FSYX™ Ocular Pressure Adjusting Pump (OPAP) as an Adjunct Therapy for Lowering Intraocular Pressure During Nightly Use in Patients with Open Angle Glaucoma and Intraocular Pressure ≤ 21 mmHg

Ophthalmic Devices Panel

March 21, 2024

Introduction

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Cataract, Cornea, Glaucoma, and Refractive Surgeon at Vance Thompson Vision

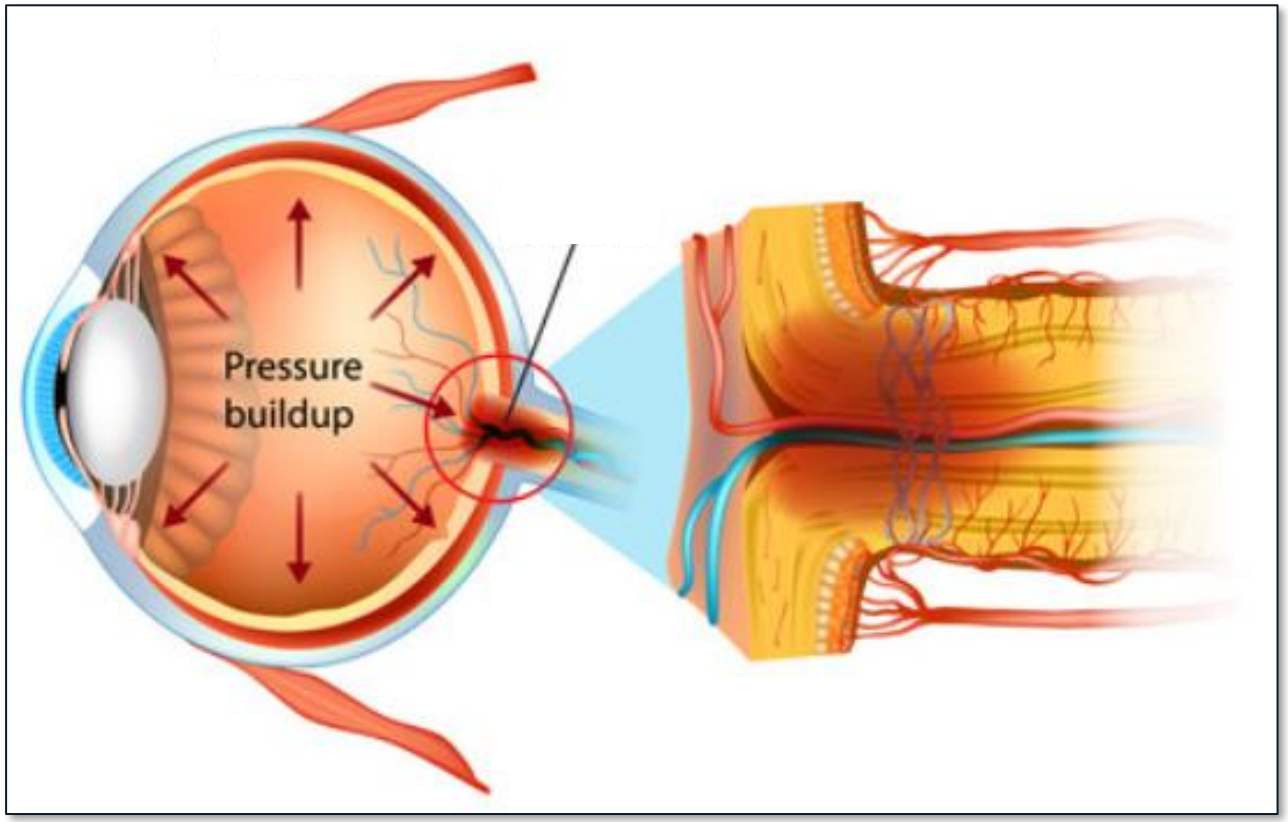
Clinician and Researcher

Professor of Surgery, University of South Dakota

Founder and Chair, Balance Ophthalmics

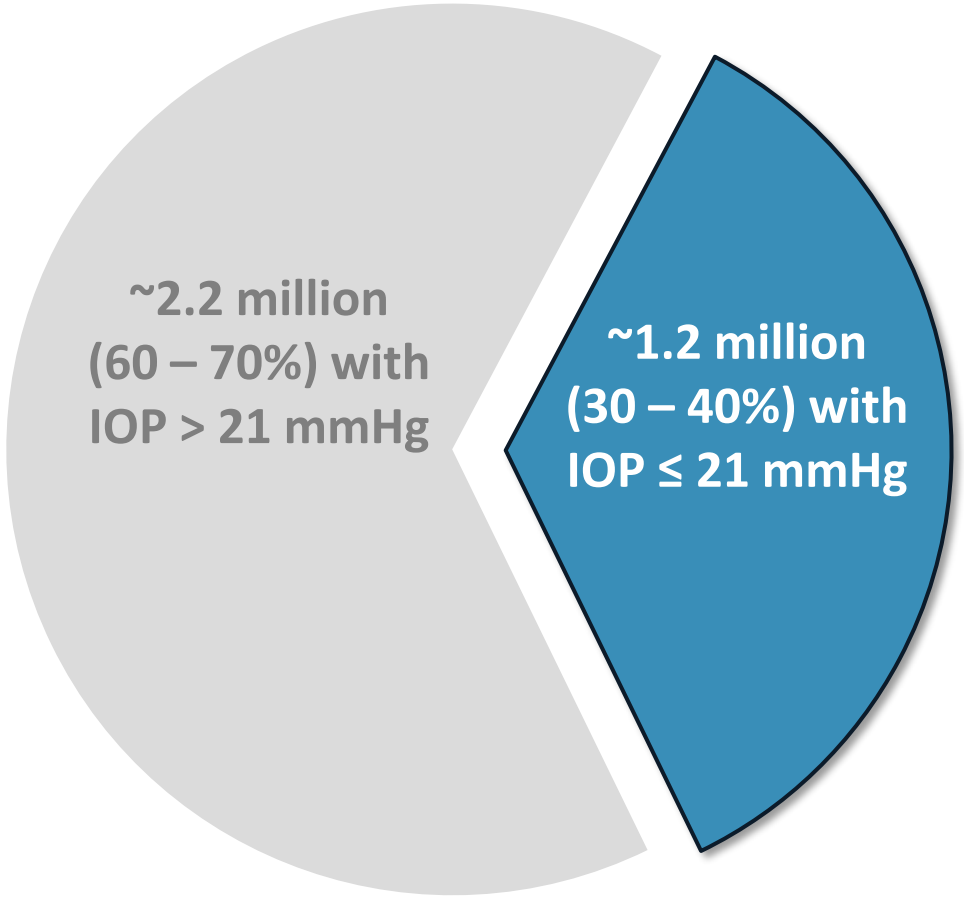
Glaucoma is One of Most Difficult Problems Ophthalmologists Face

- Optic neuropathy that results in loss of retinal ganglion cells and visual field loss
- Second leading cause of blindness
- Leading cause of irreversible blindness[1]
- 3 – 5 million Americans with glaucoma[2]
  - 120,000 blind from glaucoma[3]
- Only way to slow progression is lowering intraocular pressure (IOP)



1. Downs, 2022; 2. CDC.gov; 3. Sheybani, 2020; Image from Sakurra/Getty Images

Target Population: Open Angle Glaucoma (OAG) Patients with IOP ≤ 21 mmHg



- Normal tension glaucoma (NTG) is more difficult to treat
- Most available treatments are less effective at lowering nocturnal IOP
- Nocturnal IOP elevations associated with progression

Figure adapted from Sheybani, 2020

Glaucoma Patients with IOP ≤ 21 mmHg have Greatest Unmet Need

American Glaucoma Society and American Society of Cataract and Refractive Surgery highlight:

1. Importance of 24-hour IOP profile
2. Need for non-invasive therapeutics to lower IOP

Especially "in challenging patients who do not adequately respond to current therapies or those in whom IOP is <u>already within the normal range</u>"

Downs, 2020

The Problem is Difficult and Personal

Right Eye	Left Eye
20 / 400	Complete vision loss
IOP: 11 – 16 mmHg	
9 eye surgeries	Complications from glaucoma surgery
Still going blind	

Continued loss of vision in right eye and complete vision loss in left eye despite multiple glaucoma surgeries

OPAP Nonsurgical, Noninvasive Removable Device

Lightweight goggles

Quiet, programmable pump

Intended Use

- Lowers IOP during nightly use, when most IOP elevations occur
- Bilateral application
- Adjunct to currently prescribed therapies
- Provides clinicians with compliance data

How OPAP Works

- Atmosphere pressurizes entire body
- By reducing atmospheric pressure over the eye, IOP goes down
- OPAP reduces IOP by ~40 – 60% of applied negative pressure (NP)

Proposed Indication

The FSYX™ Ocular Pressure Adjusting Pump (FSYX 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

Key Topics FDA is Asking Panel to Discuss

1 Clinical Benefit

Do you believe there is clinical benefit to the lowering of this alternative IOP parameter and increasing of TCPD on a daily basis for several hours?

