniculate nucleus; RG=retinal ganglion.
Note: Glaucomatous optic neuropathy involves damage and remodeling of the optic disc tissues and LC that lead to vision loss. With elevated intraocular pressure, the LC is posteriorly displaced and thinned, leading to deepening of the cup and narrowing of the rim.
Source: Weinreb (2014).

2.1.3 Importance of Nocturnal Intraocular Pressure in Glaucoma Management.

While most people experience nocturnal IOP elevation as part of the 24-hour circadian rhythm (Figure 8), glaucomatous eyes have both greater nocturnal IOP elevations and elevations of longer duration than healthy eyes (Agnofili et al., 2015).

Figure 8: Circadian Intraocular Pressure in Patients Diagnosed with Glaucoma vs Patients without Disease

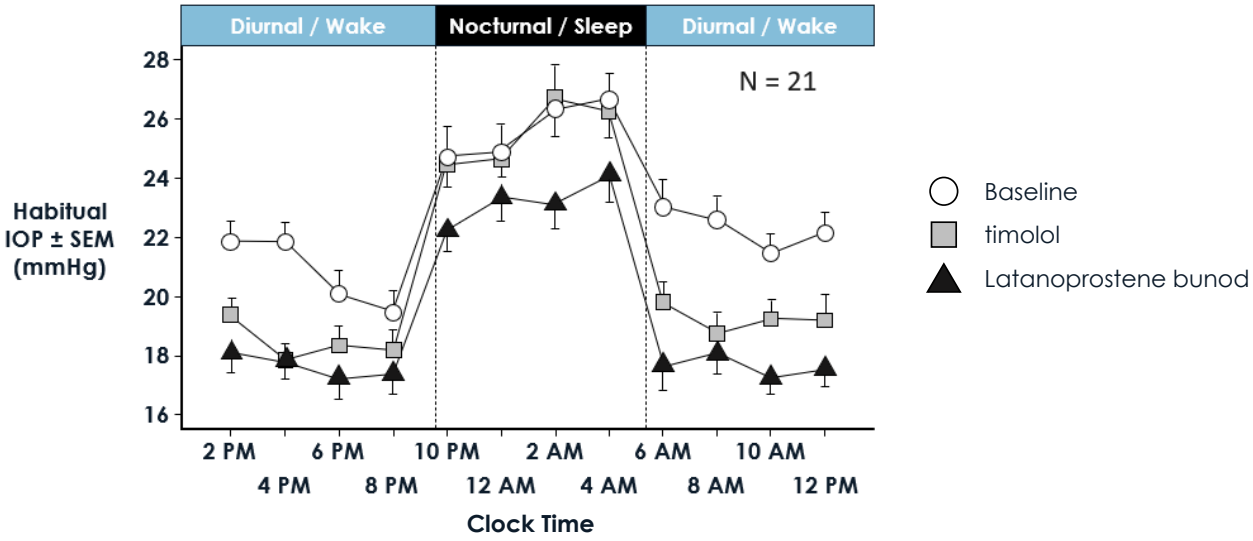


IOP=intraocular pressure; SEM=standard error of the mean.
Adapted from: (Mosaed, Liu, and Weinreb 2005).

Several recent studies have shown a relationship between nocturnal IOP elevation and glaucomatous disease progression (De Moraes et al. 2016; Yang et al. 2021; Kim et al. 2020; Dubey et al. 2020). As illustrated in Figure 9, continuous 24-hour monitoring devices have confirmed the pattern of IOP elevation occurring at night, even in the presence of IOP-lowering medications (Mansouri, Weinreb, and Liu 2015; Agnifili et al. 2015).

Similarly, both peak-to-mean IOP ratio and magnitude of elevation predict faster disease progression and visual field degradation (De Moraes et al. 2016). Another study highlighted the correlation between elevated nocturnal IOP and faster decline in visual field (Yang et al. 2021). Moreover, a recent study found that the majority of patients with controlled daytime IOP whose glaucoma continued to progress had elevated nocturnal IOP, thus supporting the association between nocturnal IOP elevations and disease progression (Dubey et al. 2020).

Figure 9: Nocturnal Intraocular Pressure Acrophase in Patients with Ocular Hypertension or Primary Open-Angle Glaucoma



IOP=intraocular pressure; SEM=standard error of the mean.
Adapted from: (J.H.K. Liu et al. 2016).

2.2 Patient Unmet Medical Need

A recent joint paper by the American Glaucoma Society (AGS) and American Society of Cataract and Refractive Surgeons (ASCRS) emphasized two key unmet needs: (1) 24-hour IOP and (2) noninvasive therapeutics to lower IOP and improve ocular blood flow. The authors noted that this was especially true “in challenging patients who do not adequately respond to current therapies or those in whom IOP is already within the normal range” (Downs 2020).

2.2.1 Current Treatment Options for Patients with OAG and IOP in the Normal Range

Prevalence studies estimate that approximately one-third of US patients with OAG have unmedicated IOP ≤ 21 mmHg (Bonomi et al. 1998; Sales et al. 2014). The treatment paradigm for these patients includes a substantial reduction in IOP (≥ 20%) to slow disease progression. The Early Manifest Glaucoma Trial, which evaluated the effectiveness of reducing IOP in previously undiagnosed OAG and explored factors related to glaucoma progression, followed 255 patients with mean baseline IOP of 20.6 mmHg for 6 years. This study showed that every 1 mmHg decrease in IOP is associated with a 10% decrease in glaucomatous progression (Heijl et al. 2002). Additionally, as demonstrated in the Advanced Glaucoma Intervention Study, decreasing the total IOP burden — i.e., area under the IOP-time curve — correlates with slowed disease progression (AGIS 2000).

Several commonly prescribed topical IOP-lowering agents, such as beta-blockers, alpha agonists, and carbonic anhydrase inhibitors, have proven daytime efficacy but limited effect on nocturnal IOP (J.H. Liu, Kripke, and Weinreb 2004; J.H. Liu et al. 2010; Orzalesi et al. 2000). The only medication class to demonstrate some benefit in nocturnal IOP reduction is

prostaglandins. However, prostaglandins have a lower magnitude of IOP reduction at night in comparison with daytime efficacy (Orzalesi et al. 2006).

The LiGHT trial demonstrated that, while selective laser trabeculoplasty (SLT) reduced average IOP over a 24-hour period, this procedure did not change the 24-hour rhythm and presence of nocturnal IOP elevations (Aptel et al. 2017; Gazzard et al. 2019; Pillunat et al. 2023). To date, the only surgical procedure demonstrated to provide 24-hour control is trabeculectomy. However, this is an invasive procedure associated with significant morbidity and clinically significant side effects occurring in 63% of cases within 5 years (Gedde et al. 2012; Konstas et al. 2006; Caprioli et al. 2016; Klink et al. 2012).

Table 4: Common IOP-Lowering Treatments for Patients with Open-Angle Glaucoma

Treatment Route:	Treatment
Topical	Prostaglandins
	Beta blockers
	Alpha-adrenergic agonists
	Carbonic anhydrase inhibitors
	Miotic or cholinergic agents
	Rho kinase inhibitor
Surgical	Laser trabeculoplasty
	Minimally Invasive Glaucoma Surgery (MIGS)
	Traditional filtration surgery (e.g., trabeculectomy or tube-shunt implant)

IOP=intraocular pressure.

2.2.2 Challenges in Glaucoma Management for Patients with IOP ≤ 21 mmHg

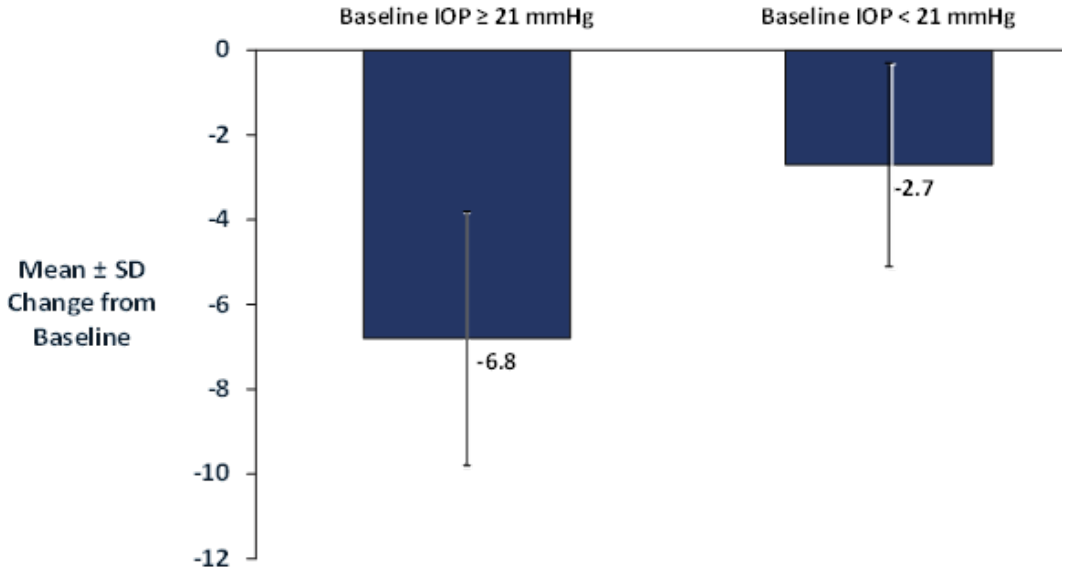
While strategies targeting IOP reduction are the foundation of glaucoma treatment in all patients, most patients with progressive disease still have elevated IOP at night (Dubey et al. 2020), highlighting the need for additional strategies to manage nocturnal IOP (Section 2.1.3). Additionally, patients with IOP in the normal range of ≤ 21 mmHg may still experience glaucomatous disease progression. In most instances, the IOP-lowering effectiveness of ocular hypotensive medications, laser procedures, and minimally invasive glaucoma surgery is diminished in these patients.

The Early Manifest Glaucoma trial showed that eyes treated with laser trabeculoplasty and topical betaxolol demonstrated nearly 2.5 times more reduction in mean IOP over a 6-year period when baseline IOP was ≥ 21 mmHg than when IOP was < 21 mmHg (Figure 10). Specifically, the study showed that IOP decreased by an average of 2.7 mmHg in eyes with baseline IOP < 21 mmHg, as compared to a 6.8 mmHg reduction in eyes with baseline IOP ≥ 21 mmHg (Heijl et al. 2002).

Likewise, a retrospective review of glaucoma outcomes with SLT showed that higher baseline IOP was strongly associated with treatment success (hazard ratio [HR]: 0.67 for baseline

IOP > 21 mmHg vs ≤ 21 mmHg) (Khawaja et al. 2020). Similarly, a retrospective review of minimally invasive glaucoma surgery (MIGS) stents showed minimal IOP-lowering effect in eyes with IOP ≤ 16 mmHg (Ferguson et al. 2016).

Figure 10: Mean Reductions in IOP over 6-Year Period for Patients with Baseline IOP < 21 mmHg vs ≥ 21 mmHg (Early Manifest Glaucoma Trial)



IOP=intraocular pressure; SD=standard deviation.
Adapted from: Heijl et al. (2002).

2.2.3 Summary of Unmet Need

Despite the availability of a range of treatment options, glaucoma remains the leading cause of irreversible blindness in the U.S. and around the world. While the only modifiable risk factor proven to slow glaucomatous progression and visual field loss is IOP reduction, many patients whose daytime IOP appears to be controlled with pharmacological and/or surgical interventions continue to show disease progression. Nocturnal elevation in IOP, which persists despite most medical and surgical therapies, has been demonstrated to be a significant risk factor associated with this continued progression.

There is a substantial need for adjunctive therapy that addresses these nocturnal IOP elevations in patients with OAG whose glaucoma continues to progress even though daytime IOP is within the range considered normal (e.g. ≤ 21 mmHg).

3 PRODUCT DESCRIPTION

Summary

- OPAP was developed as an adjunctive treatment for patients with OAG and IOP ≤ 21 mmHg to address the unmet need for lowering nocturnal IOP
  - OPAP is composed of a pair of removable goggles that are connected by pneumatic tubing to a programmable pressure pump; the pump generates a mild negative pressure over the eye(s), which reduces IOP
  - OPAP can be programmed with a different negative pressure setting in each goggle, allowing for pressure reductions tailored to the unique needs of each eye
  - Healthcare providers can program and adjust negative pressure settings via a dedicated computer in the clinic; patients cannot adjust pressure settings
- Multiple studies show that OPAP consistently reduces IOP by approximately 40% – 60% of the programmed negative pressure
  - The reduced IOP translates into a ~50% decrease in strain on the optic nerve head, based on computational modeling
  - IOP is reduced only when OPAP is worn and activated; when OPAP is removed, IOP returns to baseline

3.1 Proposed Indication

The FSYX™ Ocular Pressure Adjusting Pump (OPAP) is indicated as adjunctive therapy for the reduction of intraocular pressure during nightly use in adult patients with open-angle glaucoma and intraocular pressure ≤ 21 mmHg.

3.2 Device Overview

3.2.1 Device Description

The OPAP consists of a programmable pump and a set of removable goggles. The two devices are mechanically and pneumatically connected via the tubing system, which is integral to the goggles (Figure 1). The goggles are provided in small, medium, and large sizes with an adjustable head strap and nose bridge. The pump contains software designed to sense and deliver NP to each eye, and NP settings for each goggle chamber may be programmed independently. The pump is programmed and managed using a proprietary application developed and validated by Balance Ophthalmics and the device arrives to the patient pre-programmed according to initial physician-prescribed parameters. Physicians are provided with a dedicated computer loaded with the FSYX application, which is maintained in -clinic. Trained, designated staff connect the pump to the computer using a USB cord to enter designated pump pressure settings and to download data from the patient's at-home OPAP use.

3.2.2 Rationale for Device Development and Usage

The OPAP was designed as a noninvasive and adjunctive treatment option to further lower IOP, specifically at night when nocturnal IOP is elevated. The need for additional therapies to lower

IOP that are safe and effective is evidenced by the fact that glaucoma in many patients continues to worsen despite the currently available range of treatment options. (See Section 2.1.3 for discussion on importance of nocturnal IOP and Section 2.2 for an overview of unmet need.)

3.2.3 Mechanism of Action of the OPAP

3.2.3.1 Overview of Mechanism of Action

The OPAP consists of eye goggles connected to a programmable pressure-modulating pump that applies NP to the microenvironment inside the goggles. The application of NP within the goggle chambers causes a localized, isolated reduction of atmospheric pressure over the anterior part of the globe, which decreases IOP during NP application (Figure 2). This mechanism of action is based on Pascal's law, which states that when there is a change in pressure at any point in a confined incompressible fluid, there is an equal pressure change throughout the fluid.

Previous clinical studies have shown consistent, clinically significant IOP reduction during OPAP use, which generally ranges from 40% – 60% of the applied NP (Table 35; Appendix 9.3). This means that if a NP of -10 mmHg is applied, the resulting IOP measured is reduced by 4 to 6 mmHg. These observations are consistent with two independent modeling studies (Ethier, Yoo, and Berdahl 2020; Safa et al. 2023). Collectively, these studies have shown that IOP lowering is sustained throughout OPAP treatment because less atmospheric pressure is present over the eye and episcleral veins. Importantly, the model also demonstrated that the strains at the optic nerve head are decreased by ~50% because IOP is lowered relative to the pressure posterior to the lamina cribrosa (Safa et al. 2023).

The IOP-lowering effect of OPAP persists only during NP application; when NP application is terminated, IOP returns to baseline.

3.2.3.2 Confirmation of IOP Reduction with OPAP

Conventional tonometry has been developed as a surrogate to estimate IOP without the invasiveness of inserting a needle into the eye, as is done with manometry. With conventional tonometry, the measured transcorneal pressure difference (TCPD) is the difference between the IOP and the pressure surrounding the body (atmospheric pressure). With OPAP, the Excursion Tonometry used clinically (Figure 17; Figure 18; Section 5.1.1.6) also measures the TCPD as the difference between the IOP and atmospheric pressure. The TCPD between the IOP and the intra-goggle pressure would be greater with NP application, thus it has been important to demonstrate that OPAP reduces IOP when measured directly. To that end, two research studies have been conducted and confirmed that OPAP reduces IOP as measured directly with manometry. A thorough review of this concept by experts in the field is provided in Appendix 9.4 and was shared with FDA both in relation to a pre-submission meeting (QXXXXX8) 03 January 2021, and in DENXXXXX2/S001.

Cadaver Study

A small cadaver study allowed for direct IOP, retrobulbar pressure, and intra-goggle pressure measurements via a pressure transducer acquisition system. The OPAP was placed over the

eyes of each subject, and pressure measurements were obtained during NP application. These direct pressure measurements confirmed that NP application resulted in IOP reduction with minimal impact to retrobulbar pressure.

Confirm (CP-X24)

A basic physiological research study (Confirm Study, CP-X24) in patients undergoing routine cataract surgery evaluated the change in IOP as measured using manometry during periocular NP application with OPAP. In Confirm, 17 participants undergoing routine cataract surgery received NP application with the OPAP while IOP was measured manometrically.

NP application occurred immediately prior to surgery. After sterile prep, the eye was cannulated through a paracentesis with an anterior chamber maintainer connected to a manometer to continuously measure IOP every 0.5 seconds (500 milliseconds) for approximately 30-second intervals throughout the following sequence:

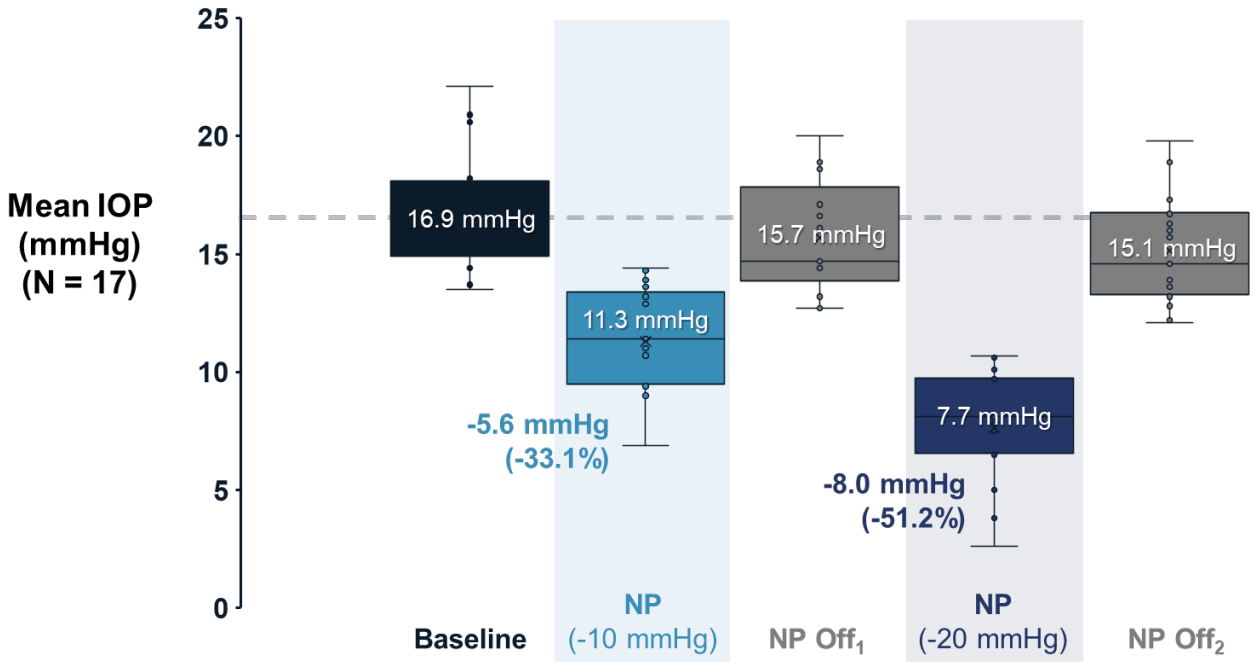
1. Baseline IOP measurement with no NP
2. -10 mmHg of NP for approximately 30 seconds
3. NP Off_1: NP stopped for approximately 30 seconds
4. -20 mmHg of NP for approximately 30 seconds
5. NP Off_2: NP stopped

After the sequence, the OPAP was removed, and cataract surgery commenced.

All eyes had a dose-dependent decrease in IOP during NP application as measured with manometry, with normalization toward baseline IOP after NP was removed (Figure 11).

The results of this study produced findings similar to those seen before and were also consistent with modeling (Ethier et al. 2020). The application of -10 mmHg NP resulted in a mean IOP decrease from baseline of 5.6 mmHg (-33.1%) and -20 mmHg NP resulted in mean IOP decrease of 8.0 mmHg (-51.2%). Importantly, no subject demonstrated an increase in IOP during NP application. This study demonstrated that NP application reduced IOP in a dose-dependent manner, as measured using manometry, and that the IOP returned to baseline following release of NP application.

Figure 11: Mean IOP Reductions before and during Negative Pressure Applications at -10 mmHg and -20 mmHg (Confirm Study)



IOP=intraocular pressure; NP=negative pressure.
Note: IOP was measured every 0.5 seconds (500 milliseconds) using manometer connected to eye via fluid cannula, inserted temporarily during cataract surgery. Negative pressure was applied for approximately 30 seconds at -10 mmHg and then for another ~30 seconds at -20 mmHg, with approximately 30-second recovery period between NP applications. Values presented reflect average readings during the NP application and recovery periods. IOP reduction at -10 mmHg NP was calculated by comparing to Baseline IOP. IOP reduction at -20 mmHg NP was calculated by comparing to NP OFF 1. This chart presents tabular data presented to FDA in DENXXXXX2/S001but has not been reviewed by FDA for accuracy; the chart was prepared for Expert Panel consideration and has not been reviewed by FDA.

3.2.4 Notes on Usage

OPAP is a quiet noninvasive device with wearable goggles put on before bed and worn while sleeping, then removed upon waking. The patient may sleep supine or on their side. Pump settings are controlled by a physician and cannot be altered by the patient; however, the patient has the option to pause or stop NP application at any time. Neither the pump nor goggles have internet connectivity; therefore, adjustments to NP settings are performed by the provider in the clinic.

4 REGULATORY AND DEVELOPMENT HISTORY

Summary

- OPAP is noninvasive, with no implantable components, and is proposed as a Class II (medium-risk) device
  - There is no predicate device upon which to base approval; therefore, the *de novo* pathway is considered the most appropriate regulatory framework
- The clinical development program encompasses 12 studies in 634 eyes of 378 participants
  - 562 eyes in the clinical program had an IOP ≤ 21 mmHg
  - 378 patients had at least one eye receive a negative pressure application
- FDA has consistently relied on primary effectiveness endpoints of IOP reduction ≥ 20% for high-risk Class III devices
- Supporting studies consistently showed statistically significant and clinically meaningful reductions in IOP during OPAP use
- The pivotal Artemis Study included 186 eyes of 93 patients with NTG
  - FDA's request for data on patients followed for a year during OPAP use is addressed with the Artemis Study
  - Findings in the Artemis Study confirmed that OPAP safely and effectively reduced IOP in patients with OAG and daytime IOP ≤ 21 mmHg during 1 year of nightly use

4.1 *De novo* Requirements

The *de novo* classification request is a type of premarket submission that uses a risk-based approach to classify novel medical devices. The *de novo* request provides a marketing pathway to classify novel medical devices for which general controls alone, or general and special controls, provide reasonable assurance of safety and effectiveness for the intended use, but for which there is no legally marketed predicate device.

All FDA-approved medical devices are classified as either Class I, Class II, or Class III. Class I devices, such as visual acuity charts, are the lowest risk. Class II devices are medium risk, and Class III devices are the highest risk.

Examples of Class II devices similar to the OPAP include continuous positive airway pressure (CPAP) devices and negative pressure wound therapy devices. Class II devices used to reduce IOP in patients with glaucoma include lasers for trabeculoplasty or surgical instruments used for viscodilation of Schlemm's canal and cutting of trabecular meshwork tissue, as well as permanently implantable devices like the Express Shunt. Class III devices include permanent MIGS implants, such the Glaukos iStent® or the Hydrus® Microstent. Based on its risk level, OPAP is proposed as a Class II device.

OPAP is a novel device, and there is no available predicate device. Therefore, the *de novo* pathway represents the most appropriate framework for application and approval because it provides for a positive benefit-risk assessment based on the totality of pre-market evidence and post-market measures.

The granting of a *de novo* request requires FDA to make a risk-based classification decision that when subject to general controls, or general and special controls, the probable benefit to health from use of the device outweighs any probable injury or illness from such use (21 CFR 860.7).

4.2 FDA Guidance on Glaucoma Study Endpoints

Both the World Glaucoma Congress and FDA prioritize reduction in IOP as the most important variable for assessment of the effectiveness of glaucoma therapies. FDA's recommended primary effectiveness endpoint for implantable glaucoma surgical devices is the percentage of study patients with a reduction of at least 20% (i.e., ≥ 20%) in mean diurnal IOP from baseline prior to surgery (FDA 2015). Notably, FDA establishes effectiveness based on IOP reduction, rather than visual field assessments, which can vary.

The pivotal Artemis Study for the OPAP, an externally worn device intended for use while sleeping, has a similar primary endpoint: the percentage of study eyes with an IOP reduction of at least 20% from baseline, during NP application, after 52 weeks of device wear. (See Section 5.1.1.7.1 for a listing of all endpoints in the Artemis Study.)

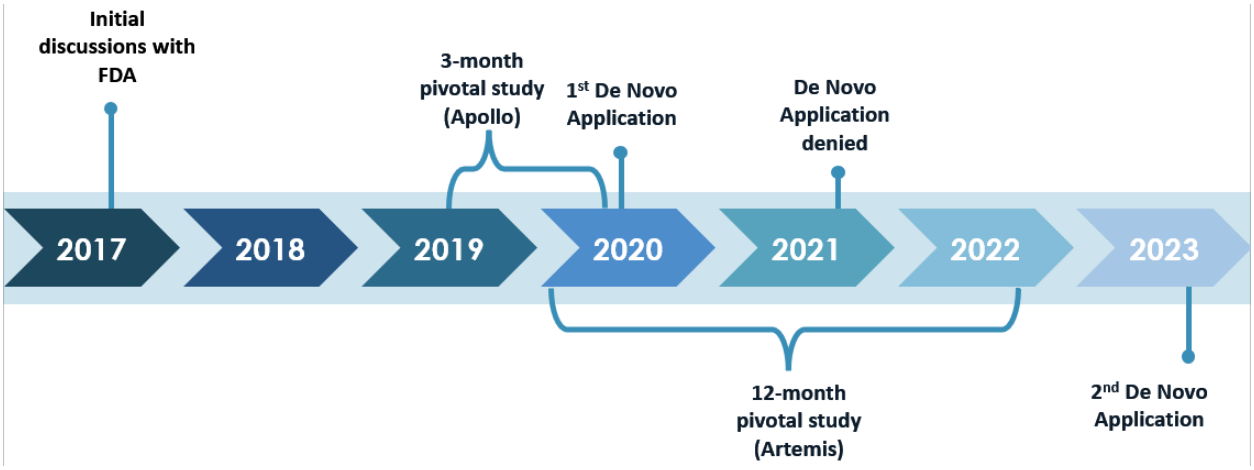
4.3 Regulatory History

Equinox Ophthalmic, Inc. was founded in September 2014 to develop the FSYX OPAP (previously referred to as the Mercury Multi-Pressure Dial [MPD] System), a novel, noninvasive medical device designed to apply localized NP to the front of the eye via goggles connected to a pressure-modulating pump to reduce IOP in eyes with glaucoma. The first OPAP prototype was developed in 2014. Based on user needs and clinical experience, the MPD components (goggles and pump) underwent continuous design improvement to optimize comfort, fit range, usability, reliability, and manufacturability.

The Sponsor began discussions with FDA about study design and submission requirements for marketing approval in 2017 (Figure 12) including a formal pre-submission meeting on Nov 17, 2017. In 2019, the 3-month pivotal study Apollo (CP-X10) was initiated. This study was submitted for Agency review as part of a *de novo* application in 2020. Also, in early 2020, as part of ongoing clinical development, Equinox initiated the 12-month Artemis Study in patients with NTG. In the fall of 2021, FDA denied the company's *de novo* application and requested a new study with at least 12 months follow-up.

A second *de novo* application was filed in 2023, with the Artemis Study providing the pivotal longer-term data (12 months), as requested by FDA for evaluation of device safety and effectiveness-.

Figure 12: Timeline of OPAP Device Regulatory History



FDA=Food and Drug Administration; OPAP=Ocular Pressure Adjusting Pump.
Note: Enrollment for Artemis Study lasted approximately 1 year during the COVID-19 pandemic. Therefore, the 12-month study has a longer-than-expected timeframe from beginning to completion.

4.4 Summary of Clinical Development Program

The OPAP clinical development program includes 12 clinical studies of 634 eyes in 378 participants (95 of whom were healthy volunteers). Results of key prior investigations are presented below. Complete summaries of study parameters and results are provided in Appendix 9.3, which includes Table 34 (summary of study designs and findings), Table 35 (summary of NP settings and results), Table 36 (summary of device-related AEs), and Table 37 (summary of device-related AEs in eyes with baseline IOP ≤ 21 mmHg).

4.4.1 Artemis Study

The Artemis Study (Section 5.1) was the pivotal trial performed to demonstrate OPAP's safety and effectiveness as an adjunct treatment for lowering IOP during use in patients with normal-tension glaucoma (NTG). A total of 93 patients with NTG were randomized and initiated the treatment plan to receive 52 weeks of nocturnal negative-pressure application on one eye, while the fellow eye acted as a control, receiving no pressure application. As the device is intended for adjunct therapy, patients continued use of concomitant IOP-reducing medications throughout the study (Section 5.1.1.2).

(See Section 5.1.1 for details of study design, Section 5.1.1.6 for details and validation of measurement techniques, and Section 5.1.2 for detailed results.)

4.4.2 Summaries of Key Prior Investigations

4.4.2.1 Apollo Study (CP-X10)

Apollo Study Design

The Apollo Study (N=64) was a multi-center, prospective, randomized, controlled, masked study in patients with OAG, ocular hypertension, or suspected glaucoma. Patients were enrolled at six

US-based investigational sites for 90 days of OPAP use. Importantly, two-thirds of patients (42/64 [65.6%]) had baseline diagnosis of OAG and IOP ≤ 21 mmHg, which is of particular relevance to the proposed indication. Similar to the Artemis Study (Section 5.1), patients completed a device use run-in period and were then randomly assigned to receive NP application in one eye while the contralateral eye acted as a control (receiving no NP application). Patients and study personnel performing IOP assessments were masked to randomization assignments, and there were no differences in the presentation of treatment. Investigational staff programmed each patient's device to administer a specified NP to the study eye using a formula based on the patient's in-clinic IOP, and patients were asked to use the device during sleeping hours.

Patients used the OPAP nightly at their habitual NP for 90 days and returned for monthly in-office- assessments. The primary effectiveness endpoint of the study was the proportion of study eyes in the mITT Population with Day 90 in-clinic IOP reduction ≥ 20% during NP application compared to baseline (measured before NP application).