2 Effectiveness

Do you believe the IOP lowering as measured by excursion tonometry during use of the device, in combination with data from the other supportive studies demonstrates a reasonable assurance of effectiveness?

3 Safety

Do you believe the available data demonstrates reasonable assurance of safety at 1 year / long-term safety?

4/5 Labeling

Do you believe the available data supports the proposed range of programmable NP / wear time?

Does the proposed IFU statement use the appropriate nomenclature and language to accurately describe the function of the device with regard to IOP?

6 Benefit-Risk

Do the probable benefits of the FSYX OPAP device outweigh the probable risks for use in patients who meet the criteria specified in the proposed IFU?

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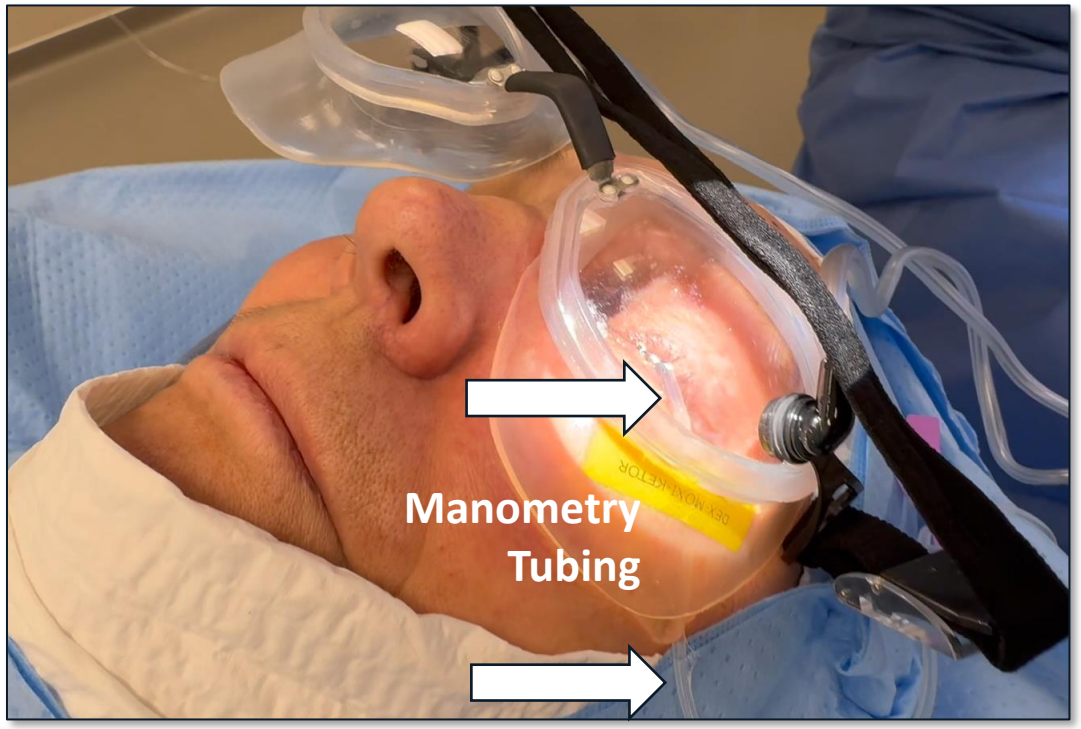
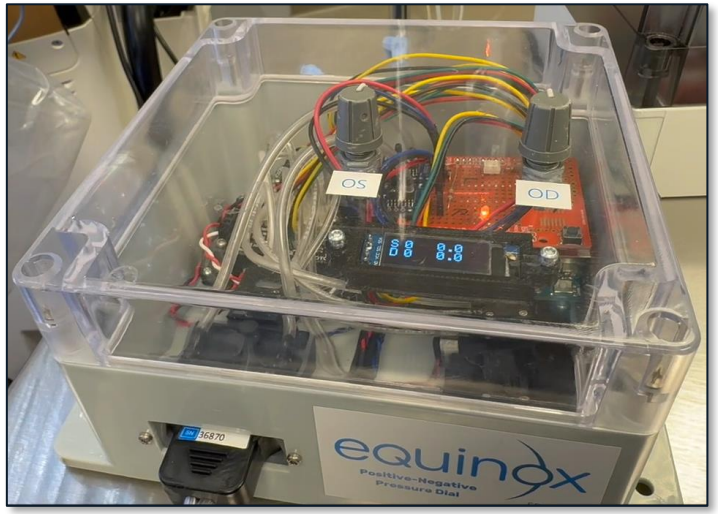
Does OPAP lower intraocular pressure?

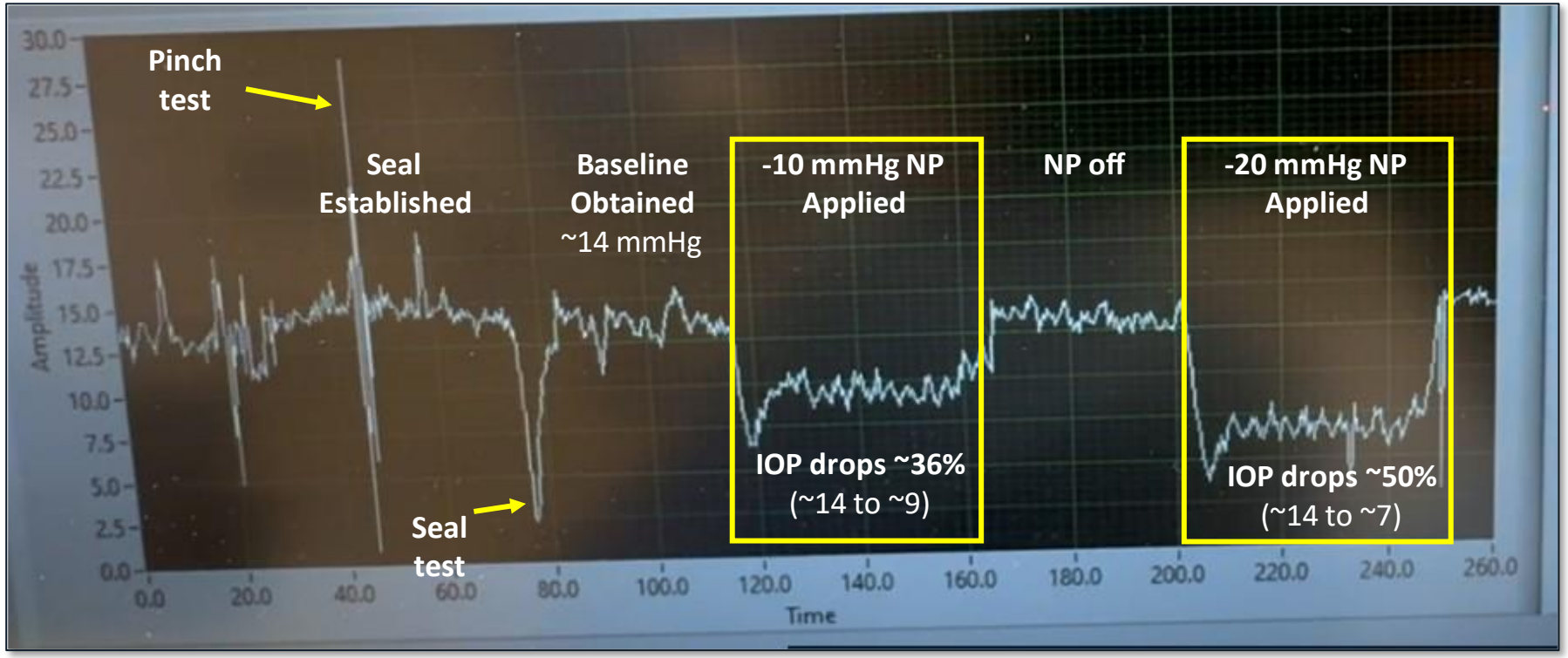
CONFIRM Study (CP-X24) Directly Measured IOP Using Manometry

- 17 patients prepped for cataract surgery
- Eye cannulated with manometer to continuously measure IOP every 0.5 seconds for 5 intervals
    1. Baseline (30 seconds)
    2. -10 mmHg NP (30 seconds)
    3. No NP (30 seconds)
    4. -20 mmHg NP (30 seconds)
    5. No NP (30 seconds)
- Eyelids closed



CONFIRM Study – Direct Cannulation of Eye





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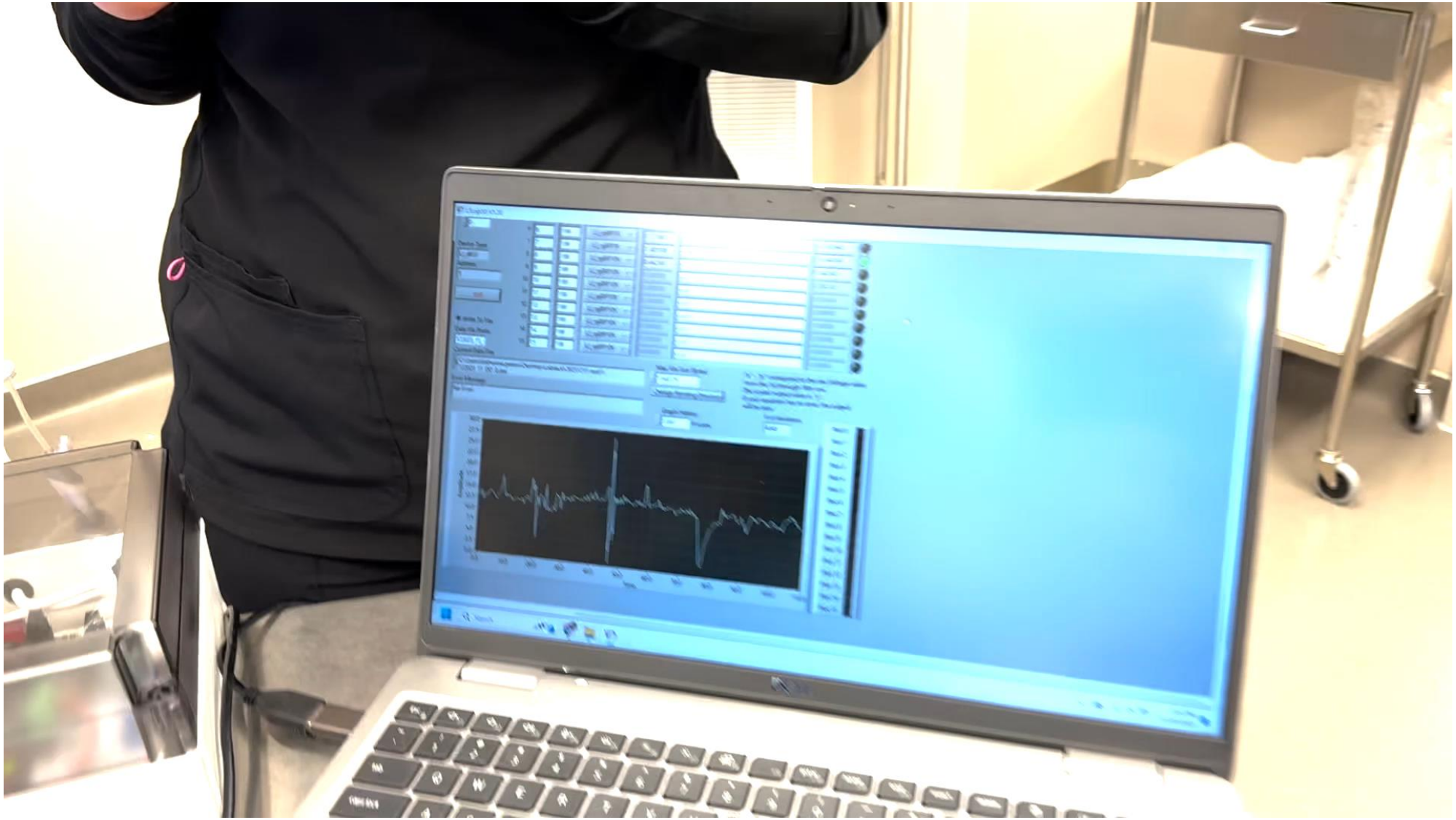
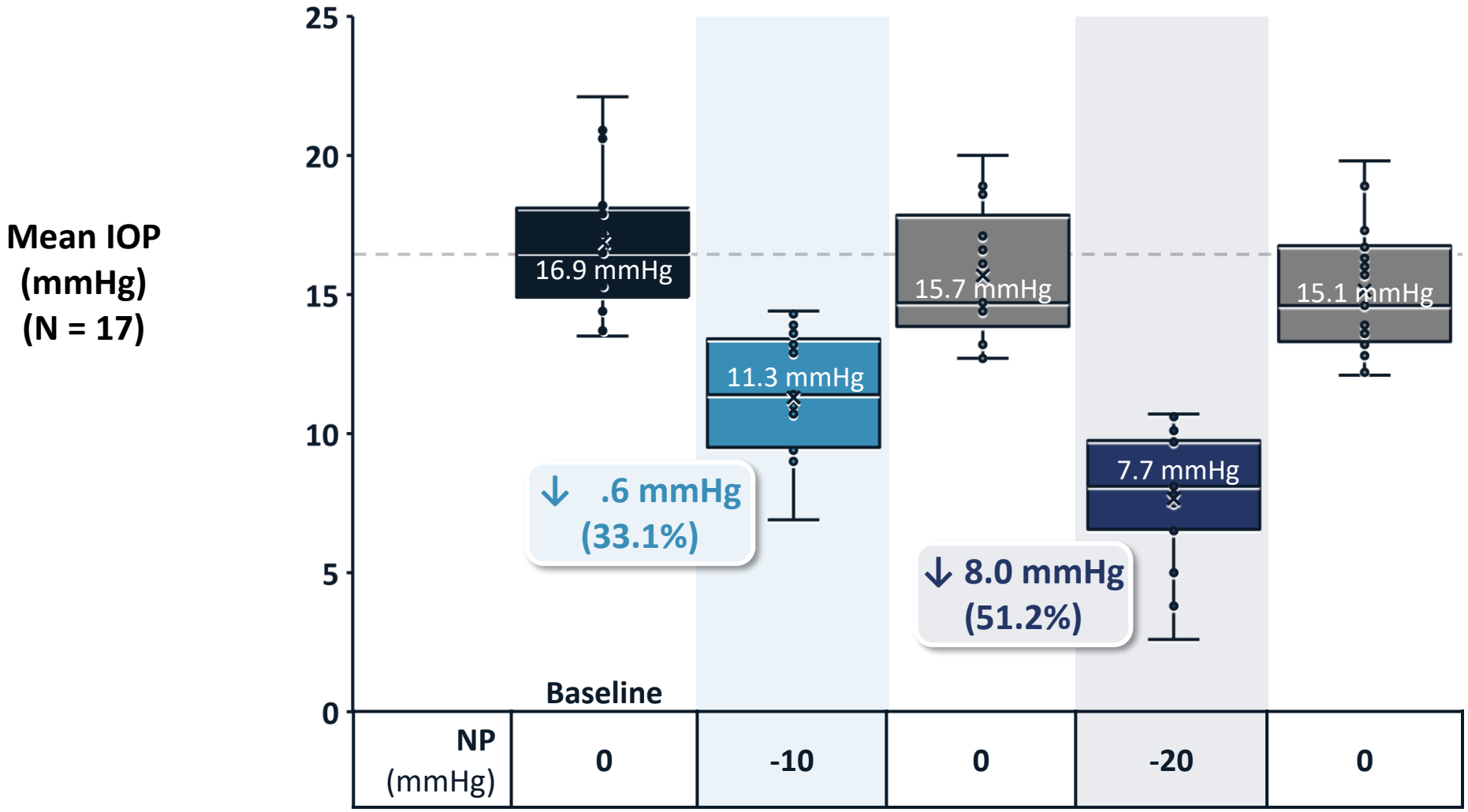