Apollo Study Results

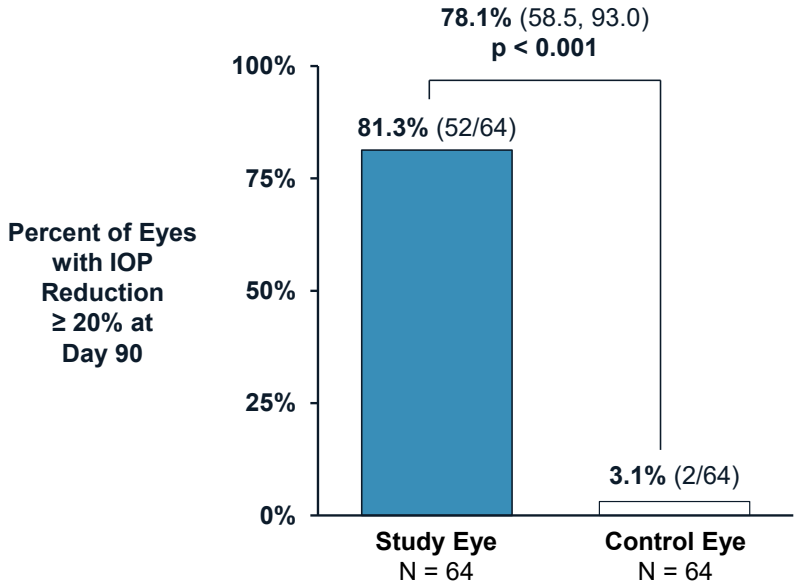
Apollo met its primary endpoint, with 52 (81.3%) study eyes vs 2 (3.1%) control eyes in the mITT Population achieving IOP reduction ≥ 20% at Day 90 ($p < 0.001$; Figure 13). For study eyes with Baseline IOP ≤ 21 mmHg (N=38), the mean IOP prior to NP application was 17.3 ± 2.0 mmHg and was reduced to 11.3 ± 2.0 mmHg after NP application, representing a 34.7% (6.0 mmHg) reduction in IOP ($p < 0.001$; Figure 14).[1]

The most commonly reported AEs were lid (17.2% study eye, 7.8% control eye) and periorbital edema (14.1% study eye, 10.9% control eye). There were no serious device-related adverse events.

Patients also completed the 18-item Symptoms and Health Problem Checklist (SHPC-18), a patient-reported outcomes tool designed to capture local eye and visual function symptoms in glaucoma (Musch et al. 2017), at baseline and Day 90. Visual function symptoms remained stable over time. No patient reported a worsening of Grade 3 or more in any vision function problem. As expected, the largest increase in symptoms involved skin sensitivity around the eyes (study eyes: 3.1% at baseline and 22.4% at Day 90; control eyes: 3.1% at baseline and 20.7% at Day 90).

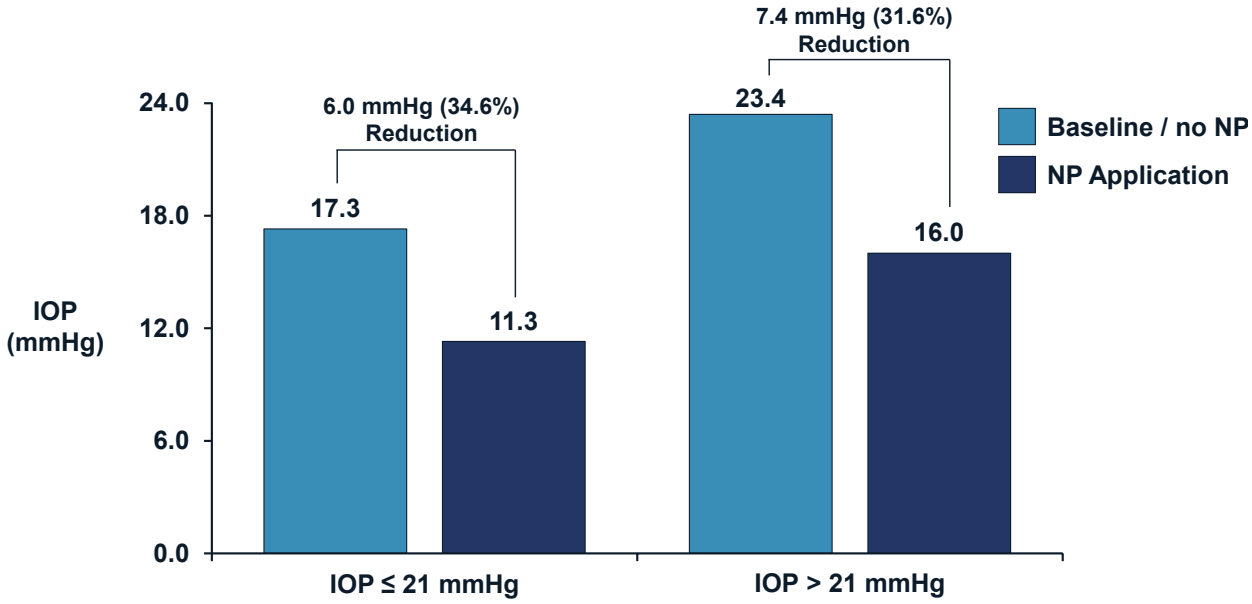
[1] The summary of effectiveness in eyes with baseline IOP ≤ 21 and > 21 mmHg in the Apollo Study (CP-X10) has not previously been reviewed by FDA. P--values/confidence intervals for this analysis were not pre-specified and not adjusted for multiple comparisons.

Figure 13: Apollo Study Primary Effectiveness Endpoint Results (mITT Population)



IOP=intraocular pressure; mITT=modified Intent-to-Treat; NP=negative pressure.
Note: Missing data and discontinuations imputed as failures; IOP measured during and prior to NP application.

Figure 14: Apollo Study Mean IOP Reduction during NP Application at Day 90, by Baseline IOP (mITT Population)



IOP=intraocular pressure; mITT=modified Intent-to-Treat, NP=negative pressure.
Note: This figure has not previously been reviewed by FDA.

4.4.2.2 Feasibility Study (CP-X18)

CP-X18 Study Design

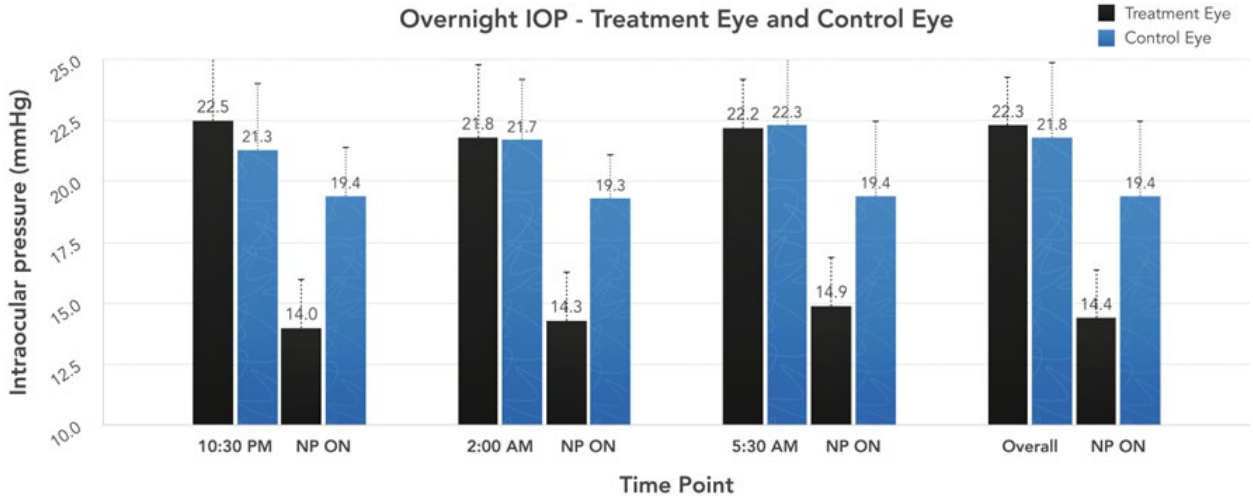
CP-X18 was a single-site, prospective, randomized, controlled study to evaluate the short-term feasibility of NP application for lowering nocturnal IOP in patients with OAG. This study was approved by the local ethics committee where the study was performed in Mexico City.

Twenty-two eyes from 11 patients were studied. All patients were using a topical prostaglandin. For each patient, the eye with the highest IOP measured in the supine position was selected as the treatment eye, and the contralateral eye served as the control. NP for the treatment eye was set to 60% of Baseline IOP with no NP in the control eye. IOP measurements were collected at 3 prespecified time points overnight in the supine position with active NP. The primary outcome measure was mean IOP with the application of NP.

CP-X18 Study Results

Baseline IOPs in the treatment and control eye were well balanced: mean (SD) of 22.2 ± 2.5 vs 21.8 ± 2.5 mmHg, respectively. During NP application, mean IOPs were 14.2 ± 2.2 vs 19.5 ± 2.4 mmHg, respectively. The mean percentage IOP reduction in the treatment eye was 35% (p = 0.001). There were 2 mild adverse events, both unrelated to device wear, and no IOP elevations ≥ 10 mmHg. These findings informed future study design and continued clinical evaluation of the OPAP.

Figure 15: Feasibility Study Results, IOP Measurements at Three Nocturnal Timepoints (CP-X18 Study)



IOP=intraocular pressure; NP=negative pressure.

4.4.2.3 Endure Study (CP-X23)

Endure Study Design

The Endure Study was a single-site, prospective, controlled, randomized, assessor-masked study to evaluate the sustainability of IOP reduction with continuous NP application via OPAP

over a single 8-hour session in 10 patients with OAG and IOP15 – 22 mmHg, inclusive. Patients were randomized such that one eye received NP treatment, and the contralateral eye acted as a control (no NP treatment). After screening, patients received an 8-hour period of continuous, uninterrupted NP application while wearing the Excursion version of the OPAP. This allowed for IOP measurement during NP application. Excursion tonometry was performed at 2-hour intervals, and an additional IOP measurement was obtained immediately following cessation of NP at the conclusion of the 8-hour study period.

Endure Study Results (CP-X23)

Nine (9 [90%]) patients completed the 8-hour study, and 1 (10%) exited during the first hour of NP application due to mild headache. The Baseline IOPs in study and control eyes were well balanced, and the mean NP setting was -12.0 mmHg. At the 8-hour timepoint, the study vs control eyes had a mean IOP reduction during NP application of 6.7 mmHg (31%) vs 0.3 mmHg (1.5%) from baseline, respectively.

Results from Endure supported further clinical development of OPAP, demonstrating that IOP reductions are sustained during NP application, with consistent results over the duration of the NP application. These results align with findings from the sleep lab data (Section 5.1.2.5) collected during the pivotal Artemis Study.

Table 5: Endure Study — Mean IOP and Percent Change in IOP at 2-Hour Intervals

IOP, mmHg:	Baseline	Hour 0	Hour 2	Hour 4	Hour 6	Hour 8
Study eye (N=9)						
Mean (SD)	21.4 (4.3)	13.3 (3.6)	15.0 (2.8)	15.1 (3.4)	14.1 (5.2)	14.7 (4.4)
Percent change*	-	↓ 38%	↓ 30%	↓ 29%	↓ 34%	↓ 31%
p-value**	-	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$
Control eye (N=9)						
Mean (SD)	20.4 (3.6)	17.6 (3.0)	19.3 (2.8)	20.8 (3.6)	19.4 (4.3)	20.1 (4.1)
Percent change*	-	↓ 14%	↓ 5%	↑ 2%	↓ 5%	↓ 1%
p-value**	-	$p < 0.05$	$p > 0.9$	$p > 0.9$	$p > 0.9$	$p > 0.9$

IOP=intraocular pressure; SD=standard deviation.
* Percent change is calculated in comparison to Baseline.
** p-value is calculated from a post-hoc paired t-test in comparison to the baseline value, and did not include study-wise type I error control

5 CLINICAL EFFECTIVENESS

Summary

- The pivotal Artemis Study (N=93) was a prospective, randomized, masked, multicenter trial of 186 eyes of 93 patients with normal-tension glaucoma
  - One eye in each patient was randomized to receive negative pressure application nightly for a year; the contralateral eye served as control and received no negative pressure
  - Patients were allowed to continue all prior medications; a minimum 30-day washout period was required for patients taking ocular hypotensive medication to confirm baseline daytime IOP was ≤ 21 mmHg; thereafter, patients resumed use of ocular hypotensives
- The Artemis Study met both the primary and secondary effectiveness endpoints of ≥ 20% IOP lowering, which is consistent with FDA guidance for minimally-invasive glaucoma surgical devices.
- Artemis demonstrated clinically meaningful, statistically significant, and consistent reductions of IOP during use in all analysis populations
- In the mITT Population for primary analysis, 58.1% vs 1.1% of study vs control eyes, respectively, achieved the primary endpoint of IOP reduced ≥ 20% during use **in-clinic** at Week 52 ($p < 0.0001$)
  - In the Per-Protocol Population, as a sensitivity analysis, 88.3% vs 1.7% of study vs control eyes, respectively, achieved IOP reduction ≥ 20% during use **in-clinic** at week 52 ($p < 0.0001$)
  - A tipping-point analysis that imputed all missing study eyes as failures and all missing control eyes as success confirmed statistical significance of the primary endpoint
- In the mITT Population, 63.4% vs 3.2% of study vs control eyes, respectively, achieved the secondary endpoint of mean IOP reduction ≥ 20% during use at Week 52, as measured while supine in the **sleep lab** ($p < 0.0001$)
  - In the Per-Protocol Population, as a sensitivity analysis, 96.7% vs 5.0% of study vs control eyes, respectively, achieved mean IOP reduction ≥ 20% during use at Week 52, as measured while supine in the **sleep lab** ($p < 0.0001$)
  - At the Week 52 **sleep lab**, mean IOP was reduced by 39.1% from baseline in study eyes vs 8.4% in the control eyes
- OPAP consistently reduced IOP, regardless of age, sex, glaucoma surgery status, baseline ocular hypotensive medication use, baseline IOP, or cup-to-disc ratio
- Among patients who completed Artemis, compliance was consistent, with patients wearing OPAP for about 5.5 hours a night, 5 nights a week, throughout the year

5.1 Artemis Study

5.1.1 Artemis Study Design

5.1.1.1 Overview of Artemis Study

The Artemis clinical study was a prospective, multicenter, randomized, controlled, patient- and assessor-masked trial that included 93 patients (186 eyes) with NTG (Figure 16).

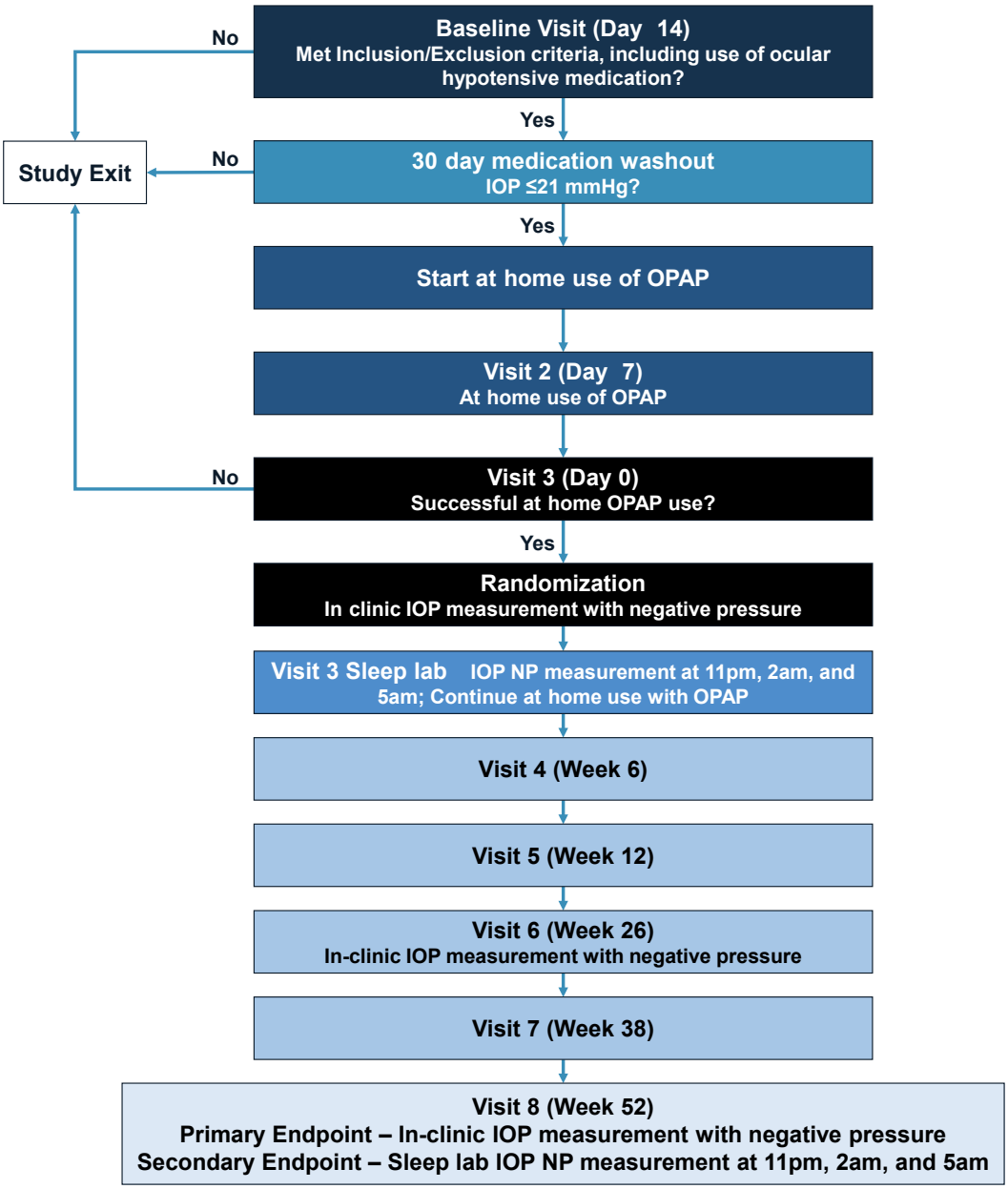
After completing a device use run-in period, patients were randomly assigned to receive NP application in one eye, while the contralateral eye acted as a control (receiving no NP application). Patients were not told of the randomization assignment for their eyes, and the goggles were symmetrical to minimize the likelihood of determining treatment assignment. At each visit, study personnel performing ophthalmic assessments and measuring IOP were masked to patient randomization assignments.

Investigational staff programmed each patient's device to administer a specified NP to the study eye using a formula based on the patient's in-clinic IOP. Patients were asked to use the device during sleeping hours for approximately 6 hours/night at least 5 nights/week. An 8-hour sleep lab was scheduled within 21 days of randomization to measure night-time IOP during use of the OPAP. At the sleep lab, baseline IOP (supine) was measured prior to OPAP use, then, patients used the OPAP while sleeping and/or resting supine during the night. At approximately 11:00 p.m., 2:00 a.m., and 5:00 a.m., IOP in both eyes was measured during NP application. If the baseline IOP (supine) at the initial sleep lab differed from that measured in-clinic, the study eye NP was reprogrammed for subsequent home use based on this baseline (supine) IOP.

Patients continued to use the OPAP at their habitual NP for 52 weeks and returned for 5 assessments at approximately 6, 12, 26, 38, and 52 weeks. Just before the Week 52 in-office visit, patients repeated the sleep lab, using the same methodology as described for the initial sleep lab.

The primary effectiveness endpoint of the study was the proportion of study eyes with Week 52 in-clinic IOP reduction ≥ 20% during NP application in comparison with baseline IOP (measured prior to NP application). The secondary effectiveness endpoint was the proportion of study eyes with Week 52 sleep lab mean (of the 11:00 p.m., 2:00 a.m., and 5:00 a.m.) IOP reduction ≥ 20% during NP application in comparison with baseline IOP (measured supine prior to NP application).

Figure 16: Study Design of Artemis Clinical Trial



IOP=intraocular pressure; M=month; NP=negative pressure; OHTN=ocular hypotensive; OPAP=Ocular Pressure Adjusting Pump.
Note: Safety and IOP without NP application were assessed at post-randomization Visits 4 (Week 6), 5 (Week 12), and 7 (Week 38). Safety and IOP before and during NP application were assessed at post-randomization Visits 3 (Day 0), 6 (Week 26), and 52 (Week 52).

5.1.1.2 Target Negative Pressure Dose and Schedule of Measurements

Parameters used for OPAP programming for in-clinic IOP measurement during NP application and subsequent home use are summarized in Table 6. As discussed in Section 3.2.3, the

expected IOP-lowering response during use of the OPAP was approximately 40% – 60% of the applied NP.

After a 14-day run-in period of OPAP use, eligible patients were randomized to their treatment assignment at Visit 3 (Day 0). At this visit, NP was programmed for the study eye by determining the difference between the baseline IOP measured in-clinic that day and a reference IOP of 6 mmHg (i.e., Programmed NP = Measured IOP – 6 mmHg); the NP for the control eye was programmed to receive no NP.

At the initial sleep lab that followed Visit 3, another baseline IOP measurement was taken with the patient wearing the Excursion Goggles and in supine position. At the completion of this sleep lab, if baseline supine IOP was different from the Visit 3 in-clinic baseline IOP, the pump was reprogrammed for patient use at home (i.e., Programmed NP = Measured Nocturnal Supine IOP – 6 mmHg).

While programming was generally intended to remain constant over the course of the study, investigators were given discretion to adjust the study eye NP setting for each subsequent home use period based on data from device home use and patient comfort. For safety purposes, however, the program could not target a reference IOP below 6 mmHg.

Table 6: Pump Programming Parameters for In-Clinic IOP Measurement During Negative Pressure Application and Home Use

<table>
<tr><th rowspan="2">Study Visit</th><th colspan="3">Pump Programming</th><th rowspan="2">Study Eye</th><th rowspan="2">Control Eye</th></tr>
<tr><th>In-Clinic IOP Measurement during NP Application</th><th colspan="2">Subsequent Home Use</th></tr>
<tr><td>Visit 1
(Day -14)</td><td>Reference IOP
of 6 mmHg</td><td colspan="2">-5 mmHg</td><td>X</td><td>X</td></tr>
<tr><td rowspan="9">Visit 2
(Day -7)</td><td rowspan="9">N/A</td><td>IOP from Visit 1</td><td>Pump Program</td><td rowspan="9">X</td><td rowspan="9">X</td></tr>
<tr><td>≤ 11 mmHg</td><td>-5 mmHg</td></tr>
<tr><td>12 mmHg</td><td>-6 mmHg</td></tr>
<tr><td>13-14 mmHg</td><td>-7 mmHg</td></tr>
<tr><td>15-16 mmHg</td><td>-8 mmHg</td></tr>
<tr><td>17-18 mmHg</td><td>-9 mmHg</td></tr>
<tr><td>19-20 mmHg</td><td>-10 mmHg</td></tr>
<tr><td>21-22 mmHg</td><td>-11 mmHg</td></tr>
<tr><td>> 22 mmHg</td><td>-12 mmHg</td></tr>
<tr><td>Visit 3
(Day 0)</td><td>Reference IOP of 6 mmHg
(seated)</td><td colspan="2">Reference IOP of 6 mmHg (seated)
or adjusted investigator prescription</td><td>X</td><td>-</td></tr>
<tr><td>Sleep Lab
(≤ Day 21)</td><td>Reference IOP of 6 mmHg
(supine) if different from Visit 3</td><td colspan="2">Reference IOP of 6 mmHg (supine)
if different from Visit 3</td><td>X</td><td>-</td></tr>
<tr><td>Visits 4 – 8
(Weeks
6 – 52)</td><td>N/A</td><td colspan="2">N/A or adjusted investigator
prescription*</td><td>X</td><td>-</td></tr>
</table>

	Pump Programming			
Study Visit	In-Clinic IOP Measurement during NP Application	Subsequent Home Use	Study Eye	Control Eye

IOP=intraocular pressure; NP=negative pressure.
* A reference IOP of 6 mmHg (measured via pneumatonometry) was used for NP programming. Pumps could not be set to reference IOP < 6 mmHg.

5.1.1.3 Prior and Concomitant Therapies

Patients using ocular hypotensive medications were required to undergo a minimum 30-day washout period, then return to clinic for unmedicated IOP measurement to determine whether they met the study IOP eligibility requirement (IOP ≥ 12 mmHg and ≤ 21 mmHg). Ocular hypotensive medication use was resumed after this assessment for all but a single subject.

There were no restrictions on medication use during the study.

5.1.1.4 Treatment Compliance

To ensure accurate assessment of device performance and valid interpretation of study results, treatment compliance was monitored using a proprietary OPAP system application. At each in clinic- visit, the OPAP was connected to the dedicated in-clinic computer, and product usage for each day during the home-use period was downloaded.

(Results of compliance at each visit are presented in Table 11 of Section 5.1.2.3.)

5.1.1.5 Key Inclusion/Exclusion Criteria

Patients were required to meet the following eligibility criteria to participate in Artemis:

- Male or female ≥ 40 years of age at the time of signing the informed consent
- Diagnosis of NTG confirmed by glaucomatous optic nerve head or retinal nerve fiber layer structural abnormalities and/or VF abnormalities (from threshold VFs performed within 60 days prior to Visit 1) and:
    - no documented unmedicated IOP > 21 mmHg in either eye, or
    - in the absence of documented unmedicated IOPs, an unmedicated IOP ≤ 21 mmHg in both eyes following ocular hypotensive medication washout
- Baseline IOP ≥ 12 mmHg and ≤ 21 mmHg (measured using GAT) in both eyes
- Demonstrate the ability to successfully average ≥ 3 hours of sleep wearing OPAP for at least 3 consecutive nights during the run-in period (between Visits 2 and 3)

Patients were ineligible to participate in Artemis if they met any of the following exclusion criteria:

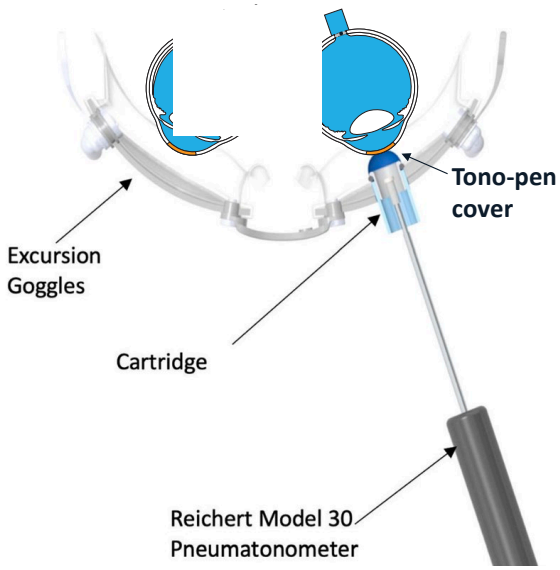
- History of any ocular disorder or condition (e.g., corneal transplant) in either eye that would likely interfere with the interpretation of the study results or compromise patient safety

- Prior or active retinal tear/detachment, unresolved cystoid macular edema, wet macular degeneration, diabetic macular edema, proliferative diabetic retinopathy, or any other fundus findings that may prevent visualization of the retina in either eye
- History of prior penetrating filtering (i.e., trabeculectomy) or tube/shunt glaucoma surgery in either eye [this did not include patients with minimally invasive glaucoma surgery (MIGS) procedures or implants]
- Narrow anterior chamber angle anatomy in either eye as visualized by gonioscopy with a Shaffer angle grade of ≤ 2 in any of the four quadrants
- Eyelid edema, festoons, or excessive skin laxity in either eye
- Uveitis or conjunctival chemosis in either eye
- Best corrected distance visual acuity of 20/200 or worse in either eye

5.1.1.6 Description and Validation of Pressure Measurement Techniques

Reichert Model 30™ pneumatonometers (not to be confused with “air puff” pneumotonometry) were utilized for effectiveness measurements of IOP because the instrument’s dynamic methodology allowed for consistent measurement with the patient away from the slit lamp and in both seated (in-clinic) and supine (sleep lab) positions. As the OPAP goggles needed to be in place to provide the designated NP, the goggle design was modified to provide an access port fitted with a silicone tube with latex Tonopen® cover (“Excursion Cartridge”) for each of the goggle lenses. These modified goggles are called “Excursion Goggles” and the IOP measurement method using the Excursion Goggles is referred to as “Excursion Tonometry” (Figure 17).

Figure 17: Excursion Pneumatonometry IOP Measurement Method through Excursion Goggles (Excursion Tonometry)



Note: Reichert Model 30™ pneumatonometers were utilized for effectiveness measurements of IOP because the instrument's dynamic methodology allowed for consistent measurement with the patient away from the slit lamp and in both seated (in-clinic) and supine (sleep lab) positions.

The Excursion Goggles allowed for the pneumatanometer probe to measure IOP as the TCPD relative to atmospheric pressure (Figure 18). This method was validated by extensive bench and clinical testing (Ferguson et al. 2020; Brambilla et al. 2022)[2] and considered by FDA to be an acceptable method for measuring IOP during NP application with OPAP.

Figure 18: Assessment of Transcorneal Pressure Difference (TCPD) Using Excursion Tonometry

IOP=intraocular pressure; TCPD=transcorneal pressure difference.

[2] Publications have been referenced in multiple submission documents but have not been submitted to FDA as individual files.

At in-clinic visits, IOP was measured with patients in the seated position and wearing Excursion Goggles prior to NP application. Then NP was initiated, and IOP was again measured by Excursion Tonometry while NP was applied.

At each sleep lab visit, lights remained darkened (< 10 lux) between 10:00 p.m. and 6:00 a.m. At the start of the session, baseline IOP was measured with Excursion Tonometry prior to NP application with the patient in the supine position. Then patients positioned their OPAP goggles and received uninterrupted NP application while laying down. At approximately 11:00 p.m. (after a minimum of 30 minutes of NP application), 2:00 a.m., and 5:00 a.m., NP application was briefly interrupted for placement of Excursion Goggles with the same NP programming, and IOP was measured using Excursion Tonometry both before and during NP application. After completing each measurement sequence, the OPAP goggles were replaced, and NP resumed.

(IOP measurement sequences at each protocol-specified visit are shown in Appendix 9.1.1.)

5.1.1.7 Statistical Considerations

5.1.1.7.1 Endpoint Definitions

Primary Effectiveness Endpoint

The primary effectiveness endpoint was the proportion of study eyes with Week 52 in-clinic IOP reduction ≥ 20% during NP application in comparison with Baseline IOP (measured prior to NP application). Results are presented in Section 5.1.2.4.1.

Secondary Effectiveness Endpoint

The secondary effectiveness endpoint was the proportion of study eyes with Week 52 sleep lab mean IOP reduction ≥ 20% during application of NP as compared with Baseline IOP (measured supine prior to NP application). Results are presented in Section 5.1.2.5.

Exploratory Effectiveness Outcomes

Additional exploratory endpoints were assessed:

- In-clinic IOP measured by Excursion Method, both before and during NP application (Section 5.1.2.8.1)
- Sleep lab IOP measured by Excursion Method, in the supine position, both before and during NP application (Section 5.1.2.8.2)

5.1.1.7.2 Determination of Sample Size

The sample size calculation was hierarchical and based on the primary effectiveness endpoint and adjusted for the secondary effectiveness endpoint. (See Section 5.1.1.7.1 for endpoint definitions.)

Primary Effectiveness Endpoint Sample Size Determination

The corresponding statistical hypotheses for the primary endpoint were as follows:

Null Hypothesis: $\pi T_1 - \pi F_1 \leq 0$

Alternate Hypothesis: $\pi T_1 - \pi F_1 > 0$

The πT_1 and πF_1 were the proportion of eyes at the Week 52 in-clinic visit with IOP reduction ≥ 20% compared to baseline for the treated and control eyes, respectively.

It was assumed that 75% of treated eyes would reach the primary effectiveness endpoint, while no more than 25% of the control eyes would achieve the endpoint. Based on McNemar's exact conditional test for paired nominal data with a correlation of ≤ 0.3, a sample size of 50 subjects at 90 days post-treatment provides a statistical power of > 95% to demonstrate superiority of treated eyes over control eyes with a ≥ 20% IOP reduction.