CONFIRM Study Demonstrates OPAP Reduces IOP in Dose-Response Fashion

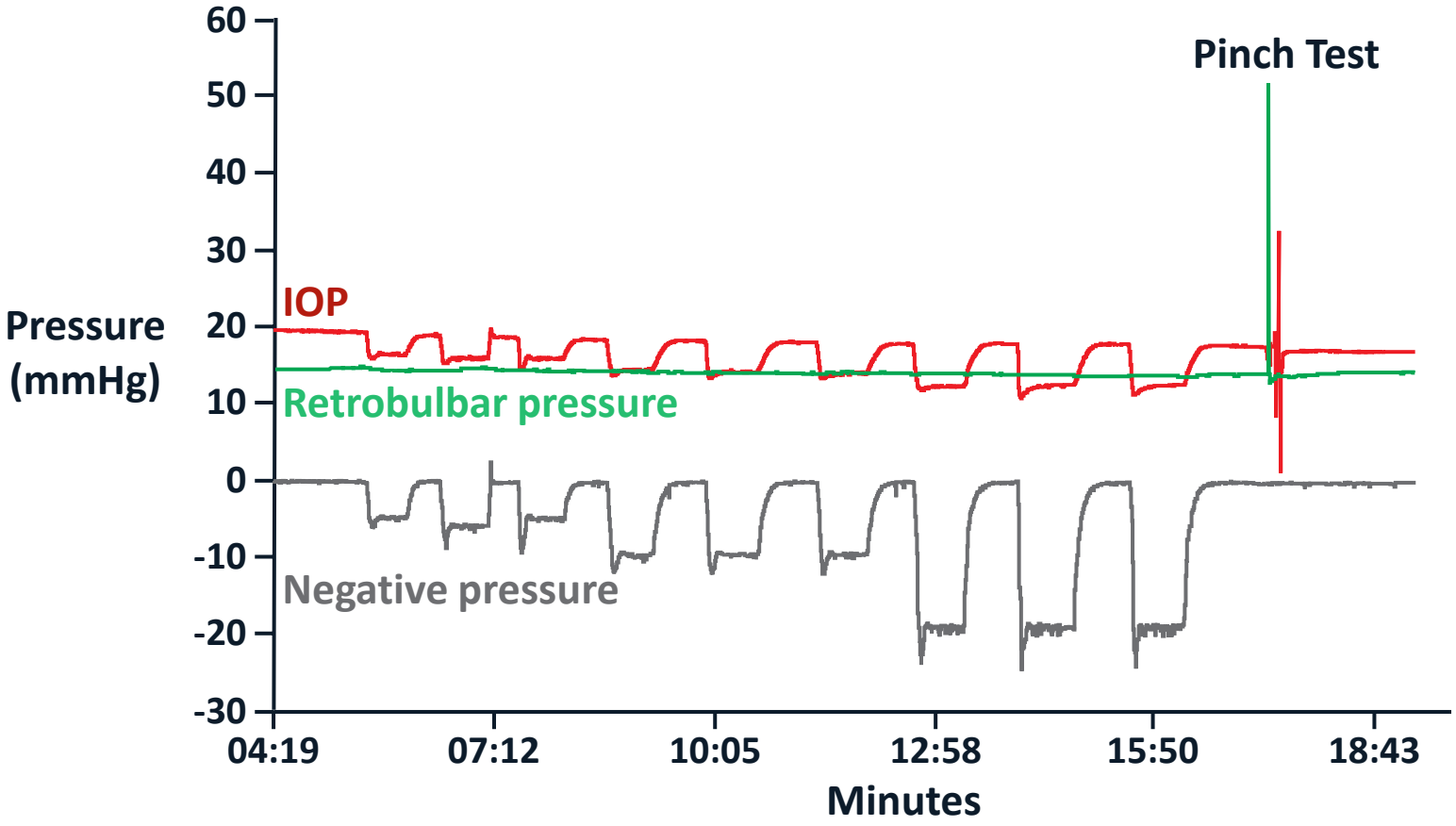


Manometer continuously measured IOP every 0.5 seconds for 5 intervals lasting ~30 seconds each (baseline, -10 mmHg NP, NP off 1, -20 mmHg NP, NP off 2)
Data have been provided to FDA but have not been reviewed

Direct Measures Obtained to Substantiate OPAP Lowers IOP

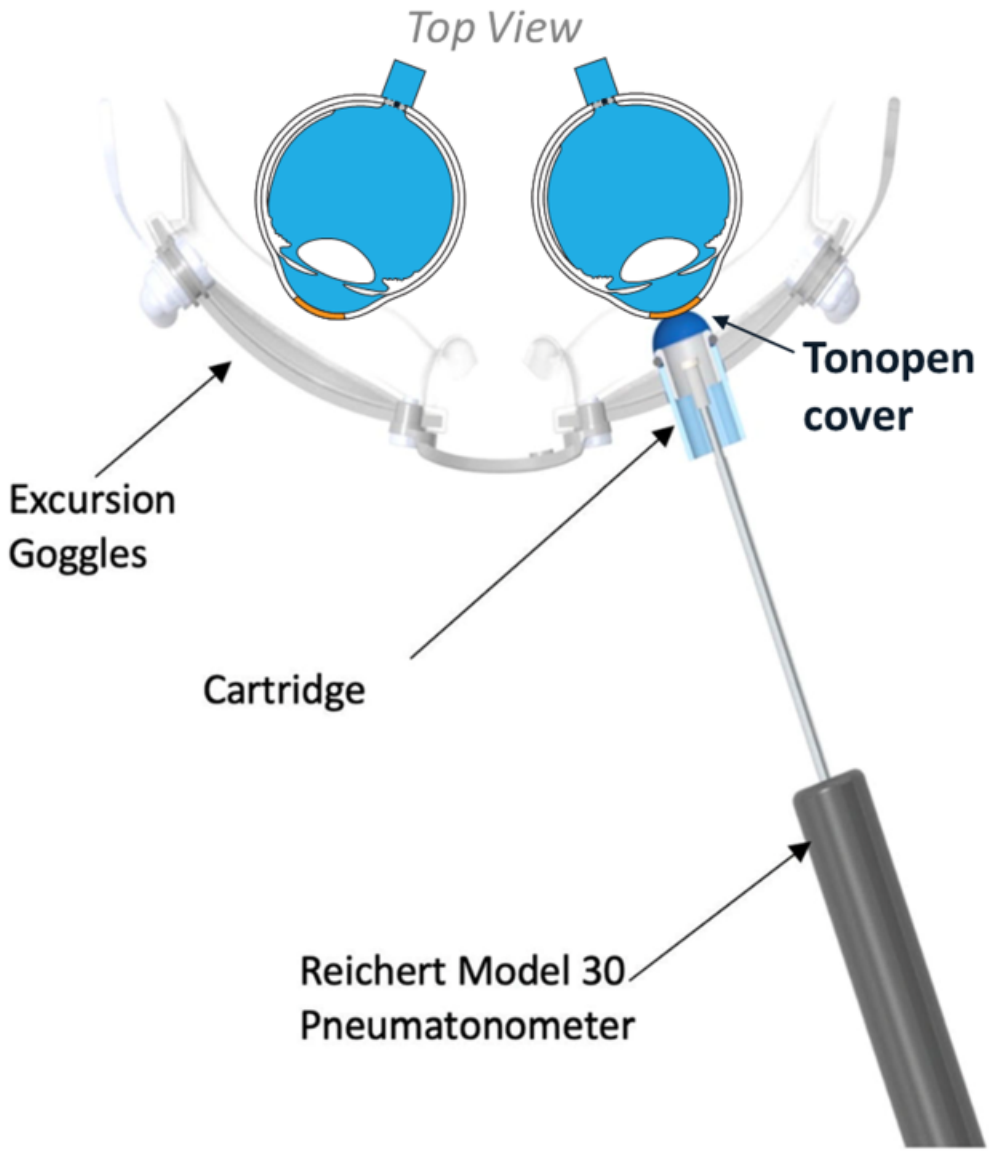
	Support OPAP Lowers IOP
Living Patient study (CONFIRM; CP-X24)	✓
Patients with implanted telemetric IOP sensor	✓
Living Donor study	✓
Cadaver study	✓