Secondary Effectiveness Endpoint Sample Size Determination

If study results showed that πT_1 was statistically superior to πF_1 for the primary endpoint, then the statistical test for the secondary effectiveness endpoint was performed. To preserve the type I- error rate on the hierarchical approach, the significance level of 0.05 was used for the secondary effectiveness endpoint. The corresponding statistical hypotheses for the secondary endpoint were the same as those for the primary effectiveness endpoints:

Null Hypothesis: $\pi T_2 - \pi F_2 \leq 0$

Alternate Hypothesis: $\pi T_2 - \pi F_2 > 0$

The πT_2 and πF_2 were the proportion of eyes at the Week 52 sleep lab mean IOP reduction ≥ 20% compared to baseline measured for the treated and control eyes, respectively.

It was expected that more patients might miss sleep lab tests than standard in-clinic examinations. As such, a dropout rate of 30% was included in the power calculations for the 12-month- sleep lab test. With this assumed dropout rate and 50 patients needed at the 12-month sleep lab test, a sample size of 72 randomized patients was required. Therefore, the study sample size of at least 72 randomized patients was considered sufficient.

5.1.1.7.3 Statistical Analysis Methodologies

Prespecified analyses of study endpoints were performed according to the following assessments:

Primary Analyses of Primary and Secondary Effectiveness Endpoints

For each set of IOP measurements, the IOP value for the eye was calculated as the average of two measurements for that eye or, if the two measurements differed by more than 2 mmHg, a third measurement was taken and the median of three measurements of the eye was used.

For the sleep lab IOP measurements of each eye, the averages from measurements taken at 11:00 pm, 2:00 am, and 5:00 am were calculated separately for the measurements taken before and during NP application. These average IOPs were treated as the sleep lab mean nocturnal IOP values for the respective eyes at the corresponding visits and used in the statistical analyses.

All IOP values were summarized by descriptive statistics for continuous variables and the 95% confidence interval of the mean for treated and control eyes separately for in-clinic tests and for sleep lab tests. The percent change in IOP (measured with goggles) from "before" NP to "during" NP at Week 52 were specified for each eye as follows:

% Change = (During NP – Before NP) ÷ Before NP × 100.

The percent change was calculated for both the in-clinic and the sleep lab (average of measurements taken at 11:00 p.m., 2:00 a.m., and 5:00 a.m.) IOPs. The percent change was summarized by descriptive statistics for continuous variables and the 95% confidence interval of the mean by eye groups for in-clinic and sleep lab measurements, separately. The number and percent of treated eyes and control eyes achieving IOP change ≤ -20% (i.e., reduction ≥ 20%) were to be summarized in 2×2 tables for the in-clinic and sleep lab IOP outcomes, separately. The 95% confidence interval of the probability of eyes with IOP reduction ≥ 20% (i.e., the marginal probability) was calculated separately by the binomial distribution for treated eyes and control eyes. The 95% adjusted Wald confidence interval of the difference between the two marginal probabilities was derived.

The McNemar test was performed to compare the percent of eyes between the treatment and control groups with IOP reduction ≥ 20% for the in-clinic and sleep lab IOP outcomes separately. The McNemar test performed for the secondary effectiveness sleep lab IOPs was to be concluded for the OPAP effect only if the McNemar test performed for the primary effectiveness in-clinic outcomes was statistically significant.

The primary analyses presented in this report are based on all mITT patients, where those with no IOP measurement available are included in the analysis conservatively as failures, not having a reduction of ≥ 20%. Multiple sensitivity analyses for missing data were performed, and conclusions were consistent with the primary analysis for all cases.

Secondary Analyses of Primary and Secondary Effectiveness Endpoints

The percent change in IOP (measured with goggles on) from “before” NP to “during” NP in the clinic and in the sleep lab (average of measurements taken at 11:00 pm, 2:00 am, and 5:00 am) was calculated for each mITT eye at Visit 3 (Day 0), Visit 6 (Week 26 for in clinic- IOP), and Visit 8 (Week 52). A generalized estimating equation (GEE) model with a logit link function and an unstructured working correlation matrix was used to assess the effect of the OPAP on IOP reduction ≥ 20% at Visits 3, 6, and 8 for in-clinic measurements and the initial and Week 52 Sleep Lab measurements, separately.

The predictors (i.e., covariates) of the GEE model included Eye Group (treated vs control), Visit (Day 0, Week 26 [for in-clinic IOP only], and Week 52), the interaction between Treatment and Visit. The difference between study and control eyes at different visits was compared based on the GEE model. Other working correlation matrices were to be considered if the use of an unstructured working correlation matrix encountered statistical calculation difficulty.

Sensitivity Analyses

A tipping point analysis on the mITT Population was performed for the primary effectiveness endpoint, where all possible combinations of missing values for responder/non-responder status were examined for eyes with missing Week 52 data based on the mITT Population.

Covariate Analyses

To investigate potential heterogeneity of the primary effectiveness results, covariate (subgroup) analyses were performed based on the following:

- Per patient
    - Gender (male vs female)

  - Age (grouped by observed median)
  - Race
- Per eye
  - Number of ocular hypotensive medications used in the study eye at Baseline Visit (Day -14) (0 medications, ≥ 1 medications)
  - Goldmann Applanation IOP in the study eye at Baseline (≤ 14.0 mmHg, > 14.0 mmHg)
  - Cup-to-disc ratio in the study eye at Baseline (< 0.8, ≥ 0.8)
  - Previous glaucoma or cataract surgery status (none, any)
  - Previous surgery status if not using medication (none, any)

A GEE model on IOP reduction ≥ 20% through the OPAP at Week 52 was used to assess each of the covariate effects on the 2 effectiveness endpoints separately. Each GEE model included the treatment, one of the covariates, and the interaction between the treatment and the corresponding covariate as the predictors. A p-value of < 0.15 for the treatment effect or the interaction effect indicated a possible significant covariate effect. The analyses presented are based on the mITT analysis set.

Exploratory Endpoints

IOP measurements at each visit were summarized descriptively with the 95% Cis of means using mITT patients with available data. The summaries were prepared for study and control eyes, separately. The difference between two eyes (study – control) were also summarized descriptively. No imputation for missing values was performed.

- Pneumatonometry IOP at each measurement condition (in-clinic or sleep lab) was summarized using descriptive statistics for continuous variables. The number and percent of eyes with IOP ≥ 6 mmHg to ≤ 21 mmHg, ≥ 6 mmHg to ≤ 18 mmHg, ≥ 6 mmHg to ≤ 15 mmHg, and ≥ 6 mmHg to ≤ 12 mmHg was calculated.
- Percent change in baseline IOP to IOP after NP application was summarized by the number and percent of eyes in the following outcome groups for the study and control eyes, separately:
  - Increases in the following ranges: ≥ 40%; ≥ 30% to < 40%; ≥ 20% to < 30%; ≥ 10% to < 20%; > 0% to < 10%
  - No Change
  - Decreases in the following ranges: > 0% to < 10%; ≥ 10% to < 20%; ≥ 20% to < 30%; ≥ 30% to < 40%; ≥ 40%

5.1.1.7.4 Definitions of Analysis Populations

Enrolled patients were included in the following analysis populations:

Intent-to-Treat (ITT) Population included all randomized patients. Eyes were grouped based on randomization assignment (study eye vs control eye).

Modified Intent-to-Treat (mITT) Population consisted of all randomized patients who had at least one full application of NP to the study eye after randomization. Eyes were grouped based on randomization assignment (study eye vs control eye).

> *Note: The original protocol specified that the primary analyses of the primary and secondary effectiveness endpoints be performed on the PP Population. The mITT Population was specified only for sensitivity analyses with imputation of missing values to evaluate robustness of study outcomes. However, for the purpose of performing a more robust analysis and to reduce the possibility of bias, the primary analyses for the primary and secondary endpoints were performed using the mITT Population.*

Per-Protocol (PP) Population included all patients in the mITT Population who had no major protocol deviations and completed the Week 52 visits (both in-clinic and sleep lab).

Safety Population consisted of all patients who received at least one application of NP post-randomization.

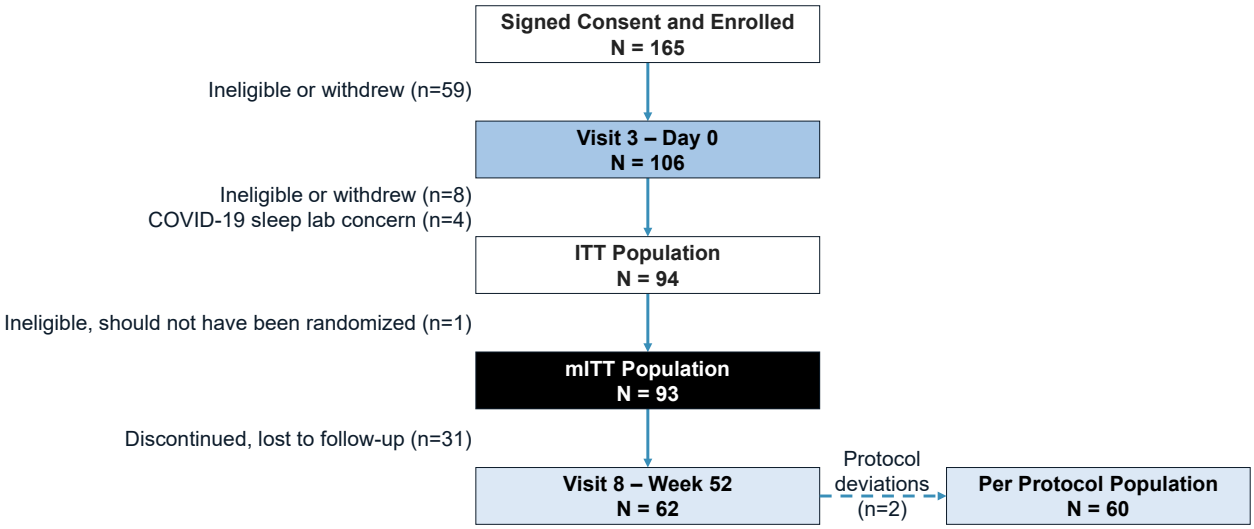
5.1.2 Artemis Results

5.1.2.1 Patient Disposition

A total of 165 patients signed the informed consent form and were enrolled at 11 US based- sites. Sixty-seven (67) of these patients failed to meet one or more study eligibility criteria, and 4 were discontinued before randomization due to COVID-19 related uncertainty about sleep lab availability for follow-up. Therefore, 94 patients were randomized and included in the ITT Population (Figure 19). One participant who was randomized was determined to be ineligible due to a previous IOP measurement greater than 21 mmHg shortly after randomization but before leaving clinic; thus, this subject did not initiate OPAP use after randomization. Therefore, the mITT Population for primary analysis includes 93 eligible participants.

The reasons for discontinuation prior to randomization (Table 7).

Figure 19: Patient Disposition (All Enrolled Patients)



ITT=Intent-to-Treat; mITT=modified Intent-to-Treat.
Note: Two patients had major protocol deviations, resulting in a Per-Protocol Population of N=60.

The primary reasons for exit from study prior to randomization were unwillingness to comply with study procedures, including at-home use of OPAP (25/165 [15.2%]), and not meeting screening IOP parameters of 12 – 21 mmHg (inclusive) in both eyes at Visit 1 (or 1a), as measured by Goldmann applanation tonometry (GAT; 20/165 [12.1%]; Table 7).

Table 7: Patient Disposition and Reasons for Study Exit Prior to Randomization (All Enrolled Patients)

Disposition, n (%):	All Enrolled Patients (N=165)
Patients who exited before randomization	71 (43.0)
Failed to meet study eligibility requirements due to 1 or more of following criteria*	67 (40.6)
Did not have diagnosis of NTG, as confirmed by glaucomatous optic nerve head or retinal nerve fiber layer structural abnormalities and/or VF abnormalities, and with no documented unmedicated IOP > 21 mmHg in either eye OR Did not have unmedicated IOP ≤ 21 mmHg in both eyes following ocular hypotensive medication washout	34 (20.6)
Did not wish to or could not comply with procedures, including home use of device or study duration	33 (20.0)
Did not meet study criteria related to periorbital anatomy, anterior chamber angles or fundus examination or had another ocular disorder likely to interfere with interpretation of results or compromise patient safety	12 (7.4)
Did not average ≥ 3 hours of sleep wear for ≥ 3 consecutive nights of run-in period	7 (4.2)
Was not likely to complete study before needing any ocular surgery (e.g., cataract extraction or glaucoma procedure, including SLT)	3 (1.8)
Was not age ≥ 40 years at the time of signing informed consent	1 (0.6)

Disposition, n (%):	All Enrolled Patients (N=165)
Was not literate, did not speak English or Spanish, or was unable to understand and follow study instructions	1 (0.6)
Withdrew due to clinic COVID-19 policy	4 (2.4)
Patients randomized (ITT Population)	94 (57.0)†
Determined to be ineligible prior to first NP application	1 (0.6)†
Patients included in primary analysis (mITT Population)	93 (56.4)

GAT=Goldmann applanation tonometry; IOP=intraocular pressure; ITT=Intent-to-Treat; mITT=modified Intent-to-Treat; NP=negative pressure; NTG=normal-tension glaucoma; SLT=selective laser trabeculoplasty.
* Patients could fail to qualify for the study based on more than one criterion.
† One patient who was randomized was subsequently determined to be ineligible because of a historical IOP > 21 mmHg; this patient was discontinued and did not receive any NP applications; therefore, the mITT Population included 93 patients for primary analysis.
Data included in this table is a summary of that presented in Table 5 in the CP-X19 CSR prepared for Expert Panel review. FDA has not reviewed this data summary.

Within the mITT Population (N=93), 31 (33.3%) were lost to follow-up and were discontinued. Therefore, 62 patients completed the study. Two of these 62 patients had major protocol deviations that would affect primary or secondary effectiveness analyses. Thus, the remaining 60 patients comprise the Per Protocol Population.

Table 8: Patient Accountability (mITT Population)

Disposition, n (%):	Visit 3 (Day 0)	Initial Sleep Lab (≤ Day 21)	Visit 4 (Wk 6)	Visit 5 (Wk 12)	Visit 6 (Wk 26)	Visit 7 (Wk 38)	Week 52 Sleep Lab	Visit 8 (Wk 52)
Available for analysis[1]	93 (100)	80 (86.0)	81 (87.1)	74 (79.6)	68 (73.1)	65 (69.9)	62 (66.7)	62 (66.7)
Missing	0	13 (14.0)	12 (12.9)	19 (20.4)	25 (26.9)	28 (30.1)	31 (33.3)	31 (33.3)
Discontinued[2]	0	6 (6.5)	12 (12.9)	19 (20.4)	25 (26.9)	28 (30.1)	31 (33.3)	31 (33.3)
Missed visit[3]	0	7 (7.5)	0	0	0	0	0	0
% Accountability[4]	93 (100)	80 (100)	81 (100)	74 (100)	68 (100)	65 (100)	62 (100)	62 (100)

GAT=Goldmann applanation tonometry; IOP-intraocular pressure; mITT=modified Intent-to-Treat; NP=negative pressure; Wk=week.
1. The mITT Population consists of all randomized patients who had at least one full application (minimum of 20 minutes in home use setting) of NP to the study eye between Visit 3 and Visit 8. All but 1 of the 94 patients randomized received at least one full NP application; therefore, the mITT Population consisted of 93 patients (1 patient, after randomization on Day 0, had GAT IOP measurement > 21 mmHg and was discontinued prior to NP application).
2. Includes withdrawal of consent, investigator decision, and reasons other than death.
3. Missed Visit = not examined at the scheduled visit, but may be seen at a subsequent visit.
4. % Accountability = [available for analysis / (enrolled – discontinued)] x 100.

5.1.2.2 Patient Demographics and Baseline Medical Characteristics

Mean (SD) age at consent was 62.4 (±10.7) years, and approximately two-thirds were female. The majority (68.8%) were white and not Hispanic or Latino (80.6%; Table 9).

Table 9: Baseline Demographics (mITT Population)

Demographic, n (%):	Patients (N=93)
Age at consent, years	
Mean (SD)	62.4 (10.7)
Median (min, max)	61 (40, 85)
Gender, n (%)	
Male	30 (32.3)
Female	63 (67.7)
Race, n (%)	
White	64 (68.8)
Black/African American	13 (14.0)
Asian	15 (16.1)
Mestizo	1 (1.1)
Ethnicity, n (%)	
Hispanic or Latino	18 (19.4)
Not Hispanic and not Latino	75 (80.6)
Study eye, n (%)	
OD / right eye	46 (49.5)
OS / left eye	47 (50.5)

mITT=modified Intent-to-Treat; OD=oculus dexter/right eye; OS=oculus sinister/left eye; SD=standard deviation.

Baseline medical characteristics of treatment and control eyes were well-matched (Table 10). A similar majority of study eyes and control eyes were on a regimen of ≥ 1 topical ocular hypotensive medication at baseline; no patient was using oral ocular hypotensive medication.

Table 10: Baseline Medical Characteristics (mITT Population)

Baseline Characteristic:	Study Eye (N=93)	Control Eye (N=93)
BCDVA at Baseline (LogMAR)		
Mean (SD) [Snellen]	0.09 (0.13) [20.0 / 26.0]	0.10 (0.14) [20.0 / 26.8]
Median (min, max) [Snellen]	0.10 (-0.1, 0.7) [20.0 / 25.0]	0.10 (-0.2, 0.9) [20.0 / 25.0]
Manifest refraction spherical equivalent		
Mean (SD)	-1.0 (2.5)	-1.4 (2.7)

Baseline Characteristic:	Study Eye (N=93)	Control Eye (N=93)
Median (min, max)	-0.3 (-8.8, 4.8)	-0.5 (-9.8, 3.8)
Baseline IOP (by GAT), mmHg (N=91 for Study and Control Eyes)		
Mean (SD)	14.7 (2.0)	14.8 (2.2)
Median (min, max)	14 (12, 20)	14 (12, 21)
Central corneal thickness, µm		
Mean (SD)	536.2 (38.4)	538.1 (37.7)
Median (min, max)	543 (413, 640)	542 (440, 620)
Gonioscopy Shaffer		
Grade III or IV, n (%)*	93 (100)	93 (100)
Vertical cup-to-disc ratio		
Mean (SD)	0.67 (0.15)	0.66 (0.16)
Median (min, max)	0.7 (0.3, 1.0)	0.7 (0.1, 1.0)
Visual field mean deviation (MD) (dB)		
Mean (SD)	-4.03 (4.89)	-3.67 (4.68)
Median (min, max)	-2.61 (-22.59, 2.38)	-1.94 (-20.37, 2.82)
Topical ocular hypotensive medications, n (%)		
0	41 (44.1)	43 (46.2)
1 or 2	45 (48.4)	45 (48.4)
3 or more	7 (7.5)	5 (5.4)
Previous surgical procedure, n (%)†		
Minimally invasive glaucoma surgery (MIGS)	5 (5.4)	5 (5.4)
Glaucoma laser procedure	14 (15.1)	18 (19.4)
Cataract surgery	19 (20.4)	18 (19.4)

GAT=Goldmann applanation tonometry; IN=inferior nasal; IOP=intraocular pressure; IT=inferior temporal; MD=mean deviation; mITT=modified Intent-to-Treat; SD=standard deviation; SN=superior nasal.
* No eyes had Shaffer grade I or II in any quadrant.
† Analysis originally submitted to FDA as Table 13 of CP-X19 CSR. The baseline characteristic, “Previous Surgical Procedure” was added to the original analysis and has not been previously reviewed by FDA.

5.1.2.3 Device Programming and Procedure Metrics

After randomization, OPAP wear time during home-use between visits for the mITT Population was captured from download of the OPAP use data and is summarized in Table 11. The mean number of days on which the OPAP was used between visits gradually decreased over the course of the study; however, patients used the OPAP on 78% or more of the days between each in-office examination, which translates to an average of more than 5 days/week.

For the 93 subjects who were randomized and initiated treatment, the NP setting for home use was adjusted for the study eye of 59 subjects because their initial sleep lab IOP measured supine was higher than the in-clinic measurement for the study eye of 59 subjects. Thereafter, additional adjustments in NP setting were made for the study eye of 45 subjects.

Table 11: OPAP Usage and Compliance (mITT Population)

OPAP Usage Metric (Days):	Day 0 to Week 6 (N=81)	Weeks 6 to Week 12 (N=74)	Week 12 to Week 26 (N=68)	Week 26 to Week 38 (N=65)	Week 38 to Week 52 (N=62)
Visit Interval	**42**	**42**	**98**	**84**	**98**
Days of OPAP use during the visit interval*					
Average days between visits	37.7	43.8	87.1	85.0	101.6
Mean (SD) days of OPAP use	33.0 (8.9)	37.5 (11.4)	71.6 (19.8)	66.4 (23.1)	79.8 (23.2)
% days of OPAP use†	87.3%	85.7%	82.2%	78.2%	78.5%
Median (min, max)	31.0 (14.0, 56.0)	38.5 (8.0, 63.0)	72.0 (5.0, 112.0)	68.0 (2.0, 132.0)	79.0 (20.0, 126.0)
Average daily wear (hours) of OPAP use during the visit interval#					
Mean (SD)	5.5 (1.2)	5.4 (1.4)	5.5 (1.6)	5.5 (1.4)	5.6 (1.3)
Median (min, max)	5.8 (2.7, 7.7)	5.8 (2.0, 7.8)	5.9 (1.0, 8.9)	5.9 (2.1, 9.0)	5.9 (2.0, 8.3)

OPAP=Ocular Pressure Adjusting Pump; SD=standard deviation.
* Days where treatment was dispensed for more than 20min.
† Percentage = (Mean days of use ÷ Average days between visits) × 100.
# Sum of the usage of ONLY the days above 20min (any usage less than 20min is considered zero, and its corresponding day is not considered a usage day), divided by “Days of MPD use during the visit interval”, divided by 3600 seconds, then converted into hours.

5.1.2.4 Primary Endpoint Results

5.1.2.4.1 Primary Analysis of Primary Endpoint — Effectiveness in mITT Population

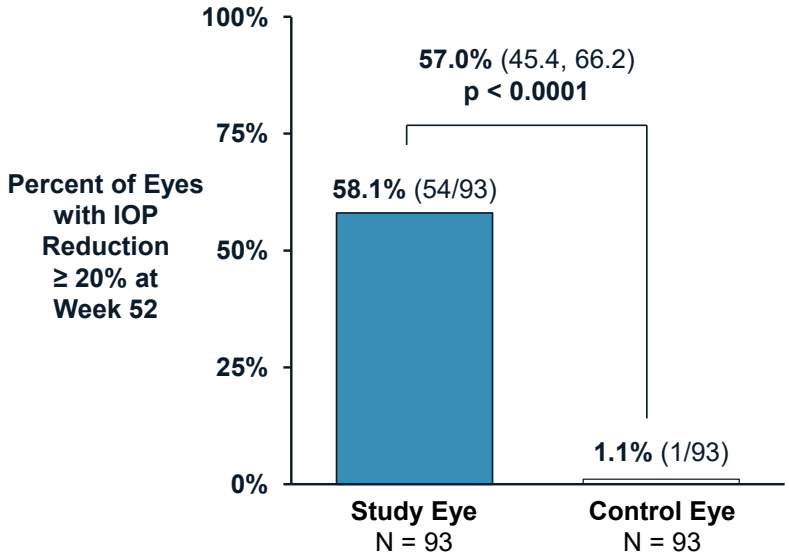
OPAP achieved its primary effectiveness endpoint. In the mITT Population, 58.1% of study eyes had ≥ 20% reduction in IOP during NP application, as compared to 1.1% of control eyes ($p < 0.0001$; Table 12; Figure 20).

Table 12: Primary Effectiveness Endpoint Results, IOP Reduction ≥ 20% during Negative Pressure Application (In Clinic-, mITT Population)

Effectiveness Endpoint, n (%):	Study Eye (N=93)	Control Eye (N=93)	Difference (95% CI)[1]	p-value[2]
IOP reduction ≥ 20% during NP application in mITT Population	54 (58.1)	1 (1.1)	57.0% (45.4%, 66.2%)	< 0.0001

CI=confidence interval; IOP=intraocular pressure; mITT=modified Intent-to-Treat.
Note: Missing data/dropouts imputed as failure; IOP assessed during NP application.
1. (Bonett and Price 2012).
2. McNemar test with two-sided significance level of 0.05.

Figure 20: Primary Effectiveness Endpoint Results, IOP Reduction ≥ 20% during Negative Pressure Application (In Clinic-, mITT Population)



IOP=intraocular pressure; mITT=modified Intent-to-Treat.
Note: Missing data/dropouts imputed as failure; IOP assessed during NP application.

5.1.2.4.2 Sensitivity Analysis of Primary Endpoint — Effectiveness in Per Protocol Population

A sensitivity analysis of the primary effectiveness endpoint was performed on the Per-Protocol Population (N=60 study and control eyes). The responder rate of eyes with in clinic- IOP reduction ≥ 20% during application of NP (relative to preceding NP application) at Week 52 in the PP Population was consistent with the primary analysis (p < 0.0001; Table 13; Figure 21).

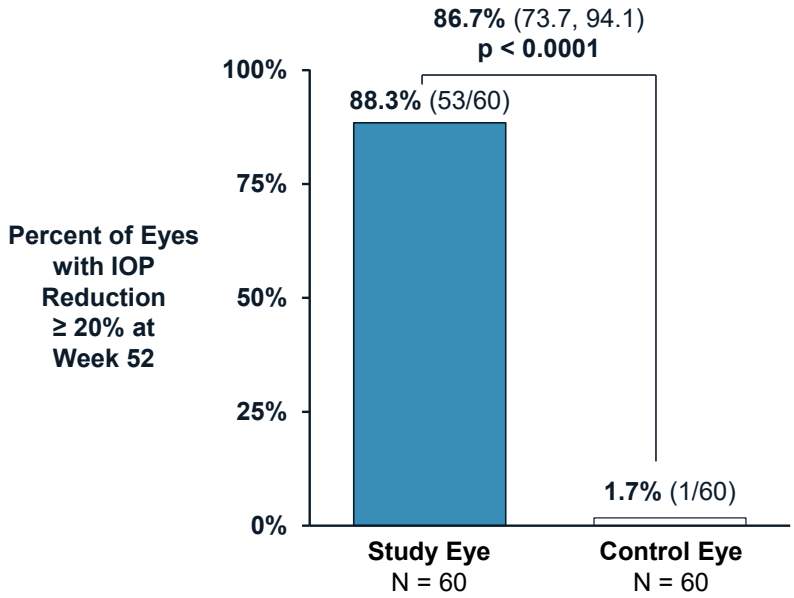
Table 13: Sensitivity Analysis of Primary Endpoint, IOP Reduction ≥ 20% during Negative Pressure Application (In-Clinic, PP Population)

Sensitivity Analysis, n (%):	Study Eye (N=60)	Control Eye (N=60)	Difference (95% CI)[1]	p-value[2]
IOP reduction ≥ 20% during NP application in PP Population	53 (88.3)	1 (1.7)	86.7% (73.7%, 94.1%)	< 0.0001

Sensitivity Analysis, n (%):	Study Eye (N=60)	Control Eye (N=60)	Difference (95% CI)[1]	p-value[2]

CI=confidence interval; IOP=intraocular pressure; PP=Per-Protocol.
1. (Bonett and Price 2012).
2. McNemar Test with a two-sided significance level of 0.05.

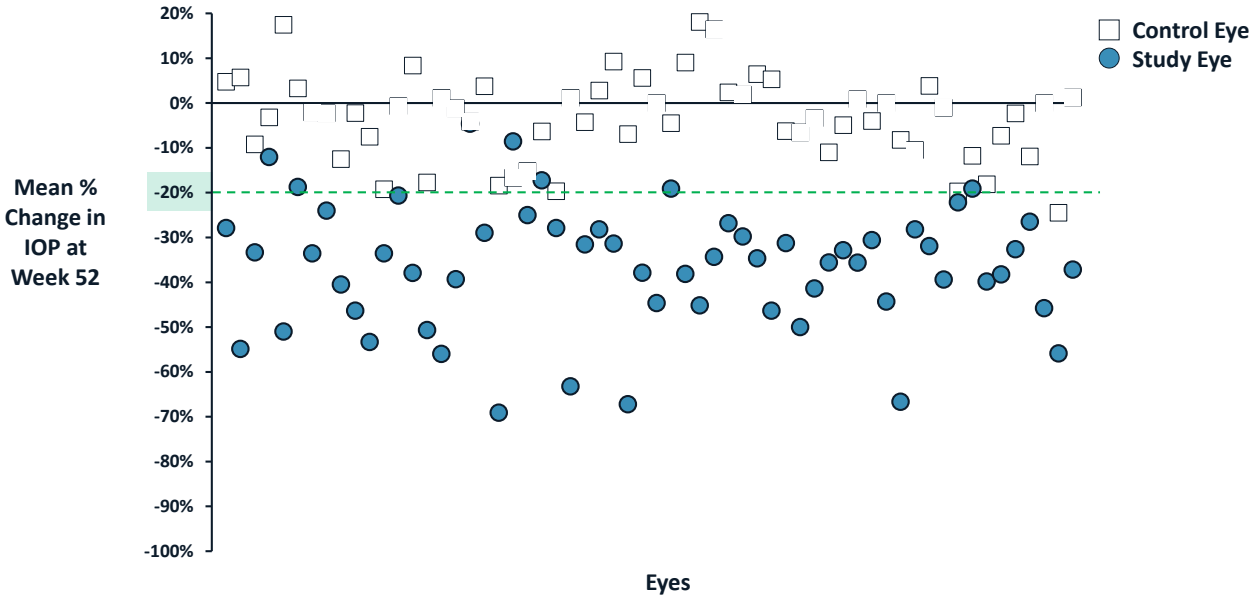
Figure 21: Sensitivity Analysis of Primary Endpoint, IOP Reduction ≥ 20% during Negative Pressure Application (In-Clinic, PP Population)



IOP=intraocular pressure; PP=Per-Protocol.
Note: IOP assessed during NP application.

Importantly, all patients in the Per-Protocol Population had an IOP reduction in the study eye during NP application at Week 52 (Figure 22).

Figure 22: Mean IOP Reduction (%), by Individual Patients at Week 52 (In Clinic-, PP Population)



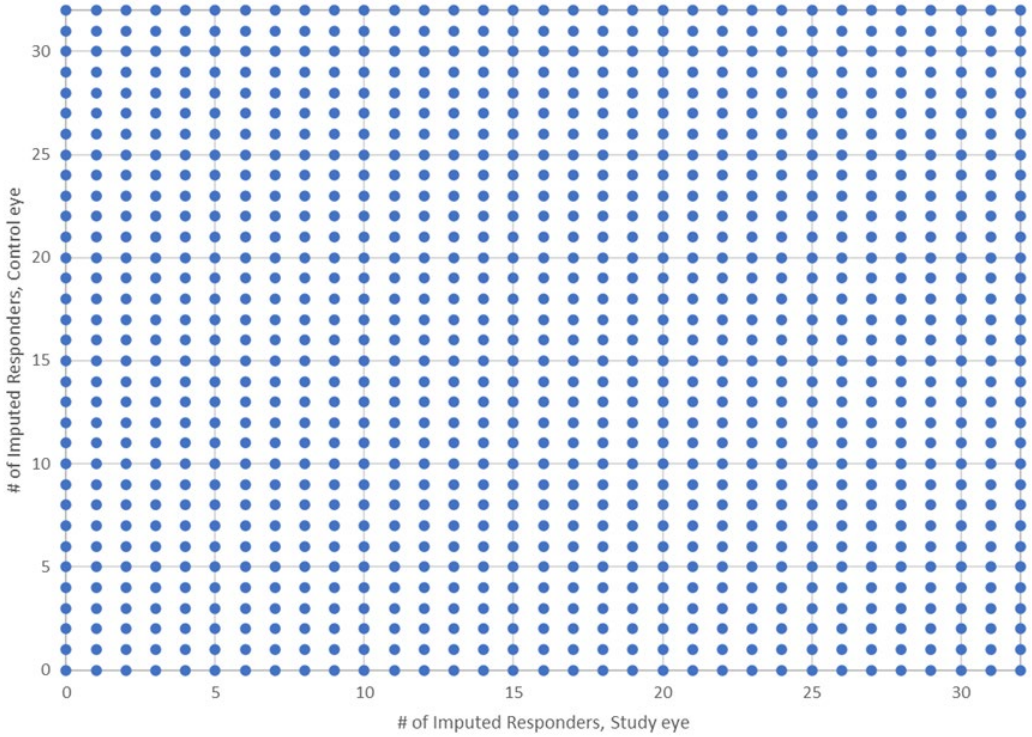
IOP=intraocular pressure; NP=negative pressure; PP=Per-Protocol.
Note: Dotted green line represents the boundary for the primary endpoint of IOP reduction ≥ 20% from baseline at Week 52, as measured in-clinic — i.e., eyes below the dotted line achieved the primary endpoint. This figure presents data originally submitted to FDA as Figure 11 of CP-X19 CSR. This chart has not been previously reviewed by FDA.

5.1.2.4.3 Sensitivity Analysis of Primary Endpoint — Tipping-Point Analysis

A tipping-point analysis was performed to evaluate the robustness of the primary endpoint. The tipping-point analysis imputed all missing study eyes as failures and all missing control eyes as success and still confirmed statistical significance in the primary endpoint. (Figure 23, cases of success on the p-value for the statistical test are shown with blue dots; the lack of red dots represents no scenarios in which a non-significant result could occur).

The McNemar test p-value was reported for each of the 1,089 possible outcome scenarios involving the 31 patients who did not complete the study and the one patient for whom control eye IOP measurement data was not available. The original conclusions were consistent for all cases, including the worst-case scenario where all missing control eyes were imputed as responders and all missing study eyes were imputed as non-responders.

Figure 23: Sensitivity Analysis of Primary Endpoint, TippingPoint Analysis of Patients with Missing Data (In Clinic-, mITT Population)



mITT=modified Intent-to-Treat.
Note: Analysis was performed on 32 patients in the mITT Population who had ≥ 1 missing IOP measurement.

5.1.2.5 Secondary Endpoint Results — Effectiveness Measured in Sleep Lab

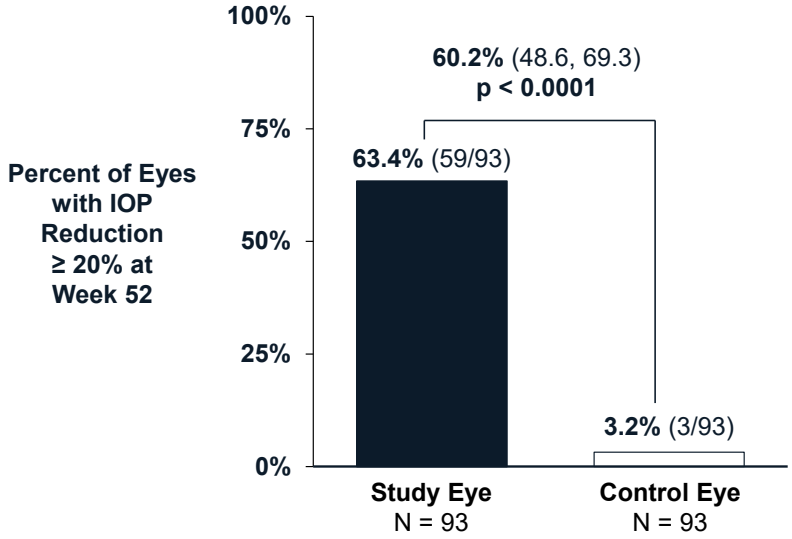
OPAP achieved the secondary effectiveness endpoint. At the Week 52 Sleep Lab visit, 63.4% of study eyes achieved ≥ 20% reduction in IOP during NP application, as compared to 3.2% of control eyes ($p < 0.0001$; Table 14; Figure 24).

Table 14: Secondary Effectiveness Endpoint Results, IOP Reduction ≥ 20% during Negative Pressure Application, at Week 52 (Sleep Lab, mITT Population)

Effectiveness Endpoint, n (%):	Study Eye (N=93)	Control Eye (N=93)	Difference (95% CI)[1]	p-value[2]
IOP reduction ≥ 20%	59 (63.4)	3 (3.2)	60.2% (48.6%, 69.3%)	< 0.0001

CI=confidence interval; IOP=intraocular pressure; mITT=modified Intent-to-Treat.
Note: Missing data imputed as failure; Sleep Lab data represent the mean IOP reduction of three overnight measurements, taken at 11:00 p.m., 2:00 a.m., and 5:00 a.m.; IOP assessed during and prior to NP application.
1. Bonett and Price (2012).
2. McNemar Test with a two-sided significance level of 0.05.

Figure 24: Secondary Effectiveness Endpoint Results, IOP Reduction ≥ 20% during Negative Pressure Application, at Week 52 (Sleep Lab, mITT Population)

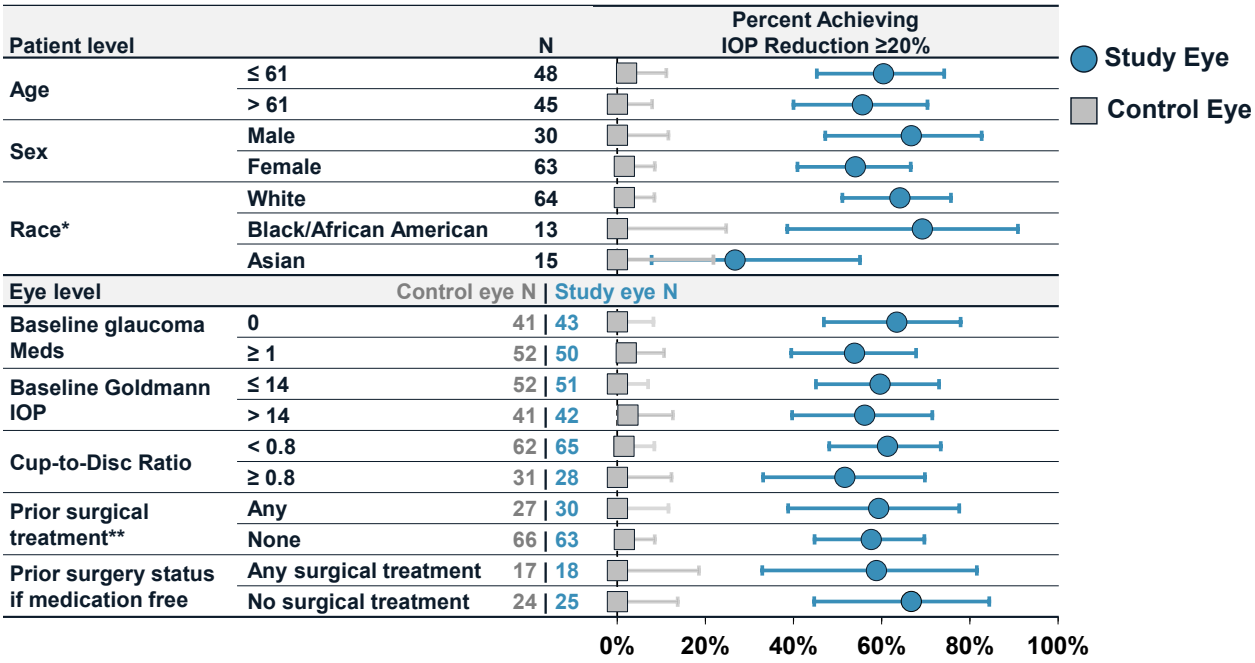


IOP=intraocular pressure; mITT=modified Intent-to-Treat.
Note: Sleep Lab data represent the mean IOP reduction of three overnight measurements, taken at 11:00 p.m., 2:00 a.m., and 5:00 a.m.; missing data/dropouts imputed as failure; IOP assessed during and prior to NP application.

5.1.2.6 Effectiveness in Subgroups — Covariate Analyses

A series of covariate analyses confirmed consistent effectiveness of OPAP, regardless of patient demographics, baseline ocular characteristics, or previous and current ocular treatments (Figure 25).

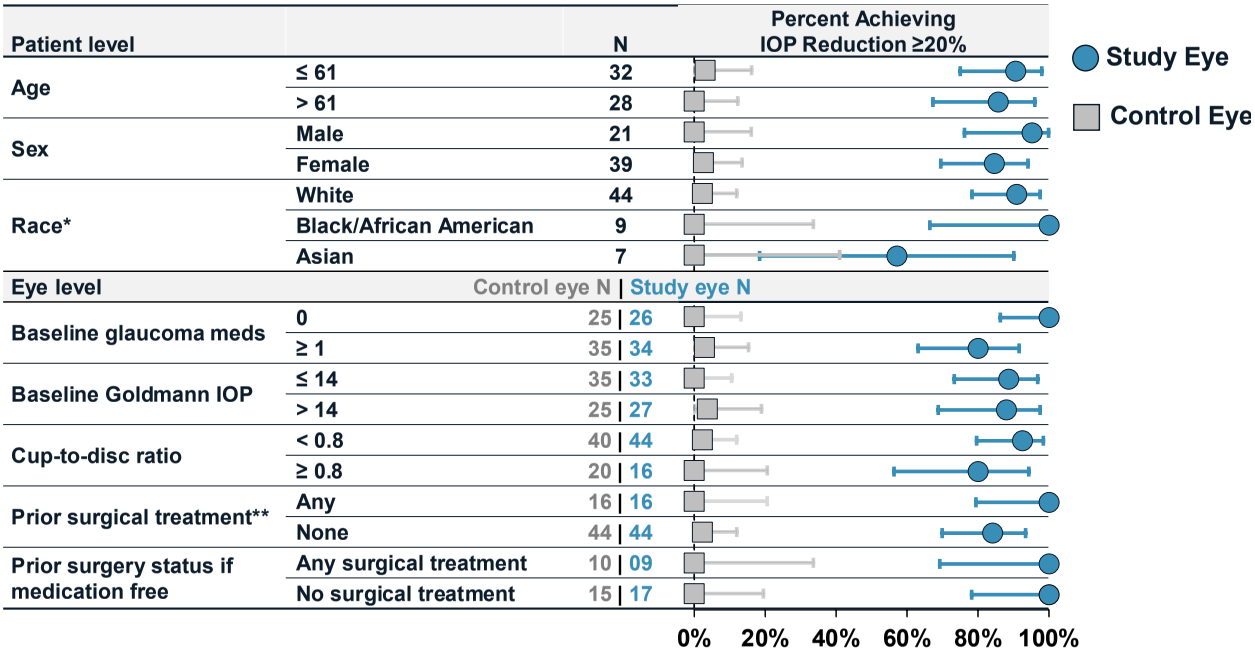
Figure 25: Analyses of Effectiveness in Subgroups — IOP Reduction ≥ 20%, by Covariate (In Clinic-, mITT Population)



IOP=intraocular pressure; mITT=modified Intent-to-Treat; NP=negative pressure.
Note: Values are presented as point estimates with 95% confidence intervals. Missing data/dropouts imputed as failure; IOP assessed during and prior to NP application. Analysis originally submitted to FDA as Table 25 in CP-X19 CSR; the following covariates were added to the original analysis: Race, Prior surgical treatment, and Prior surgery status if medication free; these additional analyses have not been previously reviewed by FDA; confidence intervals for these analyses not pre-specified.
* A fourth category (Mestizo) was excluded from covariate analysis because there was only one patient.
** Includes cataract or glaucoma surgery.

The same subgroup analyses were performed on the 60 patients in the Per-Protocol Population, (Section 5.1.1.7.4). Results amplified the primary analysis of patients in the mITT Population, with at least 80% of study eyes in all subgroups of the Per-Protocol Population achieving IOP reduction ≥ 20% during NP application (Figure 26).

Figure 26: Analyses of Effectiveness in Subgroups — IOP Reduction ≥ 20%, by Covariate (In Clinic-, PP Population)

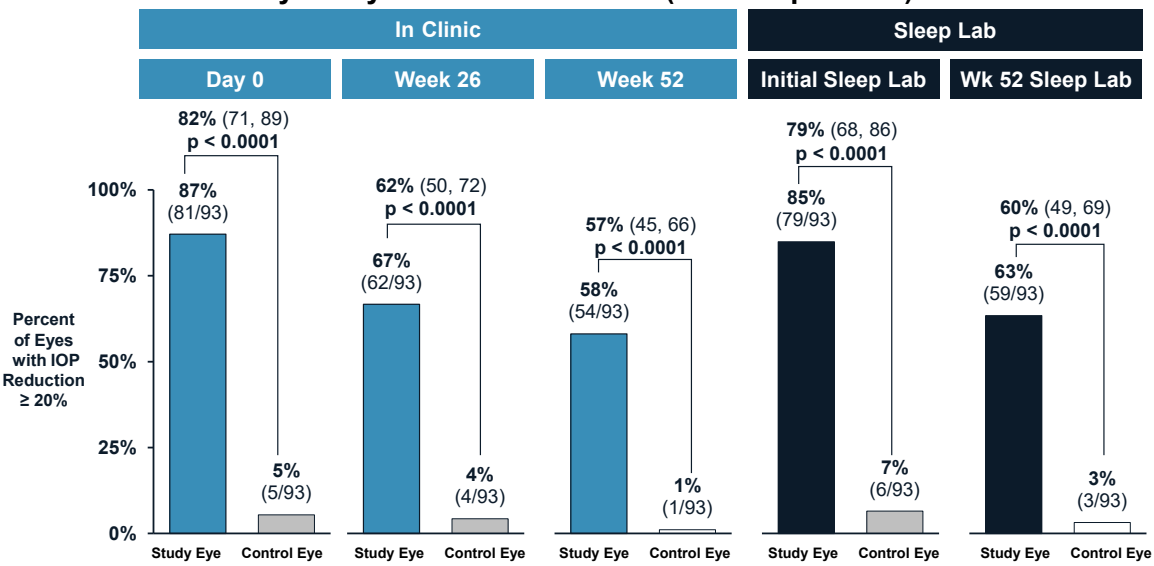


IOP=intraocular pressure; NP=negative pressure; PP=Per-Protocol.
Note: Values are presented as point estimates with 95% confidence intervals. IOP assessed during and prior to NP application. Analysis originally submitted to FDA as Table 25 in CP-X19 CSR; the following covariates were added to the original analysis: Race, Prior surgical treatment, and Prior surgery status if medication free; these additional analyses have not been previously reviewed by FDA; confidence intervals for these analyses not pre-specified.
* A fourth category (Mestizo) was excluded from covariate analysis because there was only one patient.
** Includes cataract or glaucoma surgery.
This figure is an expanded analysis from the original presentation to FDA in De Novo Petition DEN2XXXXX2.

5.1.2.7 Secondary Analyses of Primary and Secondary Effectiveness Endpoints

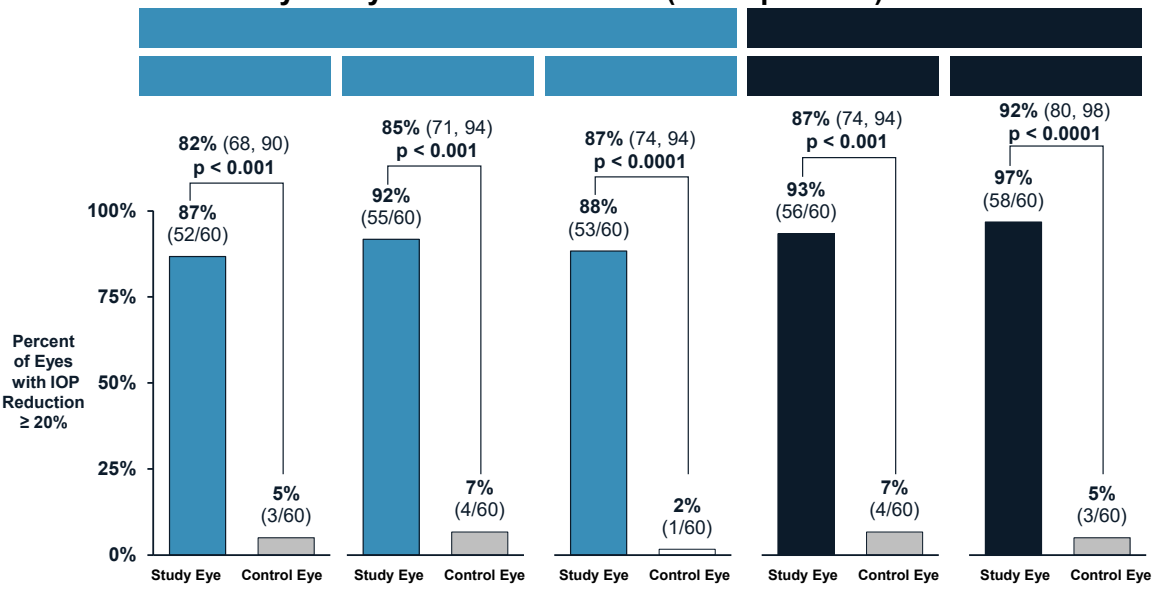
Prespecified secondary analyses of the primary and secondary effectiveness endpoints were performed to support findings of the primary analysis. (Summary figures of secondary analyses are presented Figure 27 [mITT Population] and Figure 28 [-Per Protocol Population].)

Figure 27: Secondary Analysis of Effectiveness (mITT Population)



IOP=intraocular pressure; mITT=modified Intent-to-Treat; NP=negative pressure; Wk=week.
Note: Missing data/dropouts imputed as failure; Sleep Lab data represent the mean IOP reduction of three overnight measurements, taken at 11:00 p.m., 2:00 a.m., and 5:00 a.m.; IOP comparisons performed by Excursion Tonometry during and prior to NP application. This chart presents tabular data previously presented to FDA in the CP-X19 CSR; the chart was prepared for Expert Panel consideration and has not been reviewed by FDA. P-values/confidence intervals at Day 0 and Week 26 not pre-specified not adjusted for multiple comparisons.

Figure 28: Secondary Analysis of Effectiveness (PP Population)



IOP=intraocular pressure; NP=negative pressure; PP=Per-Protocol; Wk=week.
Note: Sleep Lab data represent the mean IOP reduction of three overnight measurements, taken at 11:00 p.m., 2:00 a.m., and 5:00 a.m.; IOP comparisons performed by Excursion Tonometry during and prior to NP application. This chart presents tabular data from Week 52 previously presented to FDA in the CP-X19 CSR, with additional data from Day 0 and Week 26 In-Clinic and the Initial Sleep Lab, which have not been reviewed by FDA; the chart was prepared for Expert Panel consideration and has not been reviewed by FDA. P-values/confidence intervals at Day 0 and Week 26 not pre-specified, not adjusted for multiple comparisons.

5.1.2.7.1 Secondary Analysis of Primary Effectiveness Endpoint

At the Day 0 Visit, 87.1% of study eyes achieved ≥ 20% reduction in IOP during NP application, as compared to 5.4% of control eyes ($p < 0.0001$; Table 15; Figure 27). Week 26 results were consistent with these results: 66.7% of study eyes achieved ≥ 20% reduction in IOP during NP application, as compared to 4.3% of control eyes ($p < 0.0001$).

The GEE model was used to analyze the repeated outcomes of in-clinic IOP reduction ≥ 20% during NP application for the study vs control eyes at Day 0, Week 26, and Week 52. The predictors considered in the GEE analysis were the study visit (Day 0, Week 26, and Week 52), eye (study vs control), and their interaction. Because eyes with missing data were treated as non-responders in this analysis, patient withdrawals during the first half of the study reduced the responder rates. However, the difference in the responder rate of study vs control eyes at each visit remained statistically significant ($p < 0.0001$).

Table 15: Secondary Analysis of Primary Endpoint (In-Clinic, mITT Population)

	IOP Reduction ≥ 20%, n (%) [95% CI][1,2]		GEE Analysis[3]	
Visit:	Study Eye (N=93)	Control Eye (N=93)	95% CI[4] of % Difference	p-value[5] of % Difference
Day 0	81 (87.1) [78.5%, 93.2%]	5 (5.4) [1.8%, 12.1%]	73.9%, 89.6%	< 0.0001
Week 26	62 (66.7) [56.1%, 76.1%]	4 (4.3) [1.2%, 10.6%]	52.1%, 72.7%	< 0.0001
Week 52	54 (58.1) [47.4%, 68.2%]	1 (1.1) [0.0%, 5.8%]	46.9%, 67.1%	< 0.0001

CI=confidence interval; IOP=intraocular pressure; GEE=generalized estimating equation; mITT=modified Intent-to-Treat.
Note: Missing data/dropouts imputed as failure; IOP assessed during NP application.
1. Based on binomial distribution (Clopper-Pearson); Day 0 and Week 26 confidence intervals not prespecified.
2. All results had p-values < 0.001; Day 0 and Week 26 p-values not prespecified and not adjusted for multiple comparisons.
3. Model included Visit (Day 0, Week 26, and Week 52), eye (study and control), and interaction of the covariates and used an unstructured working correlation matrix.
4. Study % - Control %.
5. For a two-sided significance level of 0.05.

5.1.2.7.2 Secondary Analysis of Secondary Effectiveness Endpoint

At the initial sleep lab visit in the mITT Population, 84.9% of study eyes achieved ≥ 20% reduction in IOP during NP application, as compared to 6.5% of control eyes (Table 16; Figure 27). At the Week 52 Sleep Lab in the mITT Population, 63.4% vs 3.2% of study vs control eyes, respectively, achieved ≥ 20% IOP reduction.

In the Per-Protocol Population, results were even more favorable: 96.7% vs 5.0% of study vs control eyes, respectively, achieved a mean IOP reduction ≥ 20%, as measured while supine in the sleep lab (Figure 28)

The GEE was used to analyze the repeated outcomes of sleep lab IOP reduction ≥ 20% during OPAP application for the study vs control eyes at the initial and Week 52 Sleep Labs (Table 16). The predictors considered in this analysis were once again the study visit, eye, and their interaction.

The proportion of eyes with IOP reduction of ≥ 20% during OPAP application in each group at the initial and final sleep labs, is estimated based on the least-squares means. The difference in responder rate between study and control eyes in the sleep lab based on the GEE analysis decreased at the final sleep lab, a trend similar to that observed with the corresponding in-clinic analysis. Missing data, which was imputed as a failure, was a significant factor. Nevertheless, the differences in responder rates of study vs control eyes at each sleep lab were statistically significant ($p < 0.0001$).

Table 16: Secondary Analysis of Secondary Endpoint (Sleep Lab, mITT Population)

	IOP Reduction ≥ 20%, n (%) [95% CI][1,2]		GEE Analysis[3]	
Sleep Lab Visit:	**Study Eye (N=93)**	**Control Eye (N=93)**	**95% CI[4] of % Difference**	**p-value[5] of % Difference**
Initial sleep lab (Day ≤ 21)	79 (84.9) [76.0%, 91.5%]	6 (6.5) [2.4%, 13.5%]	70.1%, 86.8%	< 0.0001
Final sleep lab (Week 52)	59 (63.4) [52.8%, 73.2%]	3 (3.2) [0.7%, 9.1%]	50.3%, 70.2%	< 0.0001

CI=confidence interval; IOP=intraocular pressure; GEE=generalized estimating equation; mITT=modified Intent-to-Treat.
Note: Note: Missing data/dropouts imputed as failure; IOP assessed during NP application
1. Based on binomial distribution (Clopper-Pearson); Day 0 and Week 26 confidence intervals not prespecified.
2. All results had p-values < 0.001; Day 0 and Week 26 p-values not prespecified and not adjusted for multiple comparisons.
3. Model included Visit (Day 0, Week 26, and Week 52), eye (study and control), and interaction of the covariates and used an unstructured working correlation matrix.
4. Study % - Control %.
5. For a two-sided significance level of 0.05.

5.1.2.8 Exploratory Endpoints Results

5.1.2.8.1 IOP Measured by Excursion Tonometry before and during In-Clinic Negative Pressure Application

Following IOP measurement with pneumatonometry, IOP was measured using the Excursion Method but prior to NP application, and then again during NP application (Table 17). (the primary endpoint; Section 5.1.2.4.1), Findings were consistent with the primary endpoint: all study eyes had a decrease in IOP during NP application, and the proportions of study eyes demonstrating a reduction ≥ 20% at Day 0, Week 26, and Week 52 were 87.1%, 91.2%, and 88.5%, respectively.

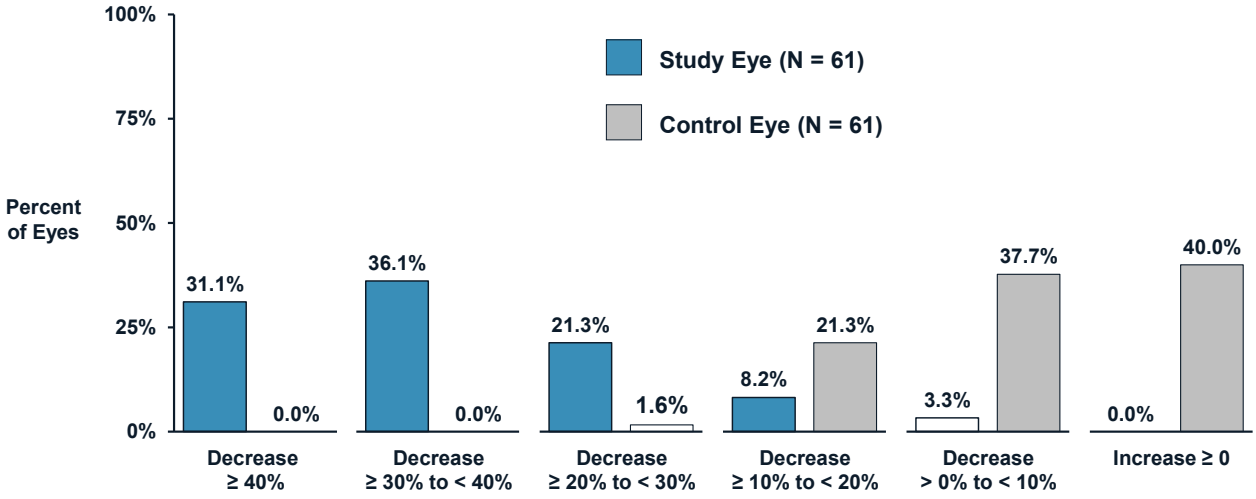
Importantly, all study eyes had a decrease in IOP during NP application, with the majority of study eyes (67.2%) having a decrease ≥ 30% at Week 52 (Figure 29).

Table 17: IOP Measurements by Excursion Tonometry, before and during Negative Pressure Application (In Clinic-, mITT Population)

	Day 0		Week 26		Week 52	
Assessment Measurement:	**Study (N=93)**	**Control (N=93)**	**Study (N=68)**	**Control (N=68)**	**Study (N=62)**	**Control (N=62)**
Excursion tonometry with NP off, mmHg						
Mean (SD)	16.8 (2.6)	16.8 (2.6)	17.2 (2.4)	17.2 (2.6)	18.0 (3.2)	17.4 (2.8)
Median (min, max)	16.8 (11.3, 23.8)	16.5 (10.5, 23.0)	17.0 (11.5, 24.5)	17.2 (11.3, 23.0)	17.8 (12.0, 26.8)	17.0 (13.0, 26.0)
Excursion tonometry with NP on, mmHg						
Mean (SD)	10.7 (2.4)	16.0 (2.9)	10.9 (2.4)	16.9 (2.9)	11.4 (3.0)	16.8 (3.0)
Median (min, max)	10.5 (6.0, 16.0)	16.3 (6.5, 21.5)	11.0 (5.5, 16.8)	16.8 (11.0, 22.3)	11.3 (5.5, 20.8)	16.3 (10.5, 26.3)
Change in IOP from NP off to NP on, mmHg						
Mean (SD)	-6.1 (2.5)	-0.8 (1.7)	-6.2 (2.5)	-0.3 (1.9)	-6.6 (3.1)	-0.6 (1.6)
Median (min, max)	-6.0 (-13.0, -1.3)	-0.7 (-8.8, 2.8)	-5.9 (-13.3, -1.5)	-0.1 (-5.5, 3.3)	-6.0 (-15.0, -1.0)	-0.5 (-6.0, 2.8)
Percent change in IOP from NP off to NP on						
Mean (SD)	-35.9 (12.7)	-4.4 (10.8)	-35.9 (12.8)	-1.4 (11.1)	-36.0 (13.9)	-3.4 (9.3)
Median (min, max)	-37.2 (-65.7, -10.2)	-4.2 (-57.5, 20.7)	-34.5 (-70.7, -9.2)	-0.7 (-28.2, 19.4)	-34.3 (-69.1, -4.6)	-2.3 (-24.5, 18.1)

IOP=intraocular pressure; mITT=modified Intent-to-Treat; SD=standard deviation.
Note: IOP assessed during and prior to NP application.

Figure 29: Change in IOP by Category of Percentage of Decrease or Increase during Negative Pressure Application at Week 52 (In-Clinic, mITT Population)



IOP=intraocular pressure; mITT=modified Intent-to-Treat
Note: IOP assessed during and prior to NP application. This figure is a graphical representation of tabular data originally submitted to FDA in Table 30 of CP-X19 CSR. This chart has not been previously reviewed by FDA.

5.1.2.8.2 IOP Measured by Excursion Tonometry before and during Negative Pressure Application in Supine Position in Sleep Lab

At each sleep lab visit, IOP was measured using Excursion Tonometry after goggle placement, both before and during NP application, with the patient in supine position (Table 18).

Consistent with measurements taken in the clinic (Section 5.1.2.8.1) all study eyes had a decrease in IOP in the Sleep Lab (Table 18), with the majority of study eyes (75.4%) having a decrease ≥ 30% at Week 52 (Figure 30).