Cadaver Study: Negative Pressure Application Resulted in IOP Reduction with Stable Retrobulbar Pressure



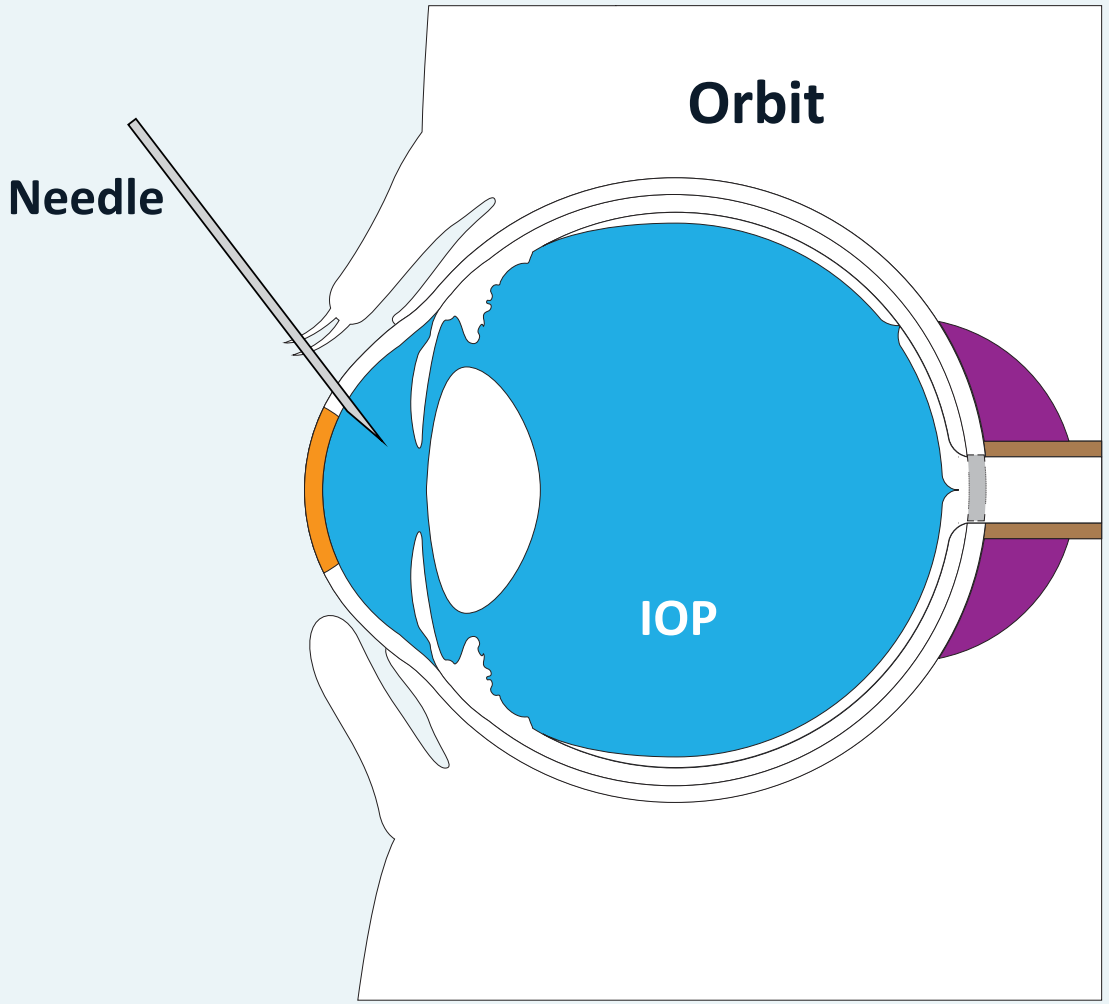
N=2

Excursion Goggles Designed for IOP Measurements



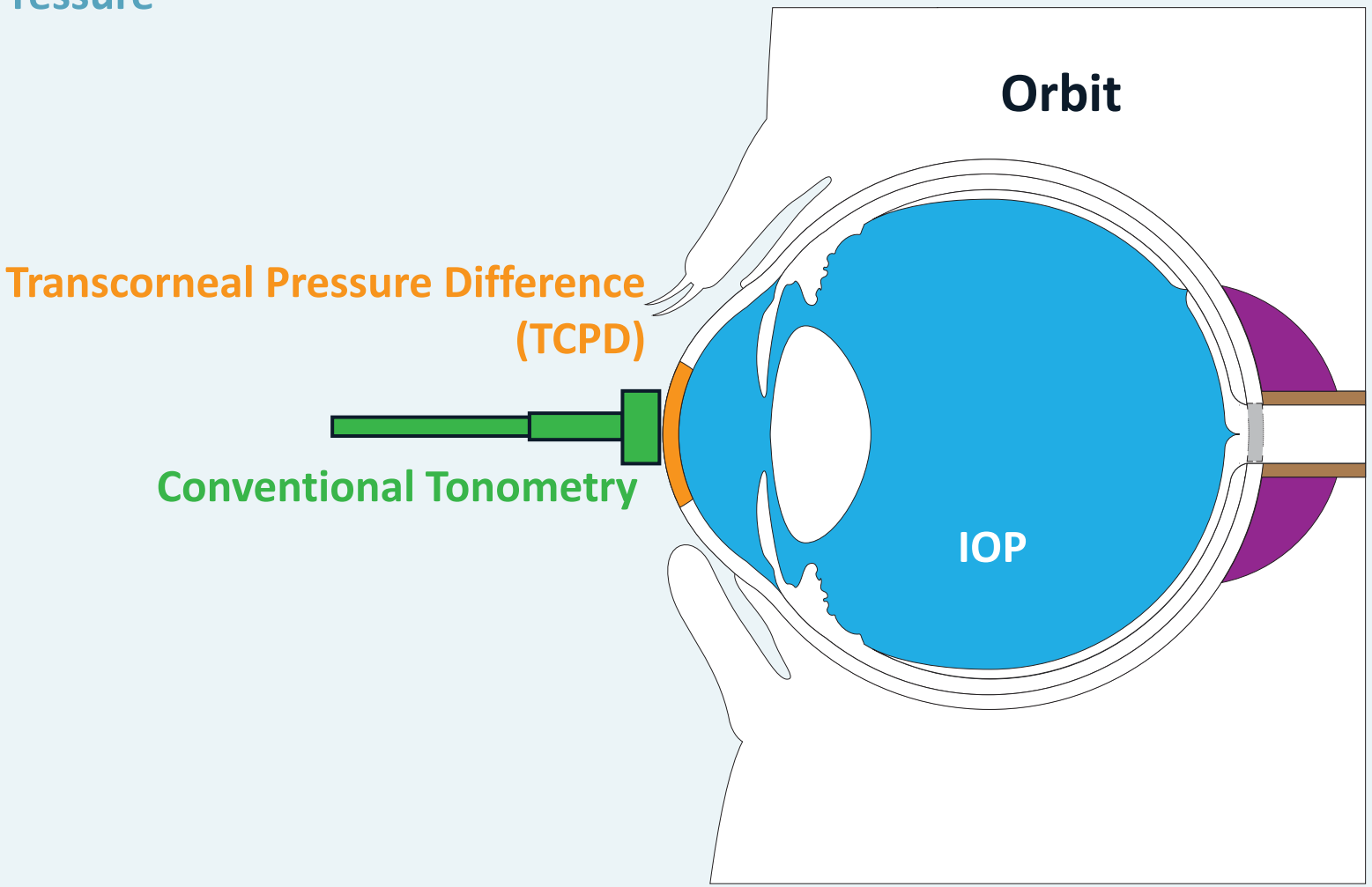
Manometry is the Gold Standard to Measure IOP

Atmospheric Pressure



Transcorneal Pressure is Surrogate to Measure IOP

Atmospheric Pressure



Excursion Tonometry Approximates Goldmann Applanation Tonometry (GAT)

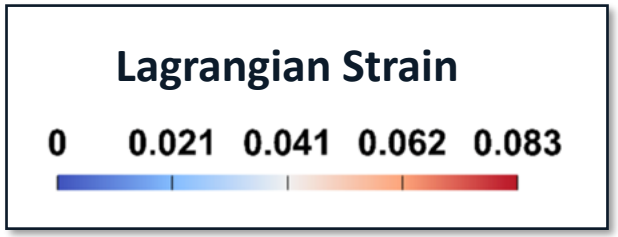
Additional Data Demonstrate Physiological Response to OPAP is Consistent with Lowering IOP

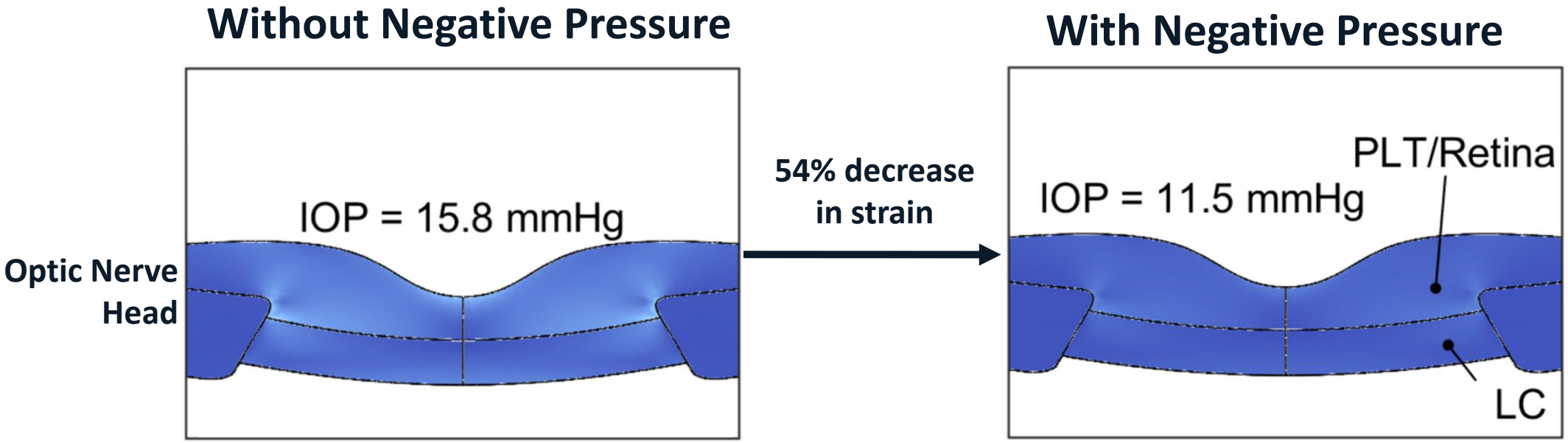
- Increase in blood flow measured by laser speckle flowgraphy[1] (Univ of IA)
- Increase in percent area perfused and capillary density measured by OCT-A[2] (UCSD)
- Improvement in pattern ERG[3] (VTV)
- Improvement in metabolic function* measured by flavoprotein fluorescence[4] (Stanford)

*** Device used to evaluate metabolic function is not FDA cleared**

1. Hashimoto, 2020; 2. Kamalipour, 2022; 3. Kudrna, 2020; 4. Sun, 2022

Reducing IOP Decreased Tissue Strain at Optic Nerve Head





Application of negative pressure led to 54% decrease in tissue strain at optic nerve head

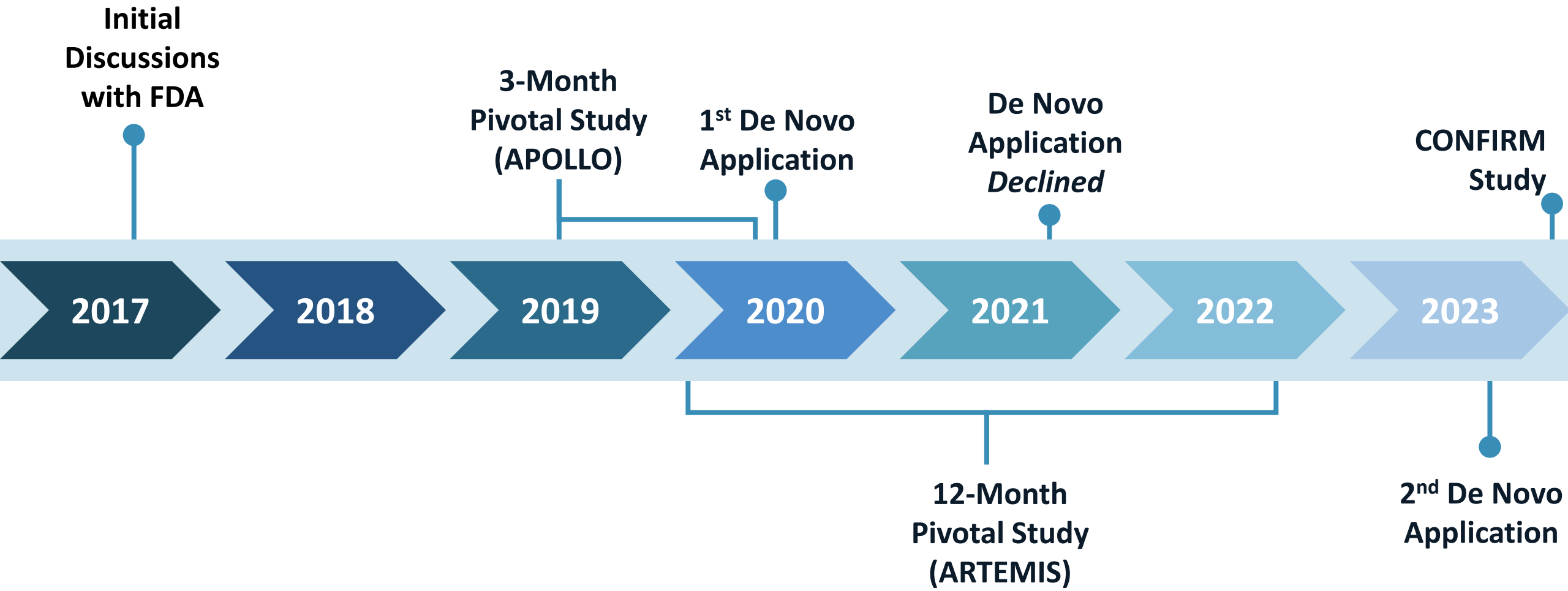
Safa, 2023; based on computational modeling

Multiple OPAP Studies Support Device Use

- 23 studies with consistent safety and effectiveness results
  - 12 clinical*
  - 11 non-clinical
- 15 peer-reviewed publications
- 634 study and control eyes evaluated (378 patients)*

*** 5 clinical studies with current version of device. Studied eyes include those with OAG, NTG, OHTN, glaucoma suspect and healthy eyes.**

Regulatory History



De Novo Request Requires FDA to Make Risk-Based Classification Decision

Key Messages for Today

Unmet Need

- 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

Effectiveness

- 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

Safety

- No device-related SAEs
- 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

Presentation Agenda

Unmet Need

Leon Herndon, MD
Professor of Ophthalmology & Chief of Glaucoma Division
Duke Eye Center

Study Design

Ginger Clasby, MS
Clinical and Regulatory Affairs Consultant

Effectiveness Results and Clinical Safety

Thomas W. Samuelson, MD
Adjunct Professor of Ophthalmology
University of Minnesota