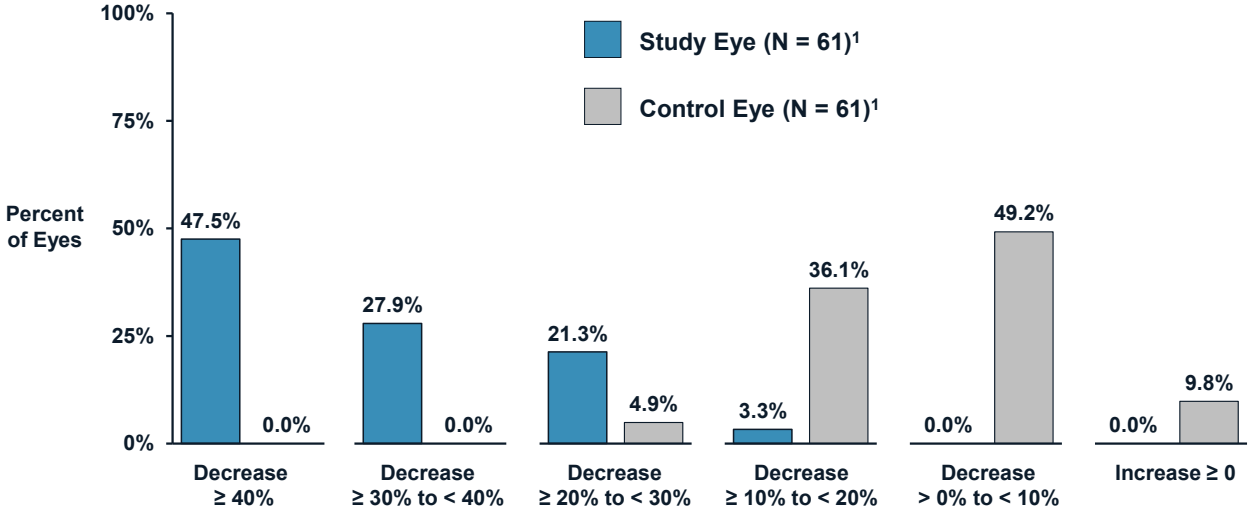
Table 18: IOP Measurements by Excursion Tonometry, before and during Negative Pressure Application (Sleep Lab, mITT Population)

	Initial Sleep Lab		Week 52 Sleep Lab	
Assessment Measurement:	**Study (N=80)**	**Control (N=80)**	**Study (N=61)[1]**	**Control (N=61)[1]**
Excursion Tonometry with NP off, mmHg				
Mean (SD)	20.1 (2.5)	18.6 (2.5)	20.4 (2.5)	19.4 (2.3)
Median (min, max)	19.8 (13.2, 28.1)	18.5 (12.1, 28.0)	20.3 (15.6, 27.9)	19.3 (14.5, 25.4)
Excursion Tonometry with NP on, mmHg				
Mean (SD)	12.5 (2.3)	16.8 (2.7)	12.4 (2.7)	17.7 (2.4)
Median (min, max)	12.3 (7.9, 20.3)	16.8 (10.6, 27.4)	12.2 (8.1, 18.5)	17.8 (12.3, 23.4)

Assessment Measurement:	Initial Sleep Lab		Week 52 Sleep Lab	
	Study (N=80)	Control (N=80)	Study (N=61)[1]	Control (N=61)[1]
Change in IOP from NP off to NP on, mmHg[2]				
Mean (SD)	-7.6 (2.2)	-1.8 (1.6)	-8.0 (2.5)	-1.6 (1.4)
Median (min, max)	-7.1 (-12.5, -2.9)	-1.6 (-8.4, 1.5)	-7.8 (-12.8, -2.9)	-1.4 (-5.6, 2.1)
Percent change in IOP from NP off to NP on, %[2]				
Mean (SD)	-37.5 (9.0)	-9.4 (8.5)	-39.1 (11.1)	-8.4 (7.3)
Median (min, max)	-36.7 (-59.3, -13.9)	-9.3 (-41.4, 10.1)	-39.4 (-58.7, -14.4)	-8.2 (-26.5, 11.7)

IOP=intraocular pressure; mITT=modified Intent-to-Treat; NP=negative pressure; SD=standard deviation.
Note: IOP assessed during and prior to NP application.
1. Measurement could not be obtained for one patient who was uncooperative and did not complete final sleep lab.
2. Higher numbers indicate improvement in IOP.

Figure 30: Change in IOP by Category of Percentage of Decrease or Increase during Negative Pressure Application at Week 52 (Sleep Lab, mITT Population)



IOP=intraocular pressure; mITT=modified Intent-to-Treat; NP=negative pressure; SD=standard deviation.
Note: IOP assessed during NP application.
1. Measurement could not be obtained for one patient who was uncooperative and did not complete the week 52 sleep lab. This figure is a graphical representation of tabular data originally submitted to FDA in Table 33 of CP-X19 CSR. This chart has not been previously reviewed by FDA.

5.1.3 Summary of Effectiveness in Artemis Study

Artemis met the primary effectiveness endpoint with 54/93 (58.1%) study eyes vs 1/93 (1.1%) control eye achieving IOP reduction of ≥ 20% during NP application at Week 52, as measured in-clinic ($p < 0.0001$; Table 12; Section 5.1.2.4.1). Results were similarly favorable on

the secondary endpoint of mean IOP reduction ≥ 20% during NP application at Week 52, as measured in the sleep lab: 59/93 (63.4%) study eyes vs 3/93 (3.2%) control eyes ($p < 0.0001$; Table 14; Section 5.1.2.5).

Two sensitivity analyses confirmed the robustness of the primary effectiveness endpoint: a responder rate analysis in the Per-Protocol Population of 60 participants who completed all study visits ($p < 0.0001$; Table 13; Section 5.1.2.4.2), and a tipping point analysis of participants with missing data in the mITT Population (Figure 23; Section 5.1.2.4.3). Secondary analyses (in clinic- IOP reduction ≥ 20% at Week 26 and GEE analysis; Section 5.1.2.7) of the primary (Table 15) and secondary (Table 16) endpoints further reinforced conclusiveness of the primary analyses. Results were consistent across all subgroups assessed, regardless of age, sex, concomitant ocular hypotensive medication use, previous glaucoma or cataract surgery, baseline IOP, and baseline cup-to-disc ratio (Figure 25; Section 5.1.2.5).

5.2 Effectiveness Conclusions

Eyes treated with OPAP showed consistent IOP reduction ≥ 20% during NP application, especially when compared to control eyes, as has been demonstrated in both the Artemis and Apollo pivotal studies.

In the 12-month Artemis Study (Section 5.1), the pivotal trial of OPAP in support of the recommended indication, eyes treated with NP application demonstrated IOP reduction that was highly statistically significant, thus supporting OPAP as an adjunct treatment to lower IOP in patients with normal-tension glaucoma (defined as having a daytime unmedicated IOP ≤ 21 mmHg). Artemis exceeded both the primary and secondary effectiveness endpoints of lowering IOP ≥ 20% during application of NP ($p < 0.001$ for both endpoints), as measured both in the clinic and during sleep in the lab. In-clinic, 58.1% vs 1.1% of study vs control eyes, respectively, had ≥ 20% reduction in IOP during NP application (primary endpoint; Section 5.1.2.4.1). These results were even more favorable in terms of the secondary endpoint: at Week 52 in the sleep lab, 63.4% vs 3.2% of study vs control eyes, respectively, had ≥ 20% reduction in mean IOP during NP application (secondary endpoint; Section 5.1.2.5).

Multiple sensitivity analyses supported these pivotal findings. In the Per-Protocol Population (defined as all patients who had no major protocol deviations and completed both the Week 52 in clinic- and sleep-lab visits), 53/60 (88.3%) vs 1/60 (1.7%) study vs control eyes, respectively, had an IOP reduction ≥ 20%, as measured in the clinic (Section 5.1.2.4.2). A tipping-point sensitivity analysis, which imputed 1,089 possible outcome scenarios for the 32 patients who dropped out during the course of the study and thus with ≥ 1 missing IOP primary analysis measurement, produced consistent results in all instances, including worst-case scenarios in which control eyes with missing data were imputed as responders and study eyes with missing data were imputed as non-responders (Section 5.1.2.4.3).

Earlier studies of OPAP, many of which also included patients with IOP ≤ 21 mmHg, support these effectiveness conclusions (Apollo [Section 4.4.2.1], Feasibility [Section 4.4.2.2], and Endure [Section 4.4.2.3]).

The literature emphasizes the importance of elevated nocturnal IOP in glaucoma's irreversible progression toward blindness (Section 2.1.3), and OPAP provides an important and immediate adjunctive therapy to mitigate elevations in IOP and preserve vision.

6 CLINICAL SAFETY

Summary

- The primary safety assessment comes from the pivotal Artemis Study (N=93), which followed 93 study vs 93 control eyes over a year of regular nightly OPAP use
- OPAP was safe and well tolerated: there were no serious device-related adverse events, and no findings reflected damage to the structure or function of the optic nerve
- One device-related transient AE was categorized as severe (lid edema); all other device-related AEs were mild-to-moderate in severity
- All device-related AEs resolved without sequelae using standard supportive care and/or modified device usage
    - As expected, device-related ocular and periorbital AEs occurred more frequently in study vs control eyes: 34.4% vs 10.8%, respectively
    - Lid edema and periorbital edema were the most common ocular and periorbital AEs, occurring in 11.8% and 12.9% of study eyes vs 1.1% and 1.1% of control eyes, respectively
    - Two patients discontinued OPAP due to mild-to-moderate periorbital contact dermatitis, which the investigator determined as a possible reaction to the goggles
- No additional assessments reflected a worsening in clinical outcomes
- An independent reading center determined that there was no worsening of visual field or OCT assessments in study eyes vs control eyes

6.1 Definition of Safety Population

The assessment of OPAP device safety in the intended population (i.e., the Safety Population) comes from the 93 patients in the mITT Population (Section 5.1.1.7.4) of the pivotal Artemis Study (Section 5.1) who received at least one NP application. Device-related AEs that occurred during the device use run-in period before randomization were not included in the primary safety analysis but are provided in Table 32 in Appendix 9.2.1. The ocular and periorbital AEs reported during the run-in period were similar to those reported throughout the study.

6.2 Ocular and Periorbital Adverse Events

Over a year of regular, nightly use, there were no serious device-related AEs and no AEs reflective of damage to the structure and function of the optic nerve or anterior segment. None of the safety assessments reflected a worsening in clinical outcomes or unanticipated adverse device effects (UADE).

6.2.1 Summary of Adverse Events

Ocular AEs were reported in 26.9% of study eyes vs 14.0% of control eyes. Periorbital AEs were reported in 18.3% of study eyes vs 7.5% of control eyes. All device-related ocular and periorbital AEs were resolved without sequelae at the time of study completion. Two (2) patients

discontinued therapy due to periorbital contact dermatitis, which the investigator assessed as a possible reaction to the OPAP goggles.

6.2.2 Non-ocular AEs were reported for 12.9% of patients. There were 5 SAEs, all of which were non-ocular in nature. None of the SAEs were related to use of the study device. Ocular Adverse Events

A total of 39 ocular AEs were reported in 25 (26.9%) study eyes vs 17 ocular AEs in 13 (14.0%) control eyes (Table 19). Two AEs occurred in ≥ 5% of study eyes: lid edema (11 [11.8%]) and mild-- signs and symptoms of dry eye (5 [5.4%]). There were no ocular SAEs. (Discussion of certain individual ocular AEs is presented in Section 9.2.2.)

Table 19: Ocular Adverse Events (Safety Population)

	Study Eyes (N=93)			Control Eyes (N=93)		
Ocular Adverse Event:	**# of Reports**	**# of Eyes**	**% of Eyes**	**# of Reports**	**# of Eyes**	**% of Eyes**
Any ocular AE	39	25	26.9%	17	13	14.0%
Lid edema	12	11	11.8%	1	1	1.1%
Symptoms and signs of dry eye	6	5	5.4%	5	5	5.4%
Conjunctival hyperemia	4	4	4.3%	2	2	2.2%
Eye pain	4	3	3.2%	0	0	-
Loss of BCDVA ≥ 10 letters from baseline	2	2	2.2%	2	2	2.2%
Lid erythema	2	2	2.2%	1	1	1.1%
Posterior vitreous detachment	2	2	2.2%	0	0	-
Anterior basement membrane dystrophy	1	1	1.1%	1	1	1.1%
Iritis	1	1	1.1%	1	1	1.1%
Meibomian gland dysfunction	1	1	1.1%	1	1	1.1%
Nuclear sclerotic cataract	1	1	1.1%	1	1	1.1%
Epithelial defect	1	1	1.1%	0	0	-
Floater	1	1	1.1%	0	0	-
Visual disturbance	1	1	1.1%	0	0	-
Conjunctival chalasis	0	0	-	1	1	1.1%
Eye pain secondary to ocular trauma	0	0	-	1	1	1.1%

AE=adverse event; BCDVA=best-corrected distance visual acuity.

6.2.3 Periorbital Adverse Events

Twenty (20) periorbital AEs were reported for 17 (18.3%) study eyes vs 7 AEs in 7 (7.5%) control eyes (Table 20). Mild--to--moderate periorbital edema was the only AE to occur in ≥ 5% of study eyes. There were no periorbital SAEs. (Discussion of certain individual ocular AEs is provided in Appendix 9.2.3.)

Table 20: Periorbital Adverse Events (Safety Population)

	Study Eyes (N=93)			Control Eyes (N=93)		
Periorbital Adverse Event:	**# of Reports**	**# of Eyes**	**% of Eyes**	**# of Reports**	**# of Eyes**	**% of Eyes**
Any periorbital AE	20	17	18.3%	7	7	7.5%
Periorbital edema	12	12	12.9%	1	1	1.1%
Periorbital contact dermatitis	4	4	4.3%	3	3	3.2%
Periorbital pain	2	2	2.2%	1	1	1.1%
Periorbital folds above eyebrows	1	1	1.1%	1	1	1.1%
Nasal abrasion	1	1	1.1%	0	0	-
Cherry hemangioma	0	0	-	1	1	1.1%

AE=adverse event.

6.2.4 Severe Ocular and Periorbital Adverse Events

Only one of the ocular and periorbital AEs reported during the 52-week study was considered severe. This event, lid edema, was reported by a patient during the at-home use period, with NP setting of –14 mmHg approximately 4 months after randomization and initiation of NP therapy. This AE resolved within a week after discontinuation of OPAP use. All other ocular and periocular AEs were mild to moderate in nature, with the majority of events considered to be mild. (See additional details in Appendix 9.2.2).

6.2.5 Device-Related Ocular and Periorbital Adverse Events

A total of 44 AEs considered possibly, probably, or definitely related to device use were reported in 32 (34.4%) study eyes. A total of 11 device-related AEs were reported in 10 (10.8%) control eyes (Table 21). As expected, the unilateral application of NP resulted in more reports of lid and periorbital edema and eye pain in study eyes than control eyes.

Table 21: Device-Related Ocular and Periorbital Adverse Events (Safety Population)

	Study Eyes (N=93)			Control Eyes (N=93)		
Device-Related Ocular or Periorbital Adverse Event:	**# of Reports**	**# of Eyes**	**% of Eyes**	**# of Reports**	**# of Eyes**	**% of Eyes**
Any device-related ocular or periorbital AE	44	32	34.4%	11	10	10.8%
Any device-related ocular AE	24	19	20.4%	5	4	4.3%
Lid edema	12	11	11.8%	1	1	1.1%
Symptoms and signs of dry eye	3	3	3.2%	2	2	2.2%
Conjunctival hyperemia	3	3	3.2%	1	1	1.1%
Eye pain	3	3	3.2%	0	0	-

Device-Related Ocular or Periorbital Adverse Event:	Study Eyes (N=93)			Control Eyes (N=93)		
	# of Reports	# of Eyes	% of Eyes	# of Reports	# of Eyes	% of Eyes
Lid erythema	2	2	2.2%	1	1	1.1%
Visual disturbance	1	1	1.1%	0	0	-
Any device-related periorbital AE	20	17	18.3%	6	6	6.5%
Periorbital edema	12	12	12.9%	1	1	1.1%
Periorbital contact dermatitis	4	4	4.3%	3	3	3.2%
Periorbital pain	2	2	2.2%	1	1	1.1%
Nasal abrasion	1	1	1.1%	0	0	-
Periorbital folds above eyebrows	1	1	1.1%	1	1	1.1%

AE=adverse event; BCDVA=best-corrected distance visual acuity.
Notes: Device-related includes AEs assessed by Investigator as Possibly, Probably, or Definitely Related to Device.

6.3 Non-Ocular Adverse Events

A total of 12 (12.9%) patients experienced non-ocular AEs, 2 of whom experienced mild-to-moderate transient headaches related to device use (Table 22). There were no SAEs (either ocular or non-ocular) related to device use. (Three patients who had non-ocular, non-device-related SAEs are discussed in Section 6.4).

Table 22: Non-ocular Adverse Events (Safety Population)

Non-ocular Adverse Event:	Patients (N=93)		
	# of Reports	# of Patients	% of Patients
Any non-ocular AE	24	12	12.9%
COVID-19	3	3	3.2%
Headache (e.g., tension, migraine, sinus, etc.)	2	2	2.2%
Acid reflux	1	1	1.1%
Arrhythmia	1	1	1.1%
Constipation	1	1	1.1%
Ganglion cyst	1	1	1.1%
Heart failure	1	1	1.1%
Mole, right calf	1	1	1.1%
Nosebleed	1	1	1.1%
Redness to upper left cheek with appearance of rash	1	1	1.1%
Pinched nerve, neck	1	1	1.1%
Pre-cancerous lesion	1	1	1.1%

	Patients (N=93)		
Non-ocular Adverse Event:	**# of Reports**	**# of Patients**	**% of Patients**
Rectal prolapse	1	1	1.1%
Right long trigger finger	1	1	1.1%
Skin abscess	1	1	1.1%
Stage 4 pancreatic cancer	1	1	1.1%
Tennis elbow	1	1	1.1%
Throat nodules	1	1	1.1%
Thyroid nodules	1	1	1.1%
Urinary tract infection	1	1	1.1%
Uterine prolapse	1	1	1.1%

AE=adverse event; IV=intravenous.

6.4 Adverse Events Leading to Discontinuation

A total of 3 patients had AEs leading to discontinuation, 2 of which were considered device-related; both resolved without sequelae. These 2 patients (2.2%) experienced mild periorbital contact dermatitis, which the investigator felt may have been a reaction to the OPAP goggles; therefore, the patients discontinued.

The one additional patient was diagnosed with Stage 4 pancreatic cancer and discontinued.

6.5 Deaths

There were no deaths in the Artemis Study.

6.6 Findings from Other Ocular Evaluations

6.6.1 Best-Corrected Distance Visual Acuity (BCDVA)

BCDVA was measured before NP application at Baseline (Day -14) and Week 52. At Week 52, the proportion of subjects with BCDVA 20/25 or better was similar to Baseline. (Table 23). During the study, BCDVA loss ≥ 10 letters as compared with baseline, considered unrelated to the study device, was reported for 2 study eyes and 2 control eyes in 4 patients. Results were consistent among the 62 patients who completed all study visits.

Table 23: Best Corrected Distance Visual Acuity, at Baseline (Day 14) and Week 52 (Safety Population)

	Baseline (Day -14)		Week 52	
BCDVA, n (%):	Study (N=93)	Control (N=93)	Study (N=62)	Control (N=62)
20/20 or better	39 (41.9)	37 (39.8)	20 (32.3)	24 (38.7)
20/25 or better	72 (77.4)	73 (78.5)	49 (79.0)	49 (79.0)
20/32 or better	84 (90.3)	84 (90.3)	60 (96.8)	59 (95.2)
20/40 or better	89 (95.7)	89 (95.7)	61 (98.4)	60 (96.8)
< 20/40 to 20/100	4 (4.3)	3 (3.2)	1 (1.6)	1 (1.6)
Worse than 20/100	0	1 (1.1)	0	1 (1.6)

BCDVA=best corrected distance visual acuity.

Results were consistent among the 62 patients who had data reported at both the Baseline (Day -14) and Week 52 Visits (i.e., the 52-Week Consistent Cohort; Table 24).

Table 24: Best Corrected Distance Visual Acuity, at Baseline (Day 14) and Week 52 (52-Week Consistent Cohort)

	Baseline (Day -14)		Week 52	
BCDVA, n (%):	Study (N=62)	Control (N=62)	Study (N=62)	Control (N=62)
20/20 or better	26 (41.9)	25 (40.3)	20 (32.3)	24 (38.7)
20/25 or better	47 (75.8)	48 (77.4)	49 (79.0)	49 (79.0)
20/32 or better	59 (95.2)	56 (90.3)	60 (96.8)	59 (95.2)
20/40 or better	61 (98.4)	60 (96.8)	61 (98.4)	60 (96.8)
< 20/40 to 20/100	1 (1.6)	1 (1.6)	1 (1.6)	1 (1.6)
Worse than 20/100	0	1 (1.6)	0	1 (1.6)

BCDVA=best corrected distance visual acuity.
Note: The 52-Week Consistent Cohort consisted of all patients in the Safety Population who had data reported at Baseline (Day -14) and Week 52.

6.6.2 Goldmann Applanation Tonometer (GAT) Measurement of IOP

The mean change in IOP after NP application as compared to prior to NP was ≤ 1 mmHg in both the study and control eyes (Table 25). The change in IOP after completion of NP in the study eye indicated no significant IOP elevations, and no instances of IOP < 6 mmHg.

Table 25: Mean IOP before and after NP Application, Measured with Goldmann Applanation Tonometry (Safety Population)

	Baseline (Day -14)		Day 0		Week 26		Week 52	
GAT, mmHg:	**Study (N=93)**	**Control (N=93)**	**Study (N=93)**	**Control (N=93)**	**Study (N=68)**	**Control (N=68)**	**Study (N=62)**	**Control (N=62)**
GAT prior to NP								
Mean (SD)	14.7 (2.0)	14.8 (2.2)	14.4 (2.4)	14.2 (2.6)	14.7 (3.0)	14.8 (3.1)	14.4 (2.8)	14.0 (3.0)
Median (min, max)	14 (12, 20)	14 (12, 21)	14 (9, 21)	14 (7.5, 22)	15 (7, 24)	15 (7, 22)	14 (9, 21)	13.75 (7.5, 20.8)
GAT after NP								
Mean (SD)	14.1 (2.1)	14.2 (2.3)	13.9 (2.4)	14.0 (2.8)	13.7 (3.1)	14.3 (3.0)	14.2 (3.0)	14.0 (3.1)
Median (min, max)	14 (10, 19.5)	14 (9, 20.5)	14 (8, 20)	14 (6, 22)	14 (6, 24)	14 (8.5, 22)	14 (8.5, 21.5)	13.5 (8, 21)
Change in GAT after NP								
Mean (SD)	-0.6 (1.5)	-0.5 (1.4)	-0.4 (1.4)	-0.3 (1.6)	-1.0 (1.8)	-0.5 (1.8)	-0.3 (2.0)	0 (2.2)
Median (min, max)	-1 (-4, 1)	-0.5 (-5.5, 4)	-0.5 (-6, 3)	0 (-5.5, 3)	-0.5 (-6, 3)	0 (-6, 3.5)	0 (-7.5, 2.5)	0 (-5, 7)

GAT=Goldmann applanation tonometry; IOP=intraocular pressure; SD=standard deviation.

6.6.3 Use of Ocular Hypotensive Medication

The mean number of ocular hypotensive medications used remained stable during the 52-week study, with ≥ 93.8% of study and control eyes reporting no change in the number of medications used at any visit.

Three (3) patients increased the number of ocular hypotensive medications used in both the study and control eyes, while 1 patient increased the number of ocular hypotensive medications only in the control eye. All 4 of these patients used ocular hypotensive medication in both eyes prior to study enrollment.

6.6.4 Results of Slit-Lamp Examinations

Slit lamp exams were conducted at each study visit. There were no reports of conjunctival chemosis, corneal epithelial defects, corneal edema, corneal endothelial keratitic precipitates, or corneal endothelial folds at any scheduled visits among randomized patients. Similarly, there were no reports of anterior cells or flare, changes in iris appearance, or anterior chamber angle.

Notable findings from slit-lamp examinations include:

- **1+ corneal endothelial guttata OU** that had not been present previously was observed in one patient at the Week 52 Visit.
- **Worsening in conjunctival hyperemia ≥ 2 grades** from baseline was observed in 5 patients (3 study eyes and 2 control eyes) at the Week 12 Visit. Three patients reported

concomitant use of ocular hypotensive medication (latanoprost, bimatoprost + timolol, dorzolamide + netarsudil, while 2 patients were not using medications; these cases were reported as AEs. All but 1 case (in a control eye) resolved by the subsequent Week 26 Visit; this persisted past Week 38.

- **Worsening in superficial punctate keratitis (SPK) ≥ 2 grades** was reported in both eyes of 3 patients; similar worsening was reported in only the study eye of 2 patients, and in only the control eye of 2 patients. All cases resolved without sequelae.
- **Lid edema**: As expected, the unilateral application of NP resulted in more reports of lid edema in study eyes than control eyes. A ≥ 2 grade worsening in this finding was reported for 9 study eyes and 1 control eye over the course of the study, and these cases were reported as AEs.
- **Lid erythema**: There was essentially no difference in the prevalence of this finding between the groups throughout the study, and 98.4% of study and control eyes were absent of this finding at the Week 52 Visit. Worsening in this finding by ≥ 2 grades from baseline was observed for both eyes of one patient at Week 6. The event resolved 2 days after discontinuation of device use.

6.6.5 Results of Dilated Fundus Examinations

Most fundus abnormalities were considered by investigators to be clinically insignificant, and slightly fewer fundus abnormalities were reported at Week 52 than at Baseline in both the study and control eyes. New abnormalities noted at Week 52 that were not noted at baseline were reported for 2 patients: 1 eye with 1+ PVD and 1 eye with 1+ superior temporal lattice degeneration. The mean (SD) cup-to-disc ratio (C:D) for both study and control eyes was 0.7 (0.2) at each visit. More than 80% of eyes in each group remained unchanged throughout the study. A slight increase from baseline was noted in 6 study eyes and 6 control eyes at the 52-week visit. In 11 of the 12 eyes with increased C:D, the change was ≤ 0.1. The remaining case involved a study eye C:D that increased from 0.5 at baseline to 0.7 at Week 52. (Additional findings from fundus examinations are provided in Table 33 of Appendix 9.2.4.)

Table 26: Summary of Dilated Fundus Examination Findings (Safety Population)

	Baseline (Day -14)		Week 52	
Parameter, n (%):	**Study (N=93)**	**Control (N=93)**	**Study (N=62)**	**Control (N=61)***
Vitreous				
Normal	79 (84.9)	77 (82.8)	54 (87.1)	54 (88.5)
Abnormal[1]	14 (15.1)	16 (17.2)	8 (12.9)	7 (11.5)
Floaters	1 (1.1)	1 (1.1)	0	0
PVD	12 (12.9)	13 (14.0)	8 (12.9)	6 (9.8)
Syneresis	1 (1.1)	2 (2.2)	0	1 (1.6)
Peripapillary atrophy	1 (1.1)	1 (1.1)	0	0

Parameter, n (%):	Baseline (Day -14)		Week 52	
	Study (N=93)	Control (N=93)	Study (N=62)	Control (N=61)*
Macula				
Normal	89 (95.7)	90 (96.8)	60 (96.8)	59 (96.7)
Abnormal[1]	4 (4.3)	3 (3.2)	2 (3.2)	2 (3.3)
Drusen	2 (2.2)	2 (2.2)	1 (1.6)	1 (1.6)
Other	2 (2.2)	1 (1.1)	1 (1.6)	1 (1.6)
Periphery				
Normal	90 (96.8)	92 (98.9)	60 (96.8)	60 (98.4)
Abnormal, not clinically significant	3 (3.2)	1 (1.1)	2 (3.2)	1 (1.6)

PVD=posterior vitreous detachment.
1. An eye could be reported with multiple abnormalities.
* Control eye examination completed but not recorded for one patient.

6.6.6 Changes in Visual Field

The average visual field (VF) mean deviation (MD) was stable during the 52-week follow-up period for both the study and control eyes (Table 27).

Mean (SD) MD at Baseline was -4.03 (4.89) dB in the study eye and -3.67 (4.68) dB (SD 4.68) in the control eye; mean MD at Week 52 was --3.5 (5.93) dB in the study eye and -3.35 (6.30) dB in the control eye. Worsening in visual field MD ≥ 2.5 dB was reported in 7 patients at Week 26 (4 study and 5 control eyes) and in 4 patients at Week 52 (3 study and 3 control eyes).

Table 27: Visual Field Mean Deviation from Baseline (Day -14), Week 26, and Week 52 (Safety Population)

Outcome:	Baseline (Day -14)		Week 26		Week 52	
	Study (N=93)	Control (N=93)	Study (N=68)	Control (N=68)	Study (N=62)	Control (N=62)
Mean (SD)	-4.03 (4.89)	-3.67 (4.68)	-3.80 (4.98)	-3.45 (4.34)	-3.50 (5.93)	-3.35 (6.30)
Median (min, max)	-2.61 (-22.59, 2.38)	-1.94 (-20.37, 2.82)	-2.21 (-22.04, 2.69)	-2.16 (-16.90, 2.71)	-2.29 (-24.90, 18.52)	-1.21 (-28.15, 18.45)
Change from Baseline, n (%)						
Improved ≥ 2.5 dB	-	-	8 (11.8)	11 (16.2)	11 (17.7)	10 (16.1)
Change < ±2.5 dB	-	-	56 (82.4)	52 (76.5)	48 (77.4)	49 (79.0)
Worsened ≥ 2.5 dB	-	-	4 (5.9)	5 (7.4)	3 (4.8)	3 (4.8)

	Baseline (Day -14)		Week 26		Week 52	
Outcome:	Study (N=93)	Control (N=93)	Study (N=68)	Control (N=68)	Study (N=62)	Control (N=62)

SD=standard deviation.
Note: Visual fields were evaluated at the University of Iowa Reading Center.

Results were consistent among the 62 patients who completed the study (Table 28).

Table 28: Visual Field Mean Deviation from Baseline (Day -14), Week 26, and Week 52 (52-Week Consistent Cohort)

	Baseline (Day -14)		Week 26		Week 52	
Outcome:	Study (N=62)	Control (N=62)	Study (N=62)	Control (N=62)	Study (N=62)	Control (N=62)
Mean (SD)	-4.23 (4.99)	-4.05 (4.93)	-3.96 (5.15)	-3.61 (4.50)	-3.50 (5.93)	-3.35 (6.30)
Median (min, max)	-2.66 (-22.59, 2.38)	-2.08 (-20.37, 2.31)	-2.21 (-22.04, 2.69)	-2.16 (-16.90, 2.71)	-2.29 (-24.90, 18.52)	-1.21 (-28.15, 18.45)
Change from Baseline, n (%)						
Improved ≥ 2.5 dB	-	-	8 (12.9)	11 (17.7)	11 (17.7)	10 (16.1)
Change < ±2.5 dB	-	-	50 (80.6)	46 (74.2)	48 (77.4)	49 (79.0)
Worsened ≥ 2.5 dB	-	-	4 (6.5)	5 (8.1)	3 (4.8)	3 (4.8)

SD=standard deviation.
Note: Visual fields were evaluated at the University of Iowa Reading Center. The 52-Week Consistent Cohort consisted of all patients in the Safety Population who had data reported at Baseline (Day -14), Week 26, and Week 52.

6.7 Independent Masked Reading Center Assessments of Glaucomatous Progression

To further characterize potential differences in glaucomatous progression in study vs control eyes, available VF data from Week 26 and Week 52 assessments were evaluated post hoc by the University of Iowa HC Visual Field Reading Center (VFRC).

6.7.1 Methodology for Independent Assessments

The Sponsor provided data to the Reading Center in the form of binders or pdfs. The data provided included the Subject ID and eye (OD/OS) only; randomization assignment information was not provided.

The reading center read, analyzed, and reported the visual field examination data for both eyes of each of the subjects in the cohort provided. Two readers were used, and any discrepancies were adjudicated by a third reader.

First, each visual field and OCT examination was read for reliability and acceptability/analyzability, respectively. Unreliable visual field examinations disqualified the eye from both analyses (determination of progression via visual field alone, and determination of progression via visual field and OCT) while an unanalyzable OCT disqualified the eye from the second analysis (determination of progression via visual field and OCT).

Next, the series of fields were analyzed over time for each eye in a masked fashion and a determination was made as to whether the series of visual fields improved, stayed the same, or worsened.

Following this, a second analysis occurred in the same manner as previous but also with consideration to OCT data.

Results of the independent assessments were recorded in a spreadsheet organized by study subject and then by right eye and left eye.

The final report consisted of each reader's outcome conclusions organized by study subject and eye (OD/OS). Outcomes data were categorized as "worse", "better", "same", or "unusable" (for visual field data). Subjects with one eye worsening more than the other were flagged.

6.7.2 Results of Independent Assessments

In the 62 patients who completed the trial, none of the eyes had VF progression that was confirmed with OCT, as assessed by the masked, independent VFRC readers (Table 29). Additionally, the VFRC found no evidence of VF progression in one eye over the other. Sponsor analysis of the VFRC's report confirmed no evidence of VF progression worsening in the study eye vs control eye.

VF series were sufficient for analysis of glaucomatous progression in 49 (79.0%) study eyes and 45 (72.6%) control eyes. VFRC analysis indicated none of the eyes identified with ≥ 2.5 dB of MD loss had manifest progression. In one patient who had not demonstrated MD worsening ≥ 2.5 dB in either eye, the VFRC identified manifest progression present OU at Week 52 with no differences noted in the rate of progression between the eyes based on review of visual field maps; however, analysis of OCT imaging from concurrent visits did not confirm glaucoma progression in either eye of this patient.

Table 29: Summary of 52-Week Visual Field and OCT in Eyes with MD Loss ≥ 2.5 dB or Glaucomatous Progression (Data Analyzed by University of Iowa VFRC; Artemis)

	VFRC Evaluation of Progression		
Eye Assignment:[1]	**VF alone**	**VF+OCT**	**Progression Relative to Contralateral Eye (Assessed by VF alone)[2]**
VF MD Worsening ≥ 2.5 dB as compared to Baseline (N=4 patients: 4 study eyes and 4 control eyes)			
Study	No	No	No
Control	Indeterminable	No	Indeterminable

	VFRC Evaluation of Progression		
Eye Assignment:[1]	**VF alone**	**VF+OCT**	**Progression Relative to Contralateral Eye (Assessed by VF alone)[2]**
Study	Insufficient	No	Insufficient
Control	Insufficient	No	Insufficient
Study	No	No	Insufficient
Control	Insufficient	No	Insufficient
Study	Insufficient	No	Insufficient
Control	Insufficient	No	Insufficient
VF MD Worsening < 2.5 dB as compared to Baseline (N=1 patient: 1 study eye and 1 control eye)			
Study	Yes	No	No
Control	Yes	No	No

MD=mean deviation; OCT=optical coherence tomography; VF=visual field; VFRC=Visual Field Reading Center.
1. VFRC readers were masked to treatment assignment. Eye assignment was determined by Equinox personnel after receipt of the VFRC report.
2. "Insufficient" means the VF examination or OCT images were of insufficient quality for progression analysis. "Indeterminable" means VFRC readers, upon review of images considered "sufficient", were not able to determine if progression was present.

6.8 Summary of Safety in Prior Investigations

Safety findings from supporting clinical studies confirm that OPAP is safe and well tolerated. Specifically:

- **Apollo (CP-X10; N=64)**: The most commonly reported adverse events were lid edema (17.2% vs 7.8% for study vs control eyes, respectively, and periorbital edema (14.1% vs 10.9%, respectively). There were no serious device-related adverse events. (See Section 4.4.2.1 for study details.) A post-hoc independent, masked review by the University of Iowa VFRC found that one study eye and one control eye in each of two patients had visual field changes suggestive of progression. When factoring OCT findings into visual field results, the VFRC concluded that no eye in any patient had a finding of progression. (See Section 6.7.1 for details on VFRC methodology.)
- **Feasibility Study (CP-X18; N=11)**: There were 2 mild adverse events, both unrelated to device wear, and no elevations in IOP ≥ 10 mmHg. (See Section 4.4.2.1 for study details).
- **Endure (CP-X23; N=9)**: Two (2) adverse events occurred, neither of which was serious. One patient proceeded through screening but discontinued device wear after 45 minutes due to a headache, which resolved promptly after removal of the device; this patient was exited from the study. A corneal abrasion, with no associated loss in BCDVA (attributed to repeated IOP measurements during the 8-hour study) was also identified. The abrasion resolved with topical therapy. (See Section 4.4.2.3 for study details.)

An overview of safety findings from all 12 OPAP clinical studies of varying duration is provided in Table 1 of Appendix 9.3 for completeness.

6.9 Safety Conclusions

Over a year of regular, nightly use in the pivotal Artemis Study (Section 6), no serious or unanticipated device-related adverse events and no clinical findings reflective of damage to the structure and function of the optic nerve or anterior segment were observed. Furthermore, no assessments suggested a worsening in clinical outcomes (e.g., visual field loss or glaucomatous progression), during the year-long study.

As expected, ocular AEs (26.9% vs 14.0%) and periorbital AEs (18.3% vs 7.5%) were more common in study eyes, which received nightly NP application. However, no device-related AEs were serious, and all resolved without sequelae by the time of study completion or early discontinuation. The most frequently reported device-related AEs (occurring at a rate ≥ 5%) in study eyes vs control eyes were mild-to-moderate lid edema (11.8% vs 1.1%), periorbital edema (14.0% vs 2.2%), and periorbital contact dermatitis (5.4% vs 4.3%), all of which resolved without sequelae shortly after termination of device use. Two patients experienced mild-to-moderate periorbital contact dermatitis, which the investigator felt might have been a reaction to a material in the OPAP goggles. These patients discontinued, and the dermatitis resolved.

The only device-related non-ocular AEs were 2 reports of mild-to-moderate transient headache during device use and a reported rash on the upper left cheek; none of these events led to device discontinuation. Slit lamp examinations were unremarkable, with no reports of conjunctival chemosis, corneal epithelial defects, corneal edema, changes in iris appearance, or changes in anterior chamber angle. There was no significant IOP elevation after OPAP use. The dilated examinations and OCT imaging of fundus were unremarkable.

Visual field mean deviation (MD) values were stable during the study. Using SITA 24-2 testing, the study eye mean MD was -4.23 dB (SD 4.99) at baseline and -3.50 dB (SD 5.93) at Week 52. Similarly, the control eye mean MD was --4.05 dB (SD 4.93) at baseline and -3.35 (SD 6.30) at Week 52. A masked post hoc evaluation of available VF and OCT data by the University of Iowa VFRC for all patients who completed the study, as well as those 6 patients who completed 26 weeks of follow-up but did not complete the study, found no evidence of VF progression worse in one eye than the contralateral eye. Sponsor analysis of the VFRC's report concluded there was no evidence of VF progression worse in the study eye as compared with the control eye.

Safety results from the pivotal Artemis Trial are supported by 11 additional clinical studies of 584 eyes in 386 participants. There were no serious device-related AEs at any time, and all AEs considered device-related resolved without sequelae across all studies.

Ultimately, OPAP is an externally worn, removable device with a favorable safety profile.

7 BENEFIT-RISK CONCLUSIONS

OPAP is a noninvasive adjunctive therapy for reducing nocturnal IOP in patients with OAG and IOP ≤ 21 mmHg. OPAP reliably and consistently lowers IOP during use with minimal safety issues, all of which are manageable with standard supportive care and/or adjusted device use. Ultimately, OPAP provides an important adjunctive therapy for patients receiving inadequate IOP reduction with currently available treatments (Table 30).

Table 30: Benefit-Risk Assessment of FSYX™ OPAP for Adjunctive Treatment of Open-Angle Glaucoma and IOP ≤ 21 mmHg

Dimension	Evidence	Conclusions
Disease Overview, Open-Angle Glaucoma	• Glaucoma is a pressure-related neurodegeneration of the optic nerve that results in progressive visual field loss • Glaucoma causes more irreversible blindness in the US than any other disease ○ 3-to-5 million US adults are living with glaucoma, approximately 120,000 of whom have developed blindness due to glaucoma • Glaucoma is typically associated with elevated intraocular pressure; however, it may also be present in patients whose daytime IOP is in the normal range ≤ 21 mmHg • Nocturnal IOP elevations can lead to glaucomatous progression	Glaucoma represents the single most common cause of irreversible blindness in the US. Fundamentally, glaucoma is a progressive pressure-related disease of the optic nerve head, a sensitive microenvironment where the nerve connects to the retina

Current Treatment Options and Unmet Need	• Reducing IOP remains the only factor proven to slow or stop glaucomatous damage
	  ○ Treatments include topical medications, laser procedures, and surgeries
	  ○ Eyes with IOP ≤ 21 mmHg do not achieve the recommended ≥ 20% reduction as frequently as eyes with higher IOP
	• IOP reduction is also more difficult at night, when IOP is elevated
	  ○ Medications and lasers have demonstrated decreased efficacy at night
		Patients with OAG and IOP ≤ 21 mmHg need adjunctive treatments to further reduce IOP.
		These patients, despite a controlled daytime IOP, also have greater risk of disease progression at night, when current therapies have diminished efficacy.

Dimension	Evidence	Conclusions
OPAP Device Description	• OPAP is a noninvasive system, which includes a pair of removeable goggles that are connected via pneumatic tubing to a programmable pressure pump; the pump applies mild negative pressure (NP) over the treated eye(s) • Application of NP over the eye reduces IOP by approximately 40% – 60% of programmed pressure (i.e., NP of -10 mmHg equals ~4-6 mmHg reduction in IOP) • Healthcare providers can program each eye to receive a different NP; patients cannot independently adjust pressure settings • There are no implantable components, and device action stops upon removal of the goggles	OPAP is a noninvasive, non-implantable, externally worn system, available in multiple sizes that can be further adjusted to fit individual patients.
Effectiveness	• The pivotal Artemis Study (N=93) met its primary and secondary endpoints with clinically meaningful, statistically significant, and consistent IOP reductions in all eyes that received NP application o 58.1% vs 1.1% of study vs control eyes in mITT, achieved the primary endpoint of IOP reduced ≥ 20% during use at Week 52 in the clinic while seated o 63.4% vs 3.2% of study vs control eyes in the mITT, achieved the secondary endpoint of IOP reduced ≥ 20% during use at Week 52 while supine in the sleep lab o All study eyes had decreased IOP at each measurement (Weeks 0, 26, and 52) o Patients used OPAP an average of 5.5 hours/night, about 5 nights/week o 88.3% vs 1.7% of study vs control eyes, achieved in-clinic IOP reduction ≥ 20% at Week 52 in the Per-Protocol Population o 96.7% vs 5.0% of study vs control eyes, achieved mean sleep lab IOP reduction ≥ 20% at Week 52 in the Per-Protocol Population o At the Week 52 Sleep Lab, OPAP reduced mean IOP by 39.1% o A tipping-point analysis confirmed benefit among patients with missing data • Results were consistent regardless of age, sex, baseline number of glaucoma medications, previous IOP-lowering surgery, baseline IOP, and baseline cup-to-disc ratio • 10 clinical studies, including the pivotal Artemis Trial, demonstrated consistent reduction of IOP that is proportional to NP application	Study eyes in the pivotal Artemis Trial showed clinically meaningful and statistically significant reductions in IOP during device use at all time points and in all patients. Reducing nighttime IOP is critical for slowing glaucomatous progression, particularly in patients with daytime IOP in the normal range of ≤ 21 mmHg. OPAP offers an important adjunctive treatment for patients with IOP ≤ 21 mmHg.

Dimension	Evidence	Conclusions

Safety	• As expected in the pivotal Artemis Study, device-related ocular and periorbital AEs occurred more frequently in study vs control eyes: 34.4% vs 10.8%, respectively
	  ○ No device-related AEs were considered serious or unanticipated
	  ○ One patient-reported device-related AE was reported as severe (lid edema)
	  ○ All other device-related AEs were mild-to-moderate in severity
	  ○ All device-related AEs resolved without sequelae using standard supportive care and/or modified device use
	  ○ An independent reading center determined that there was no evidence of glaucoma progression in either study eyes vs control eyes
	• Two patients discontinued OPAP due to mild periorbital contact dermatitis, which resolved without sequelae shortly after discontinuation
	• Fundus and slit-lamp exams revealed no unexpected new or worsening findings of clinical significance
	• No serious or unexpected device-related adverse events have been reported in any of the 12 clinical studies, including the pivotal Artemis Trial, included in the OPAP clinical development program
		OPAP was safe and well tolerated. Over a year of regular, nightly use, there were no serious device-related AEs and no clinical findings reflective of damage to the structure and function of the optic nerve or anterior segment.

Conclusions	• Reducing IOP is the only proven approach to slowing glaucomatous progression for the 3-to-5 million US adults living with the disease • OPAP safely and effectively lowers IOP during use in patients with OAG and IOP ≤ 21 mmHg • Treatment with OPAP fulfills an important unmet need by reducing IOP at night when patients are particularly vulnerable	Noninvasive treatment with OPAP offers a safe and effective adjunct to current therapies for reliably lowering IOP in patients with OAG and daytime IOP ≤ 21 mmHg

AE=adverse event; BP=blood pressure; CSFp=cerebrospinal fluid pressure; IOP=intraocular pressure; MIGS=minimally invasive glaucoma surgery; OAG=open-angle glaucoma; OPAP=Ocular Pressure Adjusting Pump; OU=oculus uterque (both eyes).

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9 APPENDICES

9.1 Additional Effectiveness Data

9.1.1 IOP Measurement Schedule for Artemis Study Visits

Table 31: Artemis Study — IOP Measurement Schedule for Study Visits

Visit Measurement:	Goldmann Applanation Tonometry	Pneumatonometry (Excursion Tonometry)
Visit 1/1a (pre-randomization)		
Initial – prior to Excursion Goggles on	X[1]	X
Excursion Goggles on – prior to NP		X
Excursion Goggles on – during NP		X
After Excursion Goggles removal	X	
Visit 3 (Day 0)		
Initial – prior to Excursion Goggles on	X[1]	X
Excursion Goggles on – prior to NP		X
Excursion Goggles on – during NP		X
After Excursion Goggles removal	X	
Initial sleep lab (within 21 days of Day 0)[2]		
Initial – prior to Excursion Goggles on (supine)		X
Excursion Goggles on – prior to NP		X
Excursion Goggles on – during NP		X
After Excursion Goggles removal (supine)		X
Visit 4 (Week 6)	X	
Visit 5 (Week 12)	X	
Visit 6 (Week 26)		
Initial – prior to Excursion Goggles on	X	X
Excursion Goggles on – prior to NP		X
Excursion Goggles on – during NP		X
After Excursion Goggles removal	X	
Visit 7 (Week 38)	X	
Final sleep lab (prior to Week 52)[2]		
Initial – prior to Excursion Goggles on (supine)		X
Excursion Goggles on – prior to NP		X – Secondary Endpoint
Excursion Goggles on – during NP		X – Secondary Endpoint
After Excursion Goggles removal (supine)		X
Visit 8 (Week 52)		
Initial – prior to Excursion Goggles on	X[1]	X
Excursion Goggles on – prior to NP		X – Primary Endpoint

Visit Measurement:	Goldmann Applanation Tonometry	Pneumatonometry (Excursion Tonometry)
Excursion Goggles on – during NP		X – Primary Endpoint
After Excursion Goggles removal	X	

IOP=intraocular pressure; NP=negative pressure.
1. For Initial IOP assessments, Goldmann tonometry was always performed prior to pneumatonometry.
2. IOP measurements were taken at 11:00 p.m. ± 1 hr. (after ≥ 30 minutes of NP application), 2:00 a.m. ± 1 hr., and 5:00 a.m. ± 1 hr., and a mean sleep lab IOP was calculated using the 3 measurements.

9.2 Additional Safety Data

9.2.1 Summary of AEs Reported During Run-in Period

A total of 9 patients in the Artemis Study experienced 15 AEs during the device use run-in period, when both eyes received NP of -5 mmHg for 7 days, followed by eye-specific NP for the next 7 days (Table 32). None of the AEs reported during the run-in period were serious, and the 1 severe AE (facial swelling due to abscessed teeth) was not related to device use. Because eyes were not randomized during this time, and several participants exited the study prior to randomization for a variety of reasons, AEs are reported individually, rather than tabulated.

Table 32: Adverse Events Reported During Device Use Run-in Period, before Randomization (Artemis Study)

Patient[1] Adverse Event:	Device Relatedness	Severity/ Expectedness	Outcome (Days after onset)
Patient 1			
Headache	Possibly related	Mild/ Expected	Resolved without sequelae (7 days)
Patient 2			
Myokymia left-lower lid	Possibly related	Mild/ Expected	Resolved without sequelae (30 days)
Patient 3			
Periorbital edema	Related	Mild/ Expected	Resolved without sequelae (33 days)
Periorbital edema	Related	Mild/ Expected	Resolved without sequelae (33 days)
Patient 4			
Headache	Possibly related	Mild/ Expected	Resolved without sequelae (97 days)
Basal cell carcinoma left-back, right clavicle	Not related	Moderate/ Unexpected	Resolved without sequelae (0 days)
Patient 5			
Abrasion on nose bridge, right side, next to right eye	Related	Moderate/ Unexpected	Resolved without sequelae (10 days)

Patient[1] Adverse Event:	Device Relatedness	Severity/ Expectedness	Outcome (Days after onset)
Periorbital contact dermatitis	Possibly related	Mild/ Expected	Unknown
Periorbital contact dermatitis	Possibly related	Mild/ Expected	Unknown
Patient 6			
Planned hospitalization for back/nerve pain	Not related	Mild/ Expected	Resolved without sequelae (1 days)
Patient 7			
Mild meibomian gland dysfunction	Not related	Mild/ Unexpected	Resolved without sequelae (7 days)
Patient 8			
Severe left side facial swelling, abscess of 2 teeth	Not related	Severe/ Unexpected	Unresolved but stable at exit (10 days)
Patient 9			
Headache	Related	Moderate/ Expected	Resolved without sequelae (0 days)
Periorbital pain	Related	Mild/ Expected	Resolved without sequelae (0 days)
Periorbital pain	Related	Mild/ Expected	Resolved without sequelae (0 days)

AE=adverse event.
Note: Participant eyes were not yet randomized during the run-in period, during which time both eyes received -5 mmHg of negative pressure nightly for one week, followed by eye-specific NP for a second week.
1. Patient numbering does not reflect study identification numbers. This table summarizes data originally submitted to FDA in Listing 34.1 in CP-X19 CSR.

9.2.2 Discussion of Ocular AEs Reported in Artemis Study

Lid Edema

One patient (1/93 [1.1%]) reported severe lid edema and discontinued due to multiple AEs (mild periorbital contact dermatitis, mild visual disturbance in the absence of BCDVA change in study eye, and moderate abrasion on the left side of the nose), all of which resolved without sequelae.

- This patient reported severe lid edema in the study eye during home-use of the device approximately 4 months after randomization (NP had been programmed to -14 mmHg since the initial sleep lab), suspended device use temporarily, and considered the AE resolved 8 days later. Upon resuming device use, she reported moderate lid edema, and device use was again discontinued. Lid appearance returned to baseline within one week. This patient terminated study participation before the Week 26 visit.

Conjunctival Hyperemia

Four study eyes had conjunctival hyperemia, three mild and one moderate. The moderate case was secondary to a possible allergic reaction to netarsudil/latanoprost ophthalmic solution, an

eye drop medication the patient had started approximately 3 months before beginning OPAP treatment. This patient terminated use of netarsudil/latanoprost, and the condition resolved within 4 weeks without sequelae.

Eye Pain

Transient pain in the study eye believed related to NP settings during device wear was reported in 3 study eyes:

- One patient reported mild, intermittent eye pain with NP setting of –15 mmHg about one hour into each treatment period. This patient reduced the device wear schedule to approximately 3 hours nightly for the duration of the study. Pain resolved with discontinuation of device use after study completion.
- Two patients who reported moderate eye pain noted pain resolution within 4 days of reducing NP settings (from –16 mmHg to –12 mmHg and from –11 mmHg to –9 mmHg) and initiating use of artificial tears. Both patients completed the 52-week- study.

BCDVA Decrease ≥ 10 Letters

Four patients experienced a temporary decrease in BCDVA ≥ 10 total letters read (TLR) from Baseline (Day -14): two in the study eye and two in the control eye. All patients with ≥ 10 TLR resolved.

BCDVA decreases in study eyes:

- One patient had BCDVA of 20/20 (55 TLR) in the study eye and 20/16 (59 TLR) in the control eye at Baseline (Day -14). At the Day 0 Visit (immediately before randomization), BCDVA was 20/25 (50 TLR) in both eyes, and 1+ anterior basement membrane dystrophy (ABMD) OU was noted on slit lamp. At the Week 6 Visit, study eye BCDVA was 20/32 (45 TLR), and control eye was 20/25 (50 TLR read). This patient's BCDVA varied between 20/25 and 20/32 in the study eye and between 20/20 and 20/25 in the control eye for the remainder of the 52-week study period.
- One patient had BCDVA 20/25 (49 TLR) in the study eye and 20/160 in the control eye at Baseline (Day -14). At the Week 26 Visit, study eye BCDVA was 20/80 (14 TLR), with 1+ SPK and 1+ ABMD noted OU. At the Week 38 Visit, ABMD OU was unchanged, but study eye BCDVA had returned to 20/40 (40 TLR). At the Week 52 Visit, study eye BCDVA was 20/25 (50 TLR).

BCDVA decreases in control eyes:

- One patient had control eye BCDVA of 20/32 (44 TLR) at Baseline (Day -14) and 20/50 (34 TLR) approximately 1 month after randomization. The patient had contracted severe COVID-19 approximately 20 days prior and withdrew consent for study participation at this visit. At a clinic visit approximately 6 months later, BCDVA in this eye had returned to baseline.
- One patient, whose control eye BCDVA was 20/20 (55 TLR) at Baseline (Day -14), was measured with BCDVA 20/32 (45 TLR) at Week 52 in the presence of 1+ blepharitis and conjunctival hyperemia. At a follow-up visit 8 weeks later, control eye BCDVA was 20/20.

9.2.3 Discussion of Periorbital AEs Reported in Artemis Study

Periorbital Edema

Moderate periorbital edema occurred in the study eye of two patients:

- One patient experienced moderate periorbital edema, periorbital pain, and headache after the first sleep lab visit, where the programmed NP was increased from -10 mmHg (set at Day 0) to -16 mmHg based on the sleep lab baseline IOP (supine). The AE was downgraded to mild after NP was returned to -10 mmHg. The edema, pain, and headache resolved within one week, and the patient completed the 52-week study.
- One patient reported moderate periorbital edema with NP setting of -6 mmHg at the Week 6 visit. The AE resolved by the Week 12 Visit after a temporary discontinuation of device use, followed by a gradual increase in NP application. Shortly thereafter, this patient withdrew consent and exited the study.

Periorbital Contact Dermatitis

All cases of periorbital contact dermatitis were mild, resolving with nothing more than over-the-counter-- medication for management.

Periorbital Pain

Periorbital pain associated with device use was reported by two patients: one who completed the study (see first bullet in periorbital edema discussion) and another who reported mild periorbital pain OU following NP treatment at -8 mmHg. This patient subsequently withdrew.

Nasal Abrasion

One patient presented with a moderate abrasion on the nose bridge between the study eye and the nose approximately 20 weeks after randomization. OPAP use was discontinued, and resolution was noted at a visit 2 weeks later. This patient withdrew consent and exited the study.

9.2.4 Vertical Cup-to-Disc Ratio Findings in Artemis Study

Table 33: Vertical Cup-to-Disc Ratio Findings (Artemis, Safety Population)

	Baseline (Day -14)		Week 26		Week 52	
Outcome:	**Study (N=93)**	**Control (N=93)**	**Study (N=68)**	**Control (N=68)**	**Study (N=62)**	**Control (N=62)**
Mean (SD)	0.7 (0.2)	0.7 (0.2)	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)	0.7 (0.2)
Median (min, max)	0.7 (0.3, 1)	0.7 (0.1, 1)	0.7 (0.4, 1)	0.7 (0.3, 1)	0.7 (0.4, 1)	0.7 (0.3, 1)
Change from baseline, n (%)						
No change from Baseline			62 (91.2)	60 (88.2)	52 (83.9)	51 (82.3)
Decrease from Baseline			2 (2.9)	4 (5.9)	4 (6.5)	5 (8.1)
≤ 0.3 increase from Baseline			4 (5.9)	4 (5.9)	6 (9.7)	6 (9.7)
> 0.3 increase from Baseline			0	0	0	0

SD=standard deviation.

9.3 Detailed Summaries of Previous Clinical Investigations

Table 34: Summary of Clinical Study Designs and Findings in the OPAP Development Program

Study Purpose Study Name:	Device	Study Design
Proof of concept and IOP measurement methodology		
CP-XXX: EyeMate 1	GEN 0	• Ramp-up/down of NP in OAG • 20-60 min of NP up to -10 mmHg • Conclusions: Each participant showed a titratable effect of the NP application on IOP. There were no adverse events. NP application with OPAP can safely lower IOP in a titratable fashion.
CP-XX1: Short-Term Safety*	GEN 0	• Open-label, non-randomized in healthy volunteers • 30-min application of NP (-15 mmHg) in study eye vs control in contralateral eye • Conclusions: OPAP was safe and well tolerated up to 1 week after 30-minute exposure. Key safety parameters remained stable, and no AEs were reported. Results supported the safety profile.
CP-XX4: EyeMate 2	GEN 1	• Open-label, non-randomized in OAG patients with previously implanted IOP measuring devices • 8-hr continuous NP application • Conclusions: IOP decreased an average of 20% from baseline during 8-hour continuous NP application
CP-XX5: Titratable IOP Reduction Study*	GEN 1	• Open-label, randomized, controlled in healthy patients • Patients randomized to no NP for 60 mins vs 25%, 50%, or 75% of baseline IOP for 20 mins • Conclusions: The differences between mean IOPs of study vs control groups were significantly different at all NP settings ($p < 0.001$) in comparison with baseline. IOP is titratable by applying additional negative pressure. One minor AE (corneal abrasion) occurred during IOP measurement.
CP-XX6: 8-Hour Safety*	GEN 1	• Open-label, randomized, controlled in OAG and Glaucoma Suspects • Eyes randomized to 8 hrs of -10 mmHg NP in study eye vs contralateral control eye • Conclusions: OPAP was safe and well tolerated, with key parameters remaining stable after 8 hrs of continuous NP. One AE (headache) occurred and resolved before end of study.

Study Purpose Study Name:	Device	Study Design
CP-XX7: Overnight Safety Study*	GEN 1	• Open-label, randomized, controlled in OAG, including treated glaucoma • Eyes randomized to 7 nights of -10 mmHg NP in study eye vs none in contralateral control eye • Conclusions: IOP decreased an average of 20.1% from baseline during NP application, in addition to concomitant therapies, after 1 week of nightly wear.
CP-X13: Pilot Study	GEN 2A	• Prospective, randomized, controlled, in OHTN, glaucoma suspect, or OAG in both eyes • Eyes randomized to NP of 50% of BL IOP in study eye vs contralateral control eye nightly for 4 weeks • Conclusions: 53.8% of study vs 38.5% of control eyes achieved IOP reduction ≥ 20%, not statistically significant. All AEs resolved without sequelae. Results informed design modifications to improve fit and comfort during NP application.
Effect of NP on ocular physiology		
Short-Term Pattern ERG Changes with NP Application	GEN 1	• Randomized, controlled in OHTN, glaucoma suspect, or mild OAG • Eyes randomized to NP of 50% of BL IOP for 2 hrs in study vs contralateral control eye, then assessed with steady-state pattern-electroretinogram (ERG) to assess retinal ganglion cell function • Conclusions: The MagnitudeD (MagD) change from BL in study vs control eyes was +0.17 vs -0.26. The change in MagD:Mag ratio was +0.14 vs -0.16.
Laser Speckle Flowgraphy Blood Flow	GEN 2B	• Interventional assessment of blood flow around ONH using laser speckle flowgraphy before, during, and after -15 mmHg NP in healthy and glaucomatous eyes • Assessments taken at: BL; minutes 1, 2, 3, 4, 5 during NP; and 3 mins after NP application • Conclusions: Glaucomatous eyes showed sustained increased blood flow during NP application to retinal arterioles, ONH tissue, peripapillary choroid, and outside watershed zone of > 20%.
OCT-A Capillary density	GEN 2B	• Assess circumpapillary retinal nerve fiber layer using OCT and capillary density using OCT-A in glaucoma • Assessments at: BL; 2 mins after NP application of -5, -10, -15, and -20 mmHg; then after return to BL • Conclusions: Circumpapillary capillary density measurements showed a dose-dependent increase during NP application, while retinal nerve fiber layer thickness measurements were unchanged.

Study Purpose Study Name:	Device	Study Design
Metabolic Changes Using Flavoprotein Fluorescence	GEN 2B	• Comparative case-series assessment of retinal thickness, retinal vascular density, and peripapillary metabolic profile in mild-to-severe OAG, using flavoprotein fluorescence (FPF) • Assessments taken at BL; 1 hour after NP application; and after 1 month of nightly use • Conclusions: FPF scores at the ONH rim improved from mean (SD) 12.7 (± 11.6) to 10.5 (± 7.5; p=0.04) during NP application; retinal nerve fiber layer scores trended better after 1 month of use, increasing from mean 69.5 to 72.0 (not statistically significant; p=0.1); vascular parameters observed using OCT-A remained unchanged at 1 hour and 1 month. All AEs were transient and resolved after removing OPAP.
Randomized, controlled studies of current device configuration		
CP-X18: Feasibility Study*	GEN 2A	• Controlled, randomized feasibility of lowering nocturnal IOP in OAG treated with prostaglandin • For each patient, eyes with highest supine IOP received NP at 60% of BL vs contralateral control eye • IOP assessments taken at 10:30 pm, 2:00 am, and 5:30 am for 1 night • Conclusions: IOP reduced by a mean 35% (p=0.001) during NP application. There were no device-related AEs and no IOP spikes ≥ 10 mmHg.
CP-X10: Apollo*	GEN 2B	• Prospective, randomized, controlled, assessor-masked trial in OAG, glaucoma suspect, or OHTN (required BL IOP: ≥ 13 to ≤ 32 mmHg) • Nightly use for 90 days • 116 Eyes randomized to NP application vs contralateral control eye • Primary effectiveness endpoint: proportion of eyes with ≥ 20% reduction in IOP at Day 90 • Conclusions: 81.3% of study vs 3.1% of control eyes achieved IOP reduction ≥ 20% at Day 90. In eyes with BL IOP ≤ 21 mmHg that received NP application (study eyes; N=38), IOP reduced by 35% during NP application. There were no serious device-related AEs.
CP-X19: ARTEMIS	GEN 2B	• Prospective, randomized, controlled, assessor-masked trial in normal-tension glaucoma for 1 year • Eyes randomized to receive nightly NP application in study eye vs contralateral control eye; primary effectiveness endpoint was proportion of eyes with ≥ 20% reduction in IOP at ~50% NP application • Conclusions: OPAP safely lowers IOP during use in patients with NTG. The primary and secondary efficacy endpoints were met: 58.1% and 63.4% of study vs 1.1% and 3.2% of control eyes achieved IOP reduction ≥ 20% at Week 52, as measured in-clinic and in the sleep lab, respectively. The

Study Purpose Study Name:	Device	Study Design
		safety profile was favorable with no device-related SAEs, and all device related AEs resolved without sequelae prior to or at the time device use was discontinued.
CP-X22: RANGER (Severe OAG)[1]	GEN 2B	• Prospective, randomized, controlled, assessor-masked study in severe OAG (POAG, NTG, and pseudoexfoliative glaucoma allowed) • 1 hr NP application at 50%, and 1 hr NP application at 75% of BL IOP • Eyes randomized to NP application vs contralateral control eye; primary effectiveness endpoint was proportion of eyes with ≥ 20% reduction in IOP at 50% NP application after 1 hour of use • Conclusions: Mean IOP reductions in study eyes were 24.4% and 31.9% from BL when NP was applied at 50% and 75% of BL IOP, respectively. There were three mild-to-moderate AEs, which were transient and resolved without sequelae. There were no serious AEs.
CP-X23: Endure	GEN 2B	• Prospective, randomized, controlled, assessor-masked study in OAG (required BL IOP: ≥ 15 to ≤ 22 mmHg) • One 8-hr NP application • Eyes randomized to NP applied at 60% of BL IOP vs contralateral control eye • Five IOP measurements taken: At BL, plus four more at 2-hr intervals during NP application • Conclusions: IOP reduction is sustained during uninterrupted NP application for 8 hours. Mean IOP reduction was 32% from BL during 8 hours of NP application. Mean IOP reduction was ≥25% for all five measurements. All study eyes had IOP reduction during NP application. There were two AEs: mild-to-moderate headache, which resolved after removing OPAP, and mild corneal abrasion, which was attributed to repeated IOP measurements.