Clinical Perspective

Leon Herndon, MD

Additional Experts for Q&A

Phil Phillips
Regulatory Consultant
President, Phillips Consulting Group

Ross Ethier, PhD
Ocular Biomechanics Expert

Chris Mullin, MS
Statistician
NAMSA

Enrico Brambilla, ME
Technical Consultant

Philip Desjardins, JD
Partner
Arnold & Porter

Unmet Need for an Adjunctive Therapy to Lower IOP in Patients with Open Angle Glaucoma and IOP ≤ 21 mmHg

Leon Herndon, MD

Professor of Ophthalmology and Chief of Glaucoma Division

Duke Eye Center

Lowering IOP is Mainstay for All Glaucoma Treatment

Lowering IOP Protects the Optic Nerve in Glaucoma

1. Lowering IOP decreases **mechanical strain** experienced by optic nerve
2. Lowering IOP improves **blood flow** to the optic nerve
3. Lowering IOP improves **metabolic function** of the optic nerve

Kingman, 2004; Sheybani, 2020; Weinreb, 2014

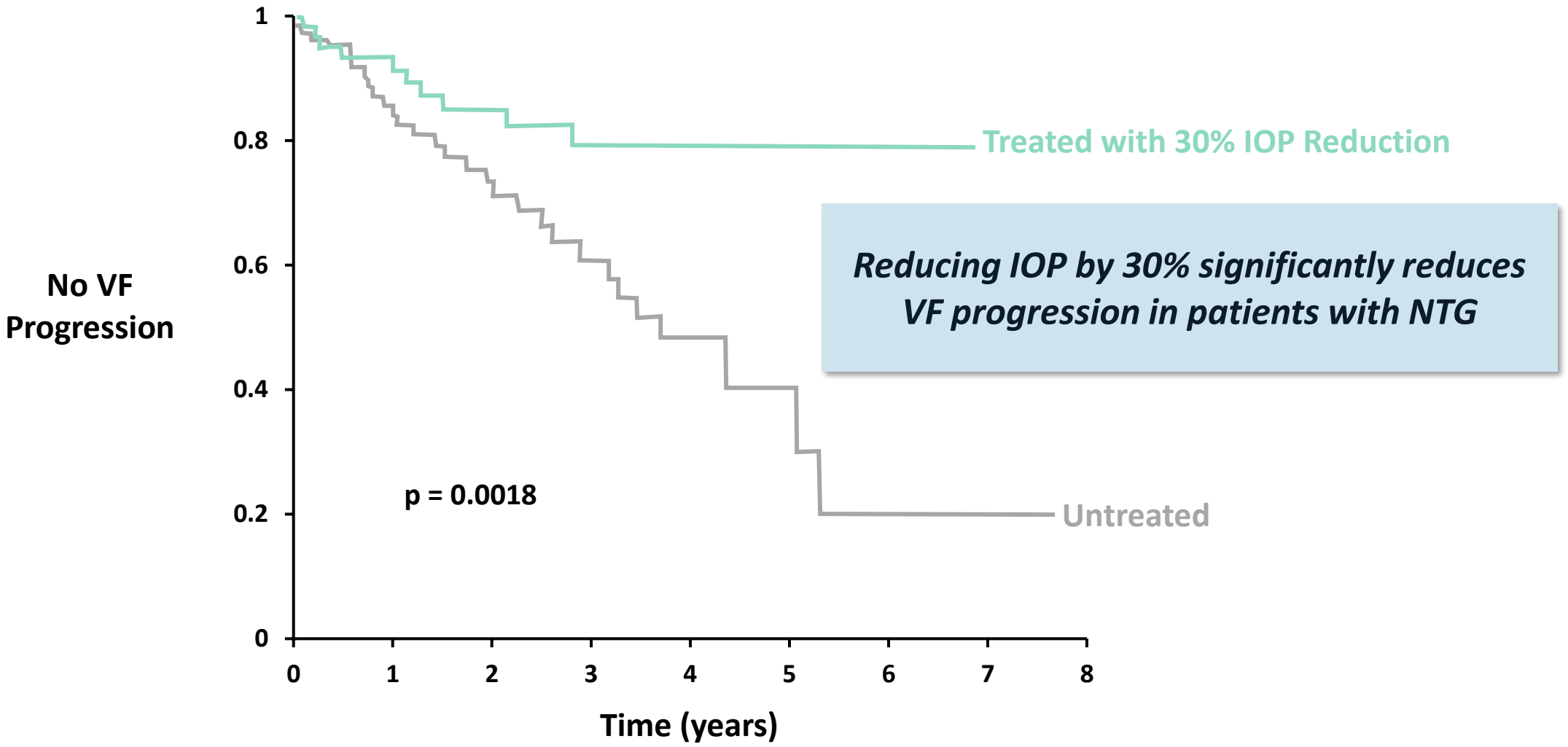
Lowering IOP Significantly Slows Loss of Vision in Patients with Controlled Daytime IOP

- Every 1 mmHg decrease in IOP results in a 10% decrease in glaucomatous progression[1]
- 20 – 30% reduction of IOP confers a 93 – 96% chance of stability[2]
- IOP reduction ≥ 30% associated with 50% reduction of risk of subsequent visual field progression[3]

Every mmHg matters

1. Heijl, 2002; 2. Aoyama, 2010; 3. Membrey, 2001

Reducing IOP by 30% Significantly Reduces Progression of VF in NTG



Collaborative Normal-tension Glaucoma Study Group, 1998: RCT, ITT Analysis, 24 centers, 145 participants

Lowering IOP is Only Proven Treatment for All Forms of Glaucoma

- **IOP lowering is the only way to slow glaucoma progression**
- **American Academy of Ophthalmology[1]**
  - "Primary open-angle glaucoma patients often have untreated IOP consistently within the normal range (i.e., normal tension glaucoma). Lowering pressure in these patients is beneficial."
- **All FDA-approved glaucoma treatments have been approved on the basis of lowering IOP**