BCDVA=best-corrected distance visual acuity; BL=baseline; Dev. Gen.=device generation; hr=hour; IOP=intraocular pressure; min=minutes; NP=negative pressure; OAG=open-angle glaucoma; OCT-A=optical coherence tomography angiography; OHTN=ocular hypertension; ONH=optic nerve head; POAG=primary open-angle glaucoma; RNFL=retinal nerve fiber layer.
1. Severe OAG was defined as having glaucomatous optic disc or RNFL abnormalities AND visual field abnormalities in both hemifields and/or loss within 5 degrees of fixation in at least one hemifield as tested with standard automated perimetry.
* Indicates the study has been published in peer-reviewed literature.

Table 35: Summary of Negative Pressure Settings and Corresponding IOP-Lowering Results (All IOP Measuring Clinical Studies)

Device	Study Identifier	Ocular Condition	Participants Enrolled/ Completed (N)	Total Number of Eyes	# Eyes with IOP ≤ 21 mmHg	IOP Measurement Technique	NP Setting (mmHg or % of BL)	Mean Baseline IOP (mmHg)	% Vacuum of Baseline IOP	Mean IOP During NP (mmHg)	% IOP Reduction During NP	% IOP Reduction to NP Applied
TOTAL	**10 studies**		**340/297**	**584**	**518**							
GEN0	CP-XXX: EyeMate 1	OAG	3/3	3	2	Implanted wireless IOP Sensor	-10 mmHg	16.5	61%	10.9	34%	56%
GEN0	CP-XX4: EyeMate 2	OAG	6/5	5	2	Implanted wireless IOP Sensor	50%	21.0	50%	16.7	20%	41%
GEN1	CP-XX7: Overnight Safety*	OAG	10/10	10	8	Excursion	-10 mmHg	18.2	55%	14.0	23%	42%
GEN1	CP-XX5: Titratable IOP Reduction*	Healthy volunteers	65/65	65	62	Excursion	25%	15.8	25%	13.5	15%	58%
							50%	15.8	50%	11.5	27%	54%
							75%	15.8	75%	10.2	35%	47%
GEN2A	CP-X13: Pilot	OAG	15/13	30	24	Excursion	50%	20.7	50%	15.9	23%	46%
GEN2B	CP-X18: Feasibility*	OAG	11/11	22	22	Excursion	60%	22.2	60%	14.2	36%	60%
GEN2B	CP-X10: Apollo*	OAG, OHT, glaucoma suspect	64/58	128	95	Excursion	60%	19.4	60%	12.9	34%	56%
GEN2B	CP-X23: Endure	OAG	10/9	9	9	Excursion	60%	21.4	60%	14.4	33%	55%
GEN2B	CP-X19: ARTEMIS	NTG	93/62	186	186	Excursion	Reference IOP of 6 mmHg	18.0	66%	11.4	36%	55%
GEN2B	CP-X22: RANGER	Severe OAG	63/61	126	108	Excursion	50%	17.6	50%	13.3	24%	49%
							75%	17.6	75%	11.9	32%	43%

IOP=intraocular pressure; NP=negative pressure; OAG=open-angle glaucoma; OHT=ocular hypertension.
* Indicates the study has been published in the peer-reviewed literature.

Table 36: Summary of Device-Related Adverse Events (All Clinical Studies)

Device	Study Identifier	Ocular Condition	Participants (N)	Total Number of Eyes	Study Setting and Duration	# Device-Related SAEs	# Device-Related AEs	# Study Eyes with Device-Related AE	# Control Eyes with Device-Related AE	Participants with Device-Related AE, n (%)
TOTAL	**12 Studies**		**378**	**634**		**0**	**155**	**61**	**34**	**82**
GEN0	CP-XXX: EyeMate 1	OAG	3	3	Daytime Clinic: 1 Hour	0	0	0	N/A	0 (0%)
GEN0	CP-XX4: EyeMate 2	OAG	5	5	Overnight Clinic: 8 Hours	0	11	4	1	4 (80%)
GEN0	CP-XX1: Short-Term Safety*	Healthy volunteers	30	30	Daytime Clinic: 1 Week	0	0	0	0	0 (0%)
GEN1	CP-XX6: 8-Hour Safety*	OAG Glaucoma Suspect	10	20	Daytime Clinic: 1 Week	0	1	0	0	1 (10%)
GEN1	CP-XX7: Overnight Safety*	OAG	10	10	Daytime Clinic: 1 Week	0	3	1	0	3 (30%)
GEN1	CP-XX5: Titratable IOP Reduction*	Healthy volunteers	65	65	Daytime Clinic: 1 Hour	0	1	1	0	1 (2%)
GEN2A	CP-X13: Pilot	OAG	15	30	Daytime Clinic: 28 Days	0	23	5	4	9 (60%)
GEN2B	CP-X18: Feasibility Study*	OAG	11	22	Overnight Clinic: 1 Day	0	0	0	0	0 (0%)
GEN2B	CP-X10: Apollo*	OAG, OHT, Glaucoma suspect	64	128	Daytime Clinic: 90 Days	0	54	22	15	27 (42%)
GEN2B	CP-X19: ARTEMIS	NTG	93	186	Overnight Clinic: 1 Year	0	57	26	13	32 (34%)
GEN2B	CP-X23: Endure	OAG	9	9	Daytime Clinic: 1 Day	0	2	1	0	2 (22%)
GEN2B	CP-X22: RANGER	Severe OAG	63	126	Daytime Clinic: 1 Day	0	3	1	1	3 (5%)

AE=adverse event; IOP=intraocular pressure; NP=negative pressure; OAG=open-angle glaucoma; OHT=ocular hypertension.
* Indicates the study has been published in the peer-reviewed literature.

Table 37: Summary of Device-Related Adverse Events in Eyes with Baseline IOP ≤ 21 mmHg (All Clinical Studies)

Device	Study Identifier	Ocular Condition	Participants (N)	# Eyes IOP ≤ 21 mmHg	Setting	# Device-Related SAEs	# Study Eyes with Device-Related AE	# Control Eyes with Device-Related AE
TOTAL	**12 Studies**		**339**	**564**		**0**	**56**	**28**
GEN0	CP-XXX: EyeMate 1	OAG	2	2	Daytime Clinic: 1 Hour	0	0	N/A
GEN0	CP-XX4: EyeMate 2	OAG	2	2	Overnight Clinic: 8 Hours	0	2	N/A
GEN0	CP-XX1: Short-Term Safety*	Healthy volunteers	29	29	Daytime Clinic: 1 Week	0	0	0
GEN1	CP-XX6: 8-Hour Safety*	OAG Glaucoma Suspect	9	17	Daytime Clinic: 1 Week	0	0	0
GEN1	CP-XX7: Overnight Safety*	OAG	8	8	Daytime Clinic: 1 Week	0	1	0
GEN1	CP-XX5: Titratable IOP Reduction*	Healthy volunteers	62	62	Daytime Clinic: 1 Hour	0	1	0
GEN2A	CP-X13: Pilot	OAG	13	24	Daytime Clinic: 28 Days	0	5	3
GEN2B	CP-X18: Feasibility Study*	OAG	11	22	Overnight Clinic: 1 Day	0	0	0
GEN2B	CP-X10: Apollo*	OAG, OHT, Glaucoma suspect	47	95	Daytime Clinic: 90 Days	0	19	11
GEN2B	CP-X19: ARTEMIS	NTG	93	186	Overnight Clinic: 1 Year	0	26	13
GEN2B	CP-X23: Endure	OAG	9	9	Daytime Clinic: 1 Day	0	1	0
GEN2B	CP-X22: RANGER	Severe OAG	54	108	Daytime Clinic: 1 Day	0	1	1

AE=adverse event; IOP=intraocular pressure; NP=negative pressure; OAG=open-angle glaucoma; OHT=ocular hypertension.
* Indicates the study has been published in the peer-reviewed literature.

9.4 White Paper: Review of the Pressure Relationships Created by the Multi-Pressure Dial

Alex Huang MD, Ross Ethier PhD, Randy Kardon MD, PhD, Leon Herndon MD, William Morgan MD, Tom Samuelson MD, Robert N. Weinreb MD

Elevated intraocular pressure (IOP) is the primary risk factor for glaucoma, and reduction of IOP is the only known therapeutic maneuver that can mitigate this risk. Historically, IOP has been determined using various methods that usually measure ocular biomechanics. The Multi-Pressure Dial (MPD) is a novel, non-invasive and non-pharmacological device that employs a negative pressure (vacuum) to reduce the local air pressure within a goggle chamber covering the eye, thereby lowering IOP relative to the atmosphere while worn. By temporarily creating a distinct pressure chamber over the eye, the MPD's mechanism of action has presented new questions about the characterization of conventional IOP measurements and their relationship to other pressure measurements. Assessing the physiological response of the eye to pressure lowering with the MPD helps address these questions and deepens our understanding of the fundamental relationship between IOP and glaucoma.

Terminology

In glaucoma, much of the established pressure-relevant terminology has reflected the commonly used methodologies to determine IOP. The resultant lack of precise terminology to characterize eye pressure measurements has led to some confusion. Clear definitions, as provided below, can alleviate the confusion. These definitions include:

Pressure: The compressive normal force that is applied per unit surface area
Absolute pressure: A pressure that is referenced to a perfect vacuum (0 mmHg)
Atmospheric pressure: The "absolute pressure" of the atmosphere, which surrounds and affects the entire body. Atmospheric pressure is ~760 mmHg at sea level.
Gauge Pressure: A pressure that is referenced to the surrounding atmospheric pressure. All clinical measurements of bodily pressures are referenced to atmospheric pressure surrounding the body.
Intraocular Pressure (IOP): The pressure inside the eye referenced to atmospheric pressure. Note that this is a gauge pressure, so that at sea level an IOP (or gauge IOP) of 20 mmHg is equivalent to an absolute IOP of 780 mmHg (20 + 760 mmHg).
Absolute IOP: The IOP referenced to absolute vacuum.

Methods to Assess IOP

There are many methods that have been employed to assess IOP. Since the true gold-standard method (manometry) is invasive and not feasible in a clinical setting, non-invasive methods have been developed for routine clinical care. The transcorneal pressure difference (TCPD)-determined IOP is one such approach. Goldmann applanation tonometry is the gold standard non-invasive TCPD method used during clinical care. When using the MPD, TCPD and manometric determination of IOP must be carefully considered and reference pressures well defined.

Transcorneal pressure difference (TCPD)-determined IOP: In TCPD-determined IOP, the difference between the anterior chamber pressure and the pressure at the surface of the cornea is determined indirectly by applying a known force to a given area on the cornea and assessing corneal biomechanical features. TCPD-determined IOP is a gauge pressure that includes several approaches such as Goldmann applanation, rebound tonometry, and pneumatonometry. A key advantage is that these methods are non-invasive. TCPD-determined IOP is a clinically established endpoint associated with glaucoma progression. It also has been shown in numerous studies that lowering this pressure will reduce the rate of glaucoma progression. Moreover, in all these studies, the TCPD-determined IOP was always

referenced to atmospheric pressure. The disadvantage of these approaches is that IOP is not actually being measured because the true measured endpoint is a corneal biomechanical response to the gauge pressure differential.

Manometry-determined IOP: In manometry-determined IOP, the difference in pressure inside the eye compared to outside the eye is directly measured via cannulation of an intraocular space that is always referenced to atmospheric pressure. This invasive approach directly measures IOP within the eye and represents the gold-standard for determining gauge IOP and absolute IOP.

The Normal Circumstance

In the absence of goggles or other external pressure manipulation, TCPD-determined IOP is referenced to atmospheric pressure and normally co-varies with manometric-determined IOP. For example, consider a case at sea level where a person with an IOP of 20 mmHg increases *by* 10 mmHg. This means that the absolute IOP changes from 780 to 790 mmHg (780 + 10 = 790 mmHg). In this case, a manometric technique would directly measure an increase of 10 mmHg, referenced to the atmosphere. For TCPD- determined IOP, as in Goldman applanation, the increase of 10 mmHg will alter corneal biomechanics such that an approximate 10 mmHg increased TCPD-determined IOP referenced to atmospheric pressure is measured. Because of this co-varying relationship, there has never been the need to assess whether it was actually TCPD- or manometry-determined IOP that mattered for glaucoma risk.

Normal circumstance (no goggles)

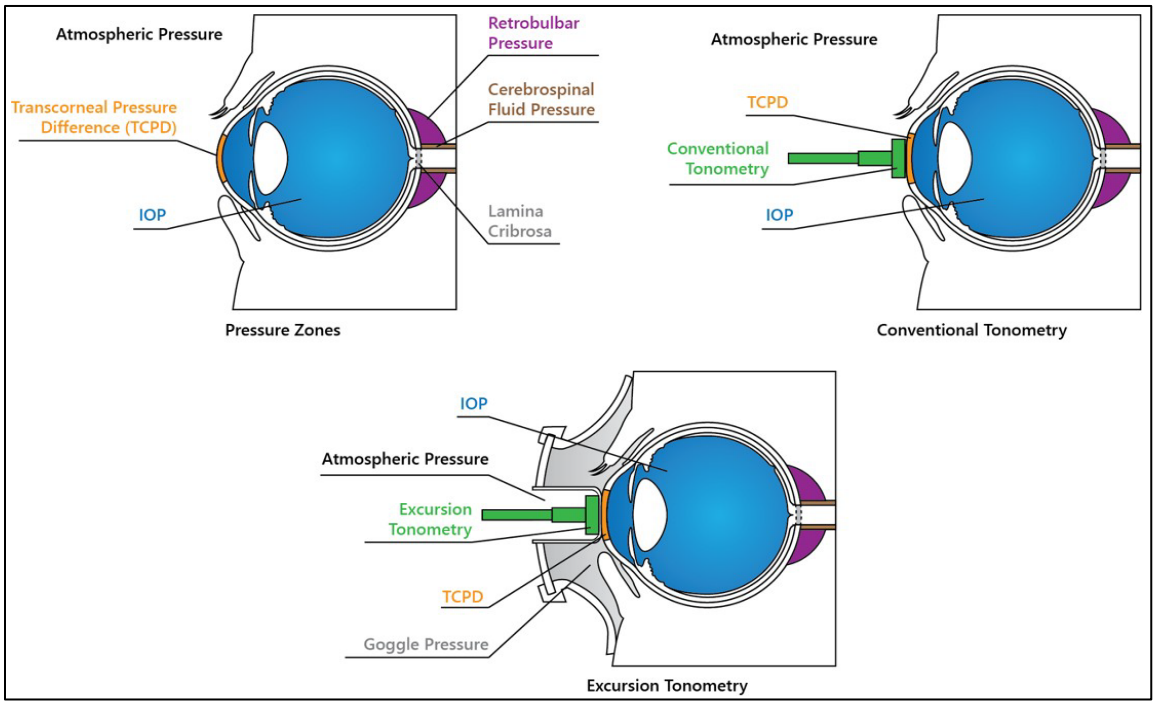
As manometry-determined IOP decreases… TCPD-determined IOP decreases as manometry-determined IOP increases… TCPD-determined IOP increases NOTE: TCPD-determined IOP in these examples are referenced to atmosphere.

The Impact of External Pressure Alteration and the Impact of a Goggle-based System

The use of external extraocular forces to manipulate IOP has been in use for many years.

Ophthalmodynanometry (CPT code 92260) applies positive pressure as an external force to the globe to increase IOP relative to atmospheric pressure and determine the pressure within ophthalmic blood vessels. Conversely, the MPD uses external negative pressure as a way for external forces to lower IOP referenced to atmospheric pressure. However, application of extraocular forces, specifically negative pressure, creates an apparent paradox which requires better specificity of current terminology to improve our understanding of the relationship of IOP to glaucoma.

Figure 1 - A novel method to approximate Goldmann applanation was developed to measure TCPD relative to atmospheric pressure while maintaining a vacuum in the goggles.



The MPD uses goggles attached to a vacuum-modulating pump to apply negative external forces over the front surface of the eye and orbit in an isolated vacuum space separate from atmospheric pressure. To evaluate the IOP-lowering effects of the MPD, a novel measurement method was developed to best approximate Goldmann applanation tonometry, which was necessary because the goggles blocked direct ocular surface access needed for conventional tonometry. A specially adapted version of the goggles with access ports (i.e., holes) on the lenses was created, through which a silicone tube fitted with a loose latex membrane (i.e., Tonopen tip cover) could be inserted and positioned to lay on the surface of the cornea. This adaptation allowed applanation of the cornea with a model 30 pneumatonometer during negative pressure application while maintaining the vacuum in the goggles (Figure 1). Since this approach of applanation across the latex membrane measures the TCPD referenced to atmosphere, it most closely approximates Goldmann applanation which also measures TCPD referenced to atmosphere.
Using this method, consistent with our unpublished pivotal study[i], some peer-reviewed published studies showed:

Study 1 (65 normal healthy volunteers)[ii]:
-Baseline TCPD-determined IOP measured using a pneumatonometer was 15.8 mmHg, without goggles.
-An external vacuum was placed in front of the eye at negative pressure of 11.9 mmHg.
-Using the access port, pneumatonometry measurements resulted in a TCPD-determined IOP relative to atmosphere of 10.2 mmHg which was ~6 mmHg (15.8-10.2 = 5.6) lower than baseline, a 35% decrease.

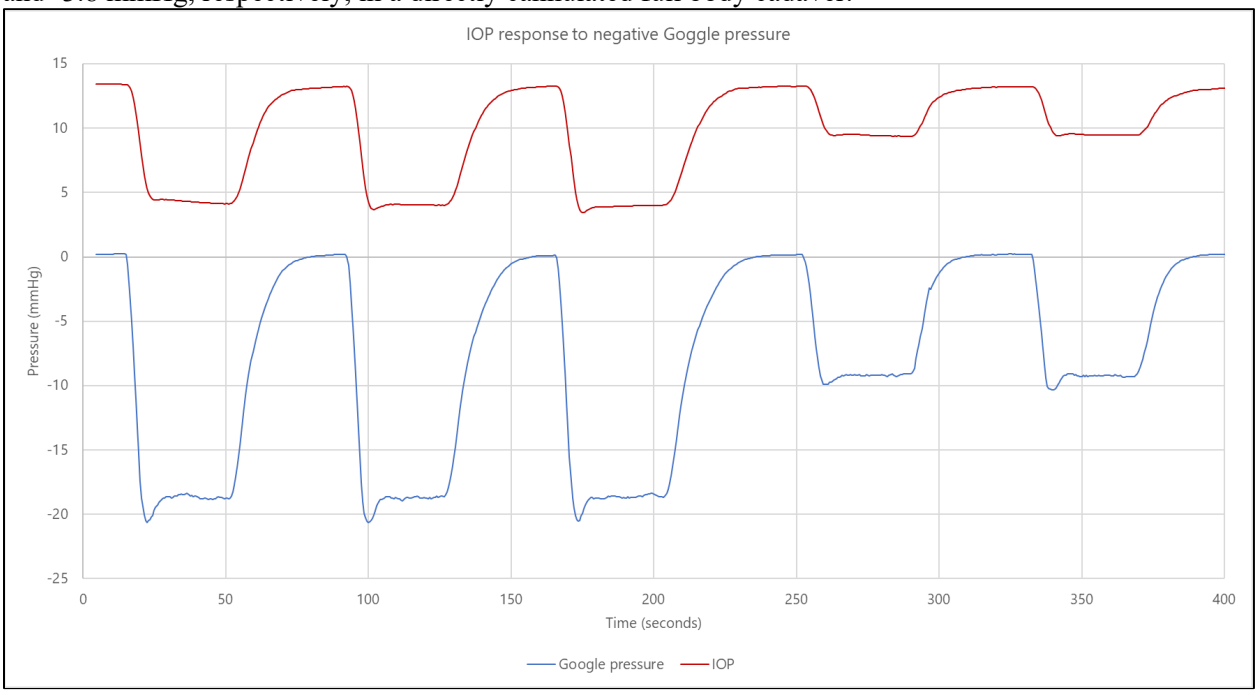
Study 2 (11 open angle glaucoma subjects[iii]):
-Baseline TCPD-determined IOP measured using a pneumatonometer was 22.2 mmHg, without goggles.
-An external vacuum was placed in front of the eye at 60% of baseline TCPD-determined IOP. This equates to an average negative pressure of ~13.3 mmHg.
-Using the access port, pneumatonometry measurements resulted in a TCPD relative to

atmospheric pressure of 14.2 mmHg which was 8.0 mm (22.2-14.2 = 8) Hg lower than baseline, a 36% decrease.

In summary, these studies demonstrated an average TCPD-determined IOP decrease of ~6 to 8 mmHg in response to ~12 to 13 mmHg of applied external negative pressure. This would imply that absolute IOP (if manometry was used) also decreased by ~6 to 8 mmHg. However, when the pneumatonometer was not being used and directly applanating the ocular surface through the latex membrane, TCPD within the goggles becomes a comparison between inside of the eye and the negative pressure air space in front of the cornea. This TCPD comparison is no longer referenced to the atmosphere, but rather to the vacuum air space. In this TCPD variant, since ~12 to 13 mmHg of applied external negative pressure was needed to result in a ~6 to 8 mmHg drop in the eye, the results indicate that TCPD relative to the airspace in the goggles actually increased (by 4 [as 12-8 = 4]] to 7 [as 13-6 = 7] mmHg). This is true as the absolute value pressure change in front of the eye in the vacuum air space (negative ~12 to 13 mmHg) was greater than the absolute value pressure change magnitude inside of the eye (negative ~6 to 8 mmHg) – as was discussed in a recent commentary.[iv]

Studies have also been performed with direct manometric determination of gauge and absolute IOP.[i] In an experiment utilizing a full body cadaver, the vitreous chamber was cannulated to obtain direct, manometric IOP measurements relative to atmosphere. Then, negative pressure was applied using the goggles. The results from a test run of one eye are illustrated below (Figure 2).

Figure 2: Application of -20 mmHg and -10 mmHg results in an average decreased IOP of -9.3 mmHg and -3.8 mmHg, respectively, in a directly cannulated full body cadaver.



Study 3 (Full Body Cadaver**):**
-Baseline manometry-determined IOP was set at approximately 13.3 mmHg (without goggles)
-Preset external vacuum pressures of 10 and 20 mmHg were applied in front of the eye (actual negative pressures achieved within the sealed goggles were 9.3 and 18.8 mmHg, respectively)
-Using the intraocular pressure transducer, average manometry-determined IOP was 9.5 and 4 mmHg.

-The respective decreases in manometry-determined IOP were respectively:

- -3.8 mmHg at 9.3 mmHg vacuum representing a 41% reduction
- -9.3 mmHg at 18.8 mmHg vacuum representing a 49% reduction

Applied vacuum (mmHg)	Manometry-determined IOP (Baseline = 13.3 mmHg)	Change in manometry-determined IOP (mmHg)	% Reduction
18.8	4	-9.3	49%
9.3	9.5	-3.8	41%

The results from Study 3 are consistent with those of Studies 1 and 2. In Study 3, there was no membrane and consideration of different types of TCPD referenced to atmosphere or the air space of the goggles in front of the cornea. The absolute value of IOP lowering achieved by the MPD was less than the absolute value of vacuum necessary to achieve it ($|-9.3| < |-18.8|$ and $|-3.8| < |-9.25|$ respectively). Therefore, while manometry-determined IOP and gauge IOP clearly lowered, the TCPD referenced to the air pressure in the goggles increased.

This apparent paradox arises because of different reference points for pressure. The normal co-varying relationship between TCPD-determined IOP when referenced to atmosphere and manometry-determined IOP is disrupted when considering TCPD referenced to the negative pressure air space within the goggle anterior to the cornea.

With Goggles and Negative pressure
As manometry-determined IOP, gauge IOP, and absolute IOP decreases… TCPD-determined IOP *decreases* when referenced to the atmosphere.
As manometry-determined IOP, gauge IOP, and absolute IOP decreases… TCPD-determined IOP *increases* when referenced to the air pressure within the goggle.

There may be some confusion with TCPD measurements in Studies 1, 2, and 3 because two different types of TCPD are being assessed. With the goggles on and when pneumatonometry is performed by applanating the cornea across the latex membrane, the TCPD-determined IOP is referenced to the atmosphere. However, with the goggles on and without acquisition of pneumatonometry data, the TCPD-determined IOP is now referenced to the vacuum space in front of the cornea via a calculation. Across all acquired data points, IOP referenced to the atmosphere ALWAYS decreases with negative pressure applied by the goggles. However, TCPD referenced to the vacuum space in front of the cornea increases. In summary:

Under negative pressure goggles:
-TCPD-determined IOP referenced to the atmosphere decreases (Studies 1 and 2)
-Manometry-determined IOP referenced to the atmosphere also decreases (Study 3)
-But, TCPD-determined IOP referenced to the vacuum air space of the goggles increases (Studies ,1 2, and 3)

Then Ultimately What Matters?
Ultimately what matters in glaucoma, the TCPD-determined IOP referenced to the air space of the goggles or to the atmosphere?

Clinical measures of bodily pressures (e.g., blood pressure, intracranial pressure, central venous

pressure, intrathoracic pressure, and eye pressure, etc.) are extremely important in medicine and always are referenced to atmospheric pressure. Atmospheric pressure surrounding the body, not the local pressures of adjacent tissues or compartments, is the reference point because all bodily compartments are subject to atmospheric pressure at all times.

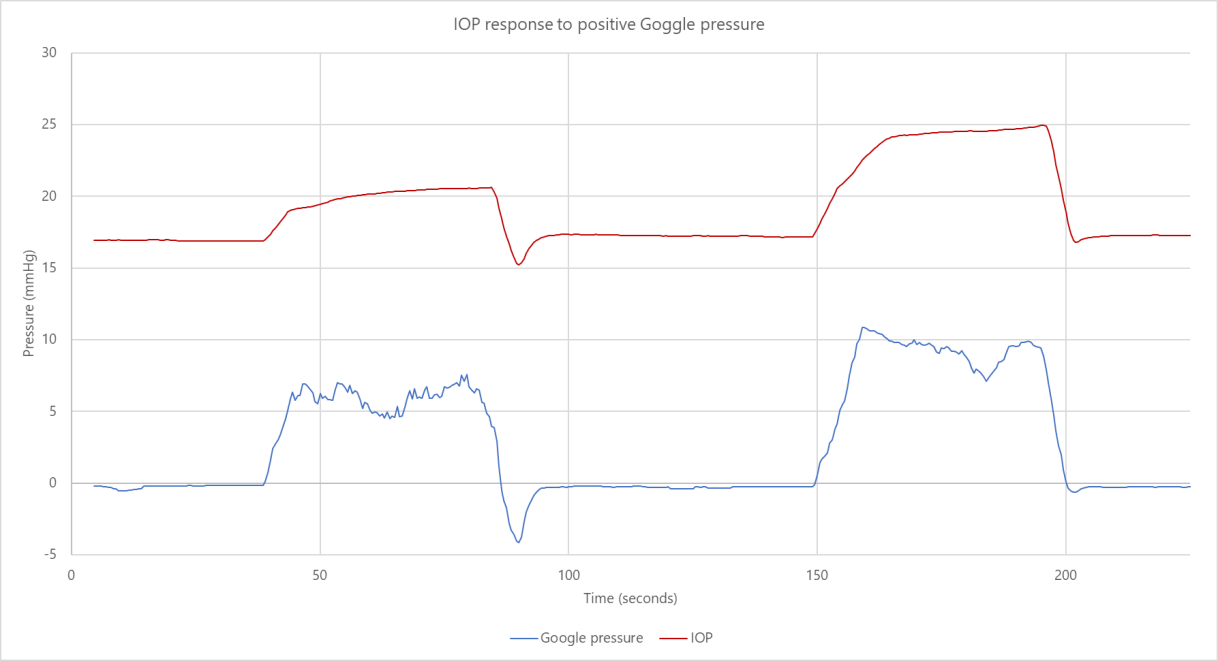
Diagnostic and therapeutic examples outside of ophthalmology illustrate why atmosphere is the proper reference pressure. Central venous pressure is exposed to many different adjacent pressures like the intra-thoracic pressure, various tissue pressures, and pressure in the overlying skin. Yet clinically, diagnostic measurement of central venous pressure is always measured relative to the atmospheric pressure, not the pressures of surrounding tissues and cavities. A therapeutic example is a patient receiving positive pressure ventilation via a mask sealed over the nose and mouth. Positive pressure air is delivered through the mask and inflates the patient's lungs. As the pressure in the mask increases, the pressure in the lungs increases. If the pressure in the lungs was referenced to the pressure within the ventilation mask, no new increase in pressure within the lungs would be apparent. However, if the pressure in the lungs were properly referenced to the atmosphere, the appropriate pressure increase in the lungs would be registered.

The effect of increased and decreased IOP on retinal blood flow.* Consider the well-established relationship between IOP and retinal blood flow. Increased IOP diminishes retinal blood flow and ocular perfusion pressure, as described above when performing clinically-accepted ophthalmodynanometry.[v] It is also well known to ophthalmic surgeons that increased eye pressure created during vitrectomy surgery leads to a narrowing of ophthalmic blood vessels and decreased blood flow.[vi] This fact is further supported by the converse observation where known IOP-lowering methods lead to increased observed retinal blood flow, increased blood vessel diameter and increased vessel density as shown by OCT- angiography after glaucoma surgery or after use of topical drops known to lower IOP.[vii] [viii]

The effect of positive and negative pressure application using goggles to blood flow is described below.

Study 4 - Positive pressure goggles (Full Body Cadaver); Figure 3 and Table 1
-A cadaveric study was performed with manometric measurement of IOP from inside of the eye. Baseline IOP was 18 mmHg.
-5 and 10 mmHg of positive pressure was applied via the goggles.
-Manometry-determined IOP referenced to the atmosphere increased by 3 and 7 mmHg, respectively.
-Therefore, the magnitude of IOP increase (3 and 7 mmHg) was smaller compared to the magnitude of positive pressure applied (5 and 10 mmHg).

Figure 3: Application of +5 mmHg and +10 mmHg results in an average increased IOP of 3mmHg and 7mmHg, respectively, in a directly cannulated full body cadaver.



Positive pressure goggles lead to an increase in IOP when referenced to atmosphere, but a decreased TCPD-determined IOP when referenced to the goggle space [Study 4]. Negative pressure goggles, on the other hand, lead to a decrease in IOP when referenced to atmosphere, but an increased TCPD-determined IOP when referenced to the goggle space [Studies 1-3, above]. With the positive pressure goggle, if the decreased TCPD relative to the goggle space was the important parameter representative of the known physiological responses to IOP, retina blood flow should increase (Table 1). However, in reality, positive pressure goggles apply positive pressure similar to ophthalmodynanometry, and ophthalmodynanometry *decreases* retinal blood flow. Therefore, the biological impact of positive pressure goggles is explained by an increase in IOP relative to atmospheric pressure which was observed by manometric measurement. The biological impact of positive pressure goggles cannot be explained by a TCPD-determined IOP decrease when referenced to the air space between the goggles and cornea. In fact, the latter consideration only results in the nonsensical conclusion that positive pressure to the eye increases retinal blood flow. The straightforward conclusion is that positive pressure application over the eye increases IOP, while negative pressure application decreases IOP.

Table 1 – Positive Pressure Goggles

IOP assessment Method	Reference Point	IOP change	Expected Impact on Retinal Blood flow	Summary Relationship to Positive Pressure	Comments
Manometry-determined IOP	Atmospheric Pressure	Increase	Decrease	Positive pressure to the eye decreases retinal blood flow	This result is anticipated and consistent with known methods such as ophthalmodynanometry
TCPD-determined IOP	Positive pressure air space in the goggles	Decrease	Increase	Positive pressure to the eye increases retinal blood flow	This result is non-sensical and in direct contradiction to known methods such as ophthalmodynanometry

The negative pressure goggles circumstance has been thoroughly described above and in our FDA submission[i] demonstrating an increase in retinal blood flow and increase in macular and optic nerve vessel density with negative pressure goggles applied. The chart below (Table 2) summarizes the thought experiment and the observed experimental results.

Table 2 - Negative pressure goggles.

IOP assessment Method	Reference Point	IOP change	Expected Impact on Retinal Blood flow	Summary Relationship to Negative Pressure	Comments
Manometry-determined IOP	Atmospheric Pressure	Decrease	Increase	Negative pressure to the eye increases retinal blood flow	*Consistent with Study 3 and observed results[i]
TCPD-determined IOP	Atmospheric Pressure	Decrease	Increase	Negative pressure to the eye increases retinal blood flow	*Consistent with Studies 1 and 2 and observed results[i]
TCPD-determined IOP	Negative pressure air space in the goggles	Increase	Decrease	Negative pressure to the eye decreases retinal blood flow	Not consistent with observed results

*These approaches are simply to demonstrate that the IOP-lowering with the MPD is similar to traditional IOP-lowering therapies, and these experiments are not intended to support additional labeling claims or substantiate that any one physiological parameter other than IOP is related to glaucomatous progression.

In conclusion, the Multi-Pressure Dial (MPD) is a novel, non-invasive, and non-pharmacological, device that employs a negative pressure (vacuum) to temporarily reduce the local air pressure within the goggle chambers to lower IOP referenced to the atmosphere while worn. Its mechanism of action is best understood by addressing inconsistencies in terminology of IOP measurement approaches. Such

an understanding provides fundamental insights into the physiologic responses of the eye to IOP changes. Pressure readings in all of medicine have always referenced bodily pressures to the atmosphere. We have demonstrated that referencing IOP to the airspace of the goggles results in unexplainable results that are inconsistent with known physiological behaviors of the eye and also contradict experimental results.

Ultimately,

- IOP referenced to atmospheric pressure is a known and a key risk factor for glaucoma progression
- The methodology employed in clinical trials of the MPD approximates Goldmann applanation since both approaches measure TCPD relative to atmospheric pressure.
- Negative pressure application of the MPD lowers IOP referenced to atmospheric pressure.
- The measurable physiologic response of the eye to MPD vacuum is similar to that of known IOP lowering methods.

Appendix - Response to commentary

FDA has cited a commentary (opinion) that was not peer-reviewed which speculated on theoretical safety and IOP-lowering effectiveness concerns about the application of negative pressure over the eye.[iv] The opinion questioned the proper reference point for IOP measurement. The author suggested the definition of IOP should be the difference between the pressures inside the eye referenced to the air pressure in the goggles at the surface of the cornea. Commenting on a manuscript authored by Ethier and the inventors of the MPD,[iv] the author noted that the TCPD relative to inside the goggles increases, as written by Ethier.[ix] The author is also correct that TCPD is conventionally measured to estimate IOP. However, the TCPD in seminal studies has always been expressed as referenced to the traditional standard of atmospheric pressure. All clinical studies of the MPD measured the TCPD referenced to atmospheric pressure in our best attempt to most closely approximate traditional Goldman applanation, i.e., applanate the cornea relative to atmospheric pressure. We agree with the author that TCPD relative the goggle space increases, and the author agreed with us that the TCPD relative to atmosphere and the absolute pressure in the eye decreases. The introduction of a depressurized airspace within the goggles raises the question of which reference pressure (atmospheric or intra-goggle) best represents known physiological response of the eye to traditional IOP lowering therapies. Speculations that were raised in the commentary did not have the benefit of our unpublished data showing how negative pressure application of the MPD results in physiological changes consistent with traditional IOP lowering therapies such as:

a) Decreased IOP relative to atmospheric pressure with no change to retro-orbital pressure, as demonstrated in full body cadavers[i]
b) Decreased IOP relative to atmospheric pressure in full body cadavers as measured directly by manometry[i]
c) Increased blood flow to the optic nerve as evaluated by laser speckle flowgraphy[i]
d) Increased venous diameter measured by OCT[x]
e) Increased area perfused of the whole eye and posterior pole as measured by OCTA[i]
f) Absence of deleterious structural effects on OCT imaging of the optic nerve and RNFL[i]
g) Clinical studies that show no difference in visual field progression at 3[i] and 6 months compared to control. (If we were raising IOP, we would expect to see worsening of visual field compared to the control eye).

The commentary raises worthwhile definitional questions but represents a theoretical concern without

supporting data. Upon further inspection, the physiological merit of referencing IOP to the air pressure within the goggle is not consistent with the known physiological responses of the eye to IOP changes; nor is it supported with data. The body of supplemental data presented above clearly demonstrates that as IOP is lowered relative to atmospheric pressure with the MPD, the eye behaves similarly to IOP lowering therapies providing further support that the important physiological parameters related to glaucoma are improved with the MPD.

[i] "Equinox Response, FDA Correspondence DEN200034/S002, Dated August 15, 2021," n.d.
[ii] Russell J. Swan et al., "Evaluation of the IOP-Lowering Effect of a Multi-Pressure Dial at Different Negative Pressure Settings," *Translational Vision Science & Technology* 9, no. 12 (November 13, 2020): 19, https://doi.org/10.1167/tvst.9.12.19.
[iii] Jeffrey L. Goldberg et al., "Short-Term Evaluation of Negative Pressure Applied by the Multi-Pressure Dial System to Lower Nocturnal IOP: A Prospective, Controlled, Intra-Subject Study," *Ophthalmology and Therapy* 10, no. 2 (June 2021): 349–58, https://doi.org/10.1007/s40123-021-00343-4.
[iv] Arthur Sit, "IOP-Lowering through Vacuum Application," *International Glaucoma Review* 21–1 (December 1, 2020), www.e-IGR.com.
[v] Alon Harris et al., "Regulation of Retinal and Optic Nerve Blood Flow," *Archives of Ophthalmology* 116, no. 11 (1998): 1491–95.
[vi] Louise C. Moorhead et al., "Dynamic Intraocular Pressure Measurements During Vitrectomy," *Archives of Ophthalmology* 123, no. 11 (November 1, 2005): 1514–23, https://doi.org/10.1001/archopht.123.11.1514.
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[viii] Ana Miguel et al., "OCT-Angiography Detects Longitudinal Microvascular Changes in Glaucoma: A Systematic Review," *British Journal of Ophthalmology*, January 15, 2021, https://doi.org/10.1136/bjophthalmol-2020-318166. [ix] C. Ross Ethier, Paul Yoo, and John P. Berdahl, "The Effects of Negative Periocular Pressure on Intraocular Pressure," *Experimental Eye Research* 191 (February 2020): 107928, https://doi.org/10.1016/j.exer.2020.107928.
[x] Tanner John Ferguson et al., "Short-Term OCT Retinal Vessel Diameter Changes Using a Multi-Pressure Dial in Healthy and Glaucomatous Subjects," *Investigative Ophthalmology & Visual Science* 62, no. 8 (June 21, 2021): 2582–2582.

9.5 White Paper: The Benefit of Nocturnal IOP Reduction in Glaucoma, Including Normal Tension Glaucoma

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Introduction

Nocturnal intraocular pressure (IOP) elevation has been implicated in the progression of open-angle glaucoma (OAG) and its subtypes including normal-tension glaucoma (NTG).[1–3] Published work has highlighted the importance of decreasing nocturnal IOP to limit glaucomatous progression, particularly in more vulnerable patients such as those with NTG. NTG is a subtype of OAG which is difficult to treat with standard treatment options such as drops, laser trabeculoplasty, and minimally invasive glaucoma surgery (MIGS) because of a lower baseline IOP.[4–8] The importance of lowering nocturnal IOP and its impact on disease progression has been reinforced by studies evaluating 24-hour IOP data.[4]

Multiple studies have explored 24-hour IOP profiles and highlighted the dynamic nature of IOP.[9–12] The measurement of IOP over a 24-hour time frame has shown that peak (acrophase) IOP primarily occurs at night, particularly in patients with glaucoma.[2,3,13,14] **Figure 1** illustrates a typical nocturnal IOP elevation. Nocturnal IOP elevation is influenced by a multitude of factors including circadian rhythm and body position. The circadian rhythm of IOP is regulated by the suprachiasmatic nucleus (SCN) with both glucocorticoids and the sympathetic nervous system potentially playing a significant role. A number of approaches have been utilized to explore 24-hour IOP profiles including overnight measurements in sleep labs[16], the use of a contact-lens sensor (CLS)[11,15] (Triggerfish; Sensimed AG), and now implantable IOP sensors[9] (EyeMate; Implandata). Further, multiple 24-hour IOP sensors are under development with some achieving FDA breakthrough designation, highlighting the importance of recognizing and treating elevated IOP, 24-hours a day.[17] Data from studies evaluating 24-hour IOP profiles have consistently demonstrated that nocturnal IOP elevation is more common and leads to glaucomatous progression in OAG patients, including those with NTG.[12,14]

The Early Manifest Glaucoma Trial demonstrated that every 1 mmHg decrease in IOP is associated with a 10% decrease in glaucomatous progression.[18] Studies have also shown the importance of decreasing the total IOP burden, e.g., the area under the curve, and its impact on slowing glaucomatous progression.[19] Thus, strategies targeting IOP reduction remain the foundation of glaucoma treatment. Although there have been considerable advances in treatment options in the last decade, there remains a need for improved 24-hour IOP control and monitoring. A recent joint paper[20] by the American Glaucoma Society (AGS) and American Society of Cataract and Refractive Surgeons (ASCRS) emphasized this notion stating that: (a) 24-hour IOP monitoring/control, and (b) non-invasive therapeutics that lower IOP and improve ocular blood flow were unmet needs, “especially in challenging patients who do not adequately respond to current therapies or those in whom IOP is already within the normal range.”

In this report, we review:

- The impact of nocturnal IOP elevation on glaucomatous progression
- The importance of decreasing nocturnal IOP on slowing glaucomatous progression
- The rationale for why lowering nocturnal IOP elevation is beneficial.
- Potential future therapies for improved management of nocturnal IOP elevation

Impact of Nocturnal IOP Elevation on Glaucomatous Progression

In the treatment of glaucoma, IOP reduction remains the only clinically-validated modifiable risk factor.[18] In the course of doing this, clinicians nearly always rely on daytime (in-office) IOP measurements to guide treatment decisions. These measurements, however, only provide a partial snapshot of a patient's 24-hour IOP profile, and it is well documented that daytime IOP measurements often miss IOP peaks,[21] leading to continued disease progression in patients whose IOP is seemingly controlled based on measurements obtained during clinic visits.[21]

A multitude of recent studies evaluating 24-hour IOP profiles have demonstrated a relationship between nocturnal IOP elevation and glaucomatous disease progression.[11,12,22,23] The introduction of continuous 24-hour monitoring devices that measure IOP and IOP-related parameters has demonstrated the expected nyctohemeral rhythm of IOP and also confirmed the pattern of peak IOP occurring at night.[24,25] In addition, patients with glaucoma not only have a more pronounced nocturnal IOP elevation but the duration of elevation is prolonged compared to healthy subjects.[25]

Studies have also highlighted the impact of nighttime IOP spikes on disease progression.[12,22] De Moraes et al. confirmed the pattern of peak IOP occurring at night and also found that the mean peak ratio and magnitude of elevation were predictive of faster progression and visual field change.[11] The mean peak ratio findings in this study imply that those patients with a higher nocturnal elevation are at greater risk. An additional recent study by Yang et al[9] found that increased elevation in nocturnal IOP correlated with faster rates of visual field loss. Furthermore, a recent study[23] in treated glaucoma, including NTG patients, found that 79% of patients with progressive glaucoma, despite an apparent controlled daytime IOP, had elevated IOP at night, supporting a clear association between nocturnal IOP spikes and disease progression. In this study, mean daytime IOP was similar between progressors and non-progressors respectively (13.57mmHG±2.16 and 13.04mmHG±2.06). However, 65% of patients with progression had nocturnal IOP elevations while 24% of patients without progression had nocturnal IOP elevations. Collectively, these studies highlight the importance of nocturnal IOP elevation and its likely impact on glaucoma progression despite an apparent "controlled" daytime IOP.[23]

Another implication of nocturnal IOP elevation is ocular perfusion pressure (OPP), where OPP is defined as the difference between mean arterial pressure (MAP) and IOP at any given time. OPP is reduced when blood pressure is low or IOP is high. Multiple, large-scale studies have shown a link between low OPP and glaucomatous disease progression, including the Baltimore Eye Survey that demonstrated a 6-fold increase in glaucoma risk in patients with reduced diastolic perfusion pressure.[26–28] A study of 24-hour IOP and blood pressure patterns in patients with NTG reported that patients with a ≥20% reduction in nocturnal BP, had a higher rate (>3-fold increase) of visual field progression.[23] An additional study[29] in newly-diagnosed NTG patients revealed that lower nocturnal diastolic BP was significantly predictive of visual field progression. Overall, these studies highlight the importance of OPP in the development and progression of glaucoma and further support the need for treatment options that lower IOP at night when these patients are likely most vulnerable to glaucomatous damage.

The decrease in nocturnal OPP is compounded by the vascular dysregulation present in glaucoma.[30,31] Typically, physiologic ocular blood flow is autoregulated to meet and maintain metabolic needs, and autoregulation involves a local change in vascular resistance in response to changes in OPP. A low OPP in the presence of vascular dysregulation can lead to insufficient blood flow of optic nerve head (ONH) tissue.[32] Prior studies using laser doppler flowmetry have demonstrated that reducing IOP can stimulate autoregulatory responses.[33] Studies have also demonstrated that reducing IOP leads to an increase in

blood flow at the ONH.[31,34] Since autoregulation and OPP is impaired in patients with glaucoma, lowering nocturnal IOP improves OPP and subsequently increases blood flow which has been demonstrated to be protective of retinal ganglion cells in model systems.[35]

The Importance of Decreasing Nocturnal IOP to Slow Glaucomatous Progression

Studies have linked extended sleep duration to glaucoma progression. A recent study in >6,000 patients demonstrated that longer sleep duration is associated with a 3-fold greater risk of progression in patients who slept ≥10 hours per night.[36] These findings suggest that decreasing the duration or magnitude of nocturnal IOP elevation could slow glaucomatous progression.

24-hour IOP profiles in patients with glaucoma are more volatile, with larger amplitudes of nocturnal elevation.[22,25] It is well established that IOP peaks at night, likely due to circadian rhythm and increased episcleral venous pressure inherent to the recumbent position. However, it remains unclear why there are larger degrees of elevation in patients with glaucoma.[3] It is possible that impaired trabecular outflow compounds the increased episcleral venous pressure observed at night.[37] Prior work has also shown that changes in IOP associated with positioning of the body (e.g., horizontal position) are more significant in patients with glaucoma.[38] Regardless of the mechanism, these findings highlight the importance of decreasing nocturnal IOP in patients with glaucoma.

A number of studies have investigated the nocturnal IOP-lowering efficacy of treatments for glaucoma.[39] Despite the growing body of evidence supporting the role and importance of nocturnal IOP in glaucoma management, therapies that specifically target nocturnal IOP reduction are limited. At night, topical agents have reduced IOP lowering efficacy, and when combined with the typically observed decrease in nocturnal blood pressure, dramatic decreases in nocturnal ocular perfusion pressure can occur.[4] Since episcleral venous pressure (EVP) increases IOP, and EVP is elevated at night and in the horizontal position, it is no surprise that treatment options like MIGS, laser treatments and topical medications are less effective at lowering nocturnal IOP because they do not impact EVP, other than rho-kinase inhibitors. Thus, there remains a need for better treatment options that safely and effectively lower nocturnal IOP.

Commonly prescribed topical IOP-lowering agents such as beta-blockers (e.g., timolol), brimonidine and carbonic anhydrase inhibitors (e.g., dorzolamide) have proven daytime efficacy but have minimal effect on nocturnal IOP.[2,40,41] The only medication class to consistently demonstrate a benefit of nocturnal IOP reduction are prostaglandins; however, the magnitude of IOP reduction at night is reduced in comparison with daytime efficacy.[42] A prior study by Liu et al. investigated the nocturnal effects of timolol or latanoprost as compared with no treatment in glaucoma patients. While both agents were effective at lowering daytime IOP, timolol's nighttime efficacy was no different than the absence of treatment and both timolol and latanoprost groups still exhibited a nocturnal IOP peak, showing reduced efficacy at night.[41] An additional study by Liu et al[16] demonstrated a benefit of adding brinzolamide to latanoprost for reducing nocturnal IOP, but the difference was minimal, and all groups still demonstrated a nocturnal IOP peak.

The recently published LiGHT trial demonstrated IOP following SLT was reduced when averaged over 24 hours but SLT did not impact the 24-hour rhythm and presence of nocturnal IOP peaks.[43] [44] To date, no studies have investigated the efficacy of MIGS procedures in lowering nocturnal IOP and the 24-hour IOP profile in patients following MIGS procedures has not been explored.[45]

To date, the only incisional surgical treatment demonstrated to provide 24-hour control is trabeculectomy, which has also demonstrated the best efficacy of slowing glaucoma progression in progressive glaucoma

with elevated or normal IOP.[46,47] Multiple studies have been published supporting the benefit of trabeculectomy in reducing nocturnal IOP elevation including work highlighting the superior 24-hour IOP control offered by trabeculectomy versus maximal medical management.[45,48] The minimization of nocturnal IOP elevation conferred by trabeculectomy may be one of the key reasons trabeculectomy leads to slowed disease progression. While trabeculectomy may provide nocturnal control in patients at greatest risk for profound vision loss, the morbidity associated with filtration surgery suggests that a safer method to lower IOP at night remains a significant unmet need in glaucoma management.

The rationale for why lowering nocturnal IOP elevation is beneficial.

While the evidence and rationale for decreasing nocturnal IOP to prevent glaucomatous progression is compelling, the reason why lowering IOP is an effective treatment for glaucoma is not fully elucidated. Early landmark studies[49,50] demonstrated that axonal transport is slowed by elevated IOP, and irreversible damage can occur starting at 4 hours. If IOP is normalized within 4 hours, axonal transport can resume without permanent damage, which supports the benefit of nocturnal and periodic IOP reduction in the treatment of glaucoma. Our understanding of glaucoma has evolved through exploring the relationship between IOP and intracranial pressure (ICP), or cerebrospinal fluid pressure (CSFp). A low ICP, even in the setting of normal IOP, has been demonstrated to have an important role in the pathogenesis of glaucoma, in particular, those with NTG.[51–55]

This difference between IOP and ICP defines the translaminar pressure difference (TLPD). When IOP is elevated relative to CSF pressure (CSFp), the TLPD is increased, which increases stress and strain on the lamina cribrosa. In contrast, a decrease in IOP relative to CSF pressure decreases the TLPD and decreases stress and strain on the lamina cribrosa.[56–58] A number of studies have explored the effects of an increased TLPD, either because of reduction of ICP or elevated IOP, on glaucomatous optic neuropathy. An early and important study by Quigley[49] in primates demonstrated that both acutely or chronically raising the IOP slowed or halted axonal transport in the optic nerve at the level of the lamina cribrosa. However, normalization of the IOP following 4 hours of IOP elevation allowed for the resumption of axonal transport without any permanent insult to the retinal ganglion cells. An additional study by Johansson et al[50] reported similar findings and found that after a transient IOP elevation to 50 mmHg for 2 hours followed by a return to baseline (IOP 15 mmHg) axonal transport was completely restored without permanent damage. A more recently performed study by Zhang et al[35] examined the impact of short-term CSFp reduction on axonal transport and identified disruption of axonal transport that recovered following normalization of the TLPD, supporting the pathogenic impact of decreased CSFp in damage to retinal ganglion cells. Collectively, these studies show that normalization of the TLPD, even if temporarily, allows for the resumption of axonal transport and potential clearance of toxic metabolites, suggesting that periodic normalization of the TLPD can help the optic nerve head and maintain the health of retinal ganglion cells.[59] When axonal transport is disrupted for an extended period of time, apoptotic signals are triggered, initiating an irreversible sequence that leads to the death of retinal ganglion cells, the hallmark of damage in glaucoma. Thus, periodic TLPD normalization, especially during periods of IOP elevation at night, is a reasonable strategy to prevent the apoptotic signal and irreversible cascade.

It's also important to consider the impact of the TLPD on blood flow and ocular perfusion pressure, which may also contribute to glaucomatous damage. Zhang et al.[35] demonstrated that low CSF pressure in combination with reduced ocular perfusion pressure damages the retinal ganglion cells more than either alone. Further, Siaudvytyte et al.[60] compared neuroretinal rim area and blood flow behind the optic nerve in patients with NTG. In this study, lower ICP was correlated with NTG and patients with ICP <8.3 mmHg had significantly lower blood flow through the ophthalmic artery than patients with ICP >8.3

mmHg, suggesting that reduced ICP could also be linked to poor blood supply at the ONH. Thus, given the concern of nocturnal systemic hypotension and the importance of ocular perfusion, lowering IOP at night promotes an increase in blood flow to the optic nerve head at a vulnerable time period for patients.

Overall, the aggregation of clinical data has shown a connection between nocturnal IOP increases and the progression of glaucoma, including normal tension glaucoma. Moreover, existing clinical and scientific literature supports the notion that reducing IOP, even periodically, particularly at night, can help mitigate retinal ganglion cell death. In summary, these findings strongly support the advantages of lowering nocturnal IOP.

Future Therapies

The evidence supporting the importance of lowering nocturnal IOP and minimizing IOP elevations throughout the 24-hour period is robust. However, the current landscape shows a very limited number of interventions that successfully minimize nocturnal IOP elevations in patients with glaucoma. New options are under development that could provide improved control of nocturnal IOP and complement existing treatments.

The ocular pressure-adjusting pump, or OPAP (Equinox, Inc.) is a novel device currently under investigation that has shown promise for lowering nocturnal IOP.[61–63] The OPAP system (formerly known as the multi-pressure dial), which consists of a pressure-modulating pump and a pair of pressure-sensing goggles, utilizes localized negative pressure to reduce IOP. The OPAP is designed for individualized negative pressure application to each periorbital region to enable targeted IOP lowering for each eye during use. The IOP-lowering effect of the device has been demonstrated in multiple studies including a study by Goldberg et al in which mean nocturnal IOP was reduced by 35% during use of the device.[63,64] In addition to IOP reduction, additional studies have demonstrated the benefits of device use on ocular blood flow. A recent study by Kamalipour et al[65] investigated changes in circumpapillary microvasculature using OCT-A and demonstrated a dose-dependent increase in retinal microcirculation corresponding to increased levels of negative pressure (-10, -15, -20 mmHg). Another recent study utilizing computational modeling evaluated the effect of negative periocular pressure using the OPAP on the biomechanics of the ONH. In this study, results demonstrated a significant reduction in biomechanical strain at the ONH, supporting the biomechanical benefit of employing negative periocular pressure to lower IOP.[66]

Conclusion

Reduction of IOP during both day and night clearly provides a therapeutic benefit in slowing the progression of OAG and the more difficult to treat NTG. The findings of recent work summarized in this paper highlight the importance of nocturnal IOP control and the likely benefit of periodic IOP reduction in slowing the progression of glaucoma. There remains an unmet need for treatment options that safely and effectively target the reduction of nocturnal IOP, especially in NTG.

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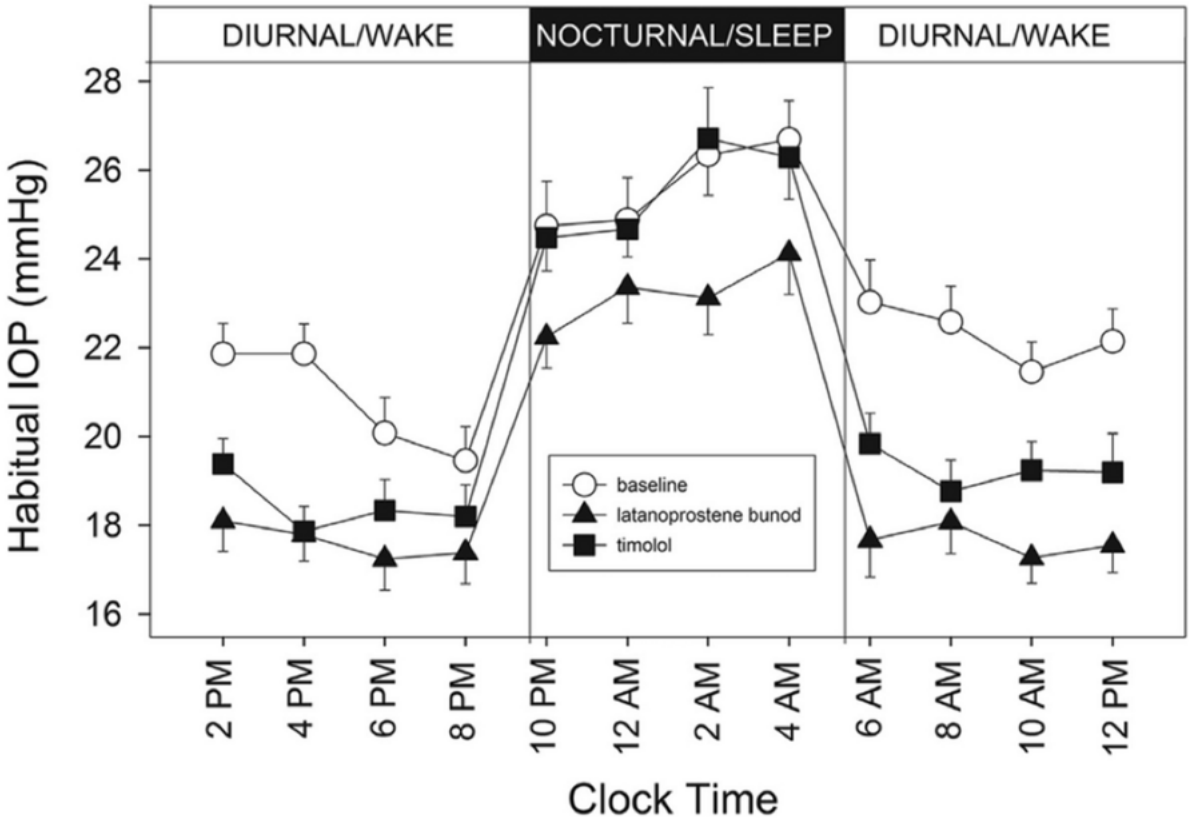

Figure 1. Nocturnal IOP acrophase is demonstrated centrally in patients with ocular hypertension or POAG. From Liu et al.[13] Reprinted under Creative Commons license.

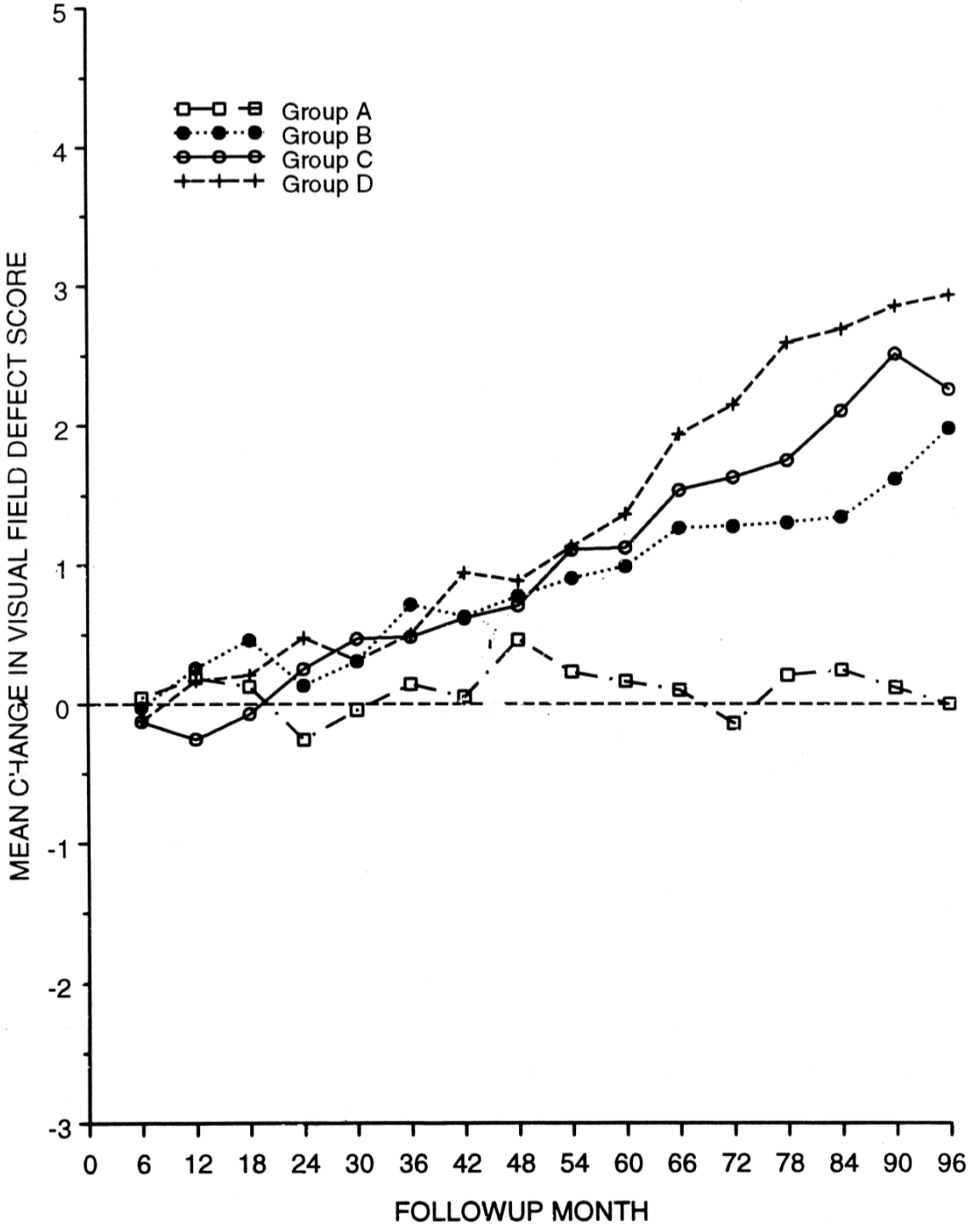

Figure 2. The mean change in visual field defect score by percent of visits over a 6-year span in which an eye presented with an IOP <18 mmHg (group A is 100%, group B is 75-99%, group C is 50-74%, group D is <50%). Reprinted under RightsLink.