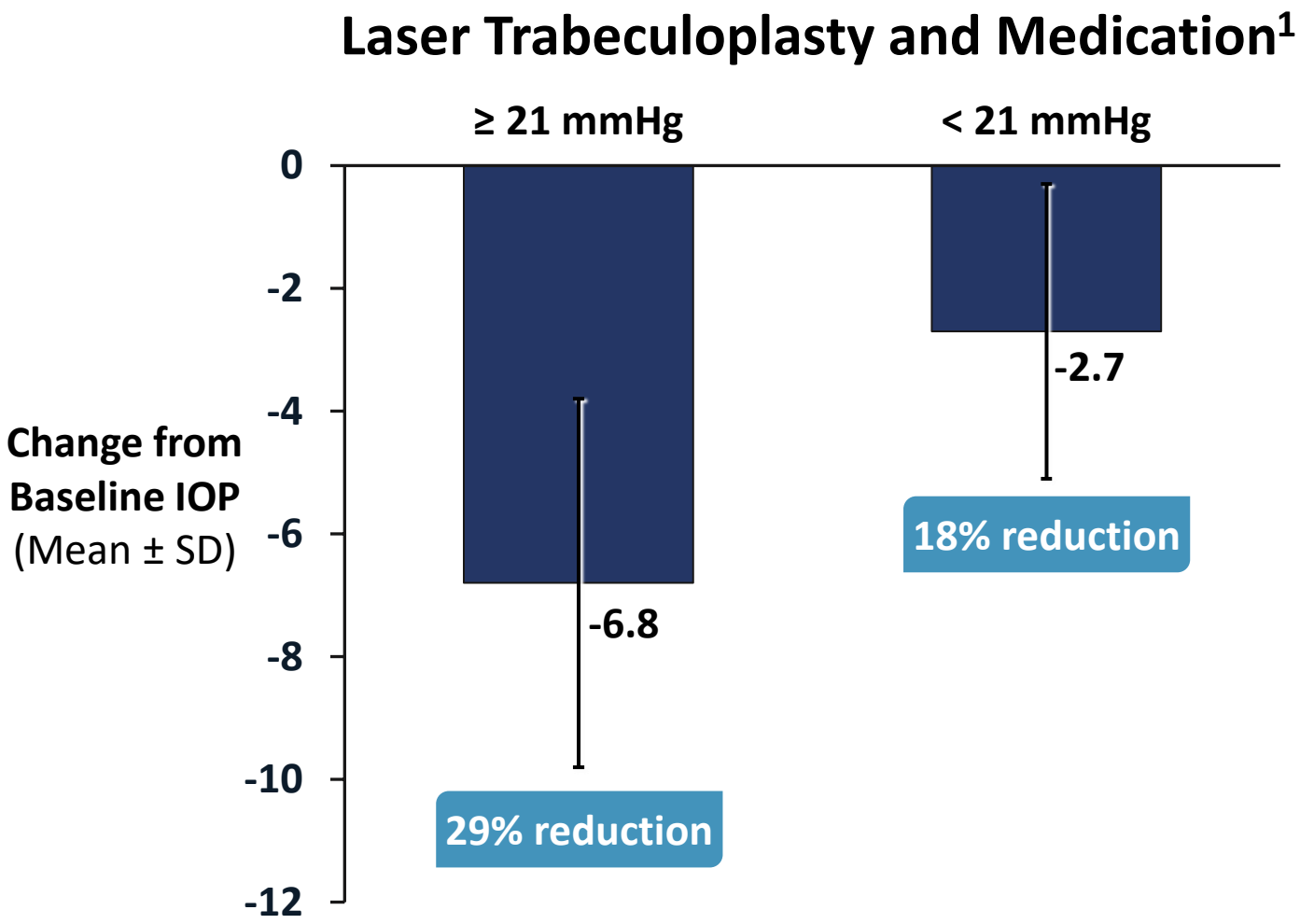
1. AAO PPP Glaucoma Committee, 2021

Current Treatment Options

- **Ocular hypotensives / eye drops**
  - beta blockers, alpha agonists, cholinergics, carbonic anhydrase inhibitors, prostaglandins, and rho kinase inhibitors
- **Laser Trabeculoplasty**
- **Surgical treatments**
  - Minimally invasive glaucoma surgery (MIGS)
  - Subconjunctival procedures (tube shunts, XEN, trabeculectomy)

Most treatments are less effective at night and in patients whose IOP is $\leq$ 21mmHg

Current Treatments are More Effective When IOP is Elevated



Minimally invasive glaucoma surgery (MIGS)[2]

- More effective in patients with IOP > 21 mmHg
- Almost no effect when IOP was ≤ 16 mmHg

1. Heijl, 2002; 2. Ferguson, 2016

Greatest Unmet Need is for Glaucoma with IOP ≤ 21 mmHg

- In NTG patients
  - Only 50% of treated eyes achieve a 30% IOP lowering[1]
  - 34% of treated patients show progression[2]
  - 10% go blind in 1 eye[3]
  - 1.5% go blind in both eyes[3]

1. Anderson, 2001; 2. Kwon, 2019; 3. Sawada, 2015

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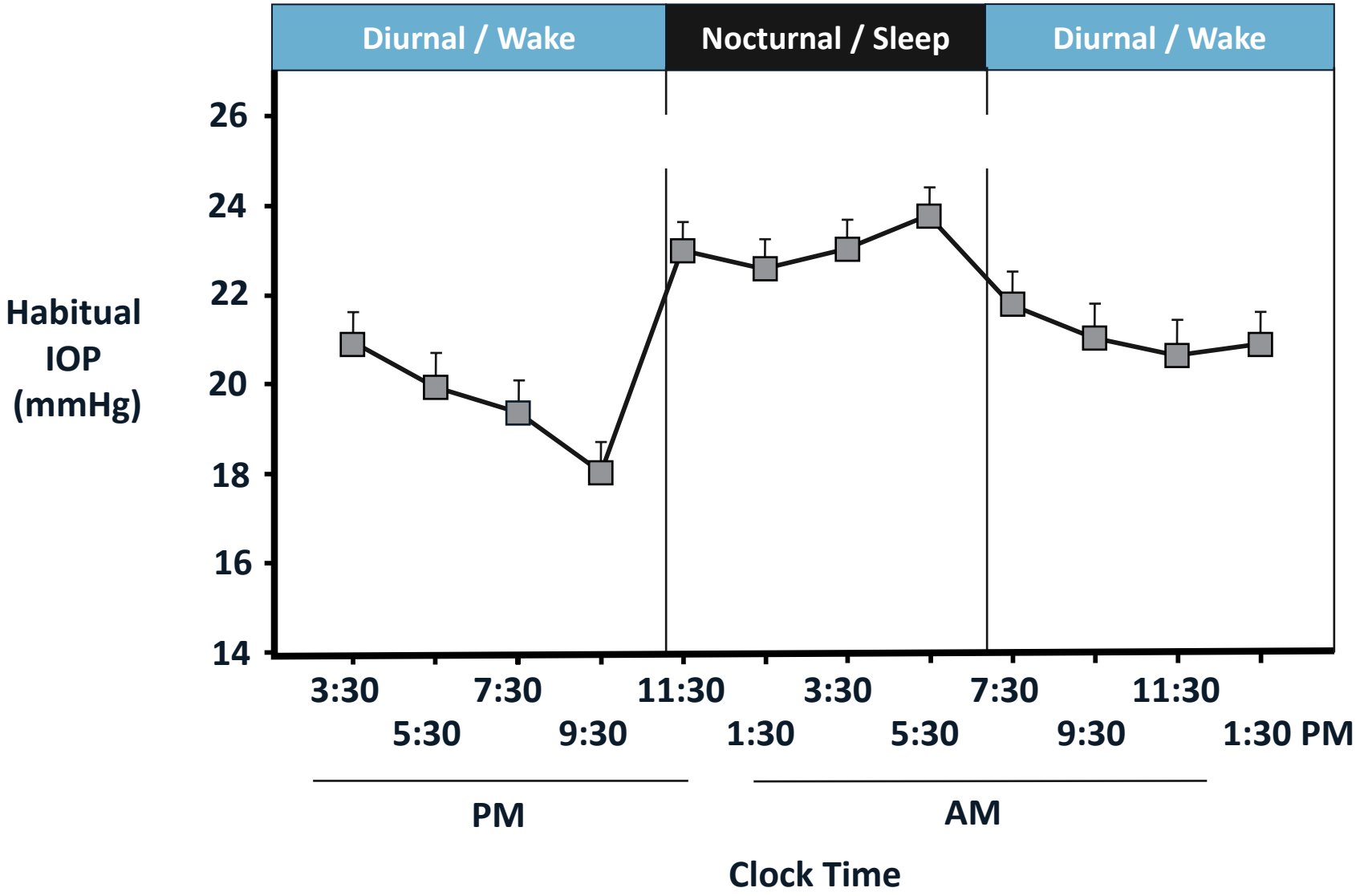
Highest IOP Occurs at Night



Adapted from Mosaed, 2005

FDA Question 1

Nocturnal IOP Elevation Correlates with Visual Field Progression

- 79% (15/19 of eyes) with progression had nocturnal IOP elevation

Table 2: Correlation between Nocturnal IOP Related Peak and Clinical and Demographic Parameters [Chi square test]

Parameters	Parameter subtype	Nocturnal IOP related peak	No nocturnal IOP related peak	*P*
No. of eyes		23	17	
Progression	Progressors-No.[%]	15 [65.21%]	4 [23.52%]	<0.009
	Non Progressors-No.[%]	8 [34.78%]	13 [76.47%]	

Dubey, 2020

FDA Question 1

Nocturnal IOP Elevation Correlates with Visual Field Progression

- Daytime IOP can miss nocturnal IOP elevations in 60% of patients[1]
- Nocturnal mean peak ratio and diurnal-nocturnal IOP elevation were correlated with visual field progression[2,3]
- Supine IOP elevation, which closely correlates with nocturnal IOP, is associated with VF progression[4]
- Patients with increased rate of glaucomatous progression associated with higher and more prolonged increase in nocturnal IOP surrogate measurements[5]
  - Glaucoma patients more likely to have prolonged nocturnal peaks

FDA Question 1

1.Mansouri, 2011; 2. Demoraes, 2016; 3. Matlach, 2019; 4. Rabiolo, 2024; 5. Gaboriau, 2023

Most Medications Do Not Fully Address Nocturnal IOP Elevation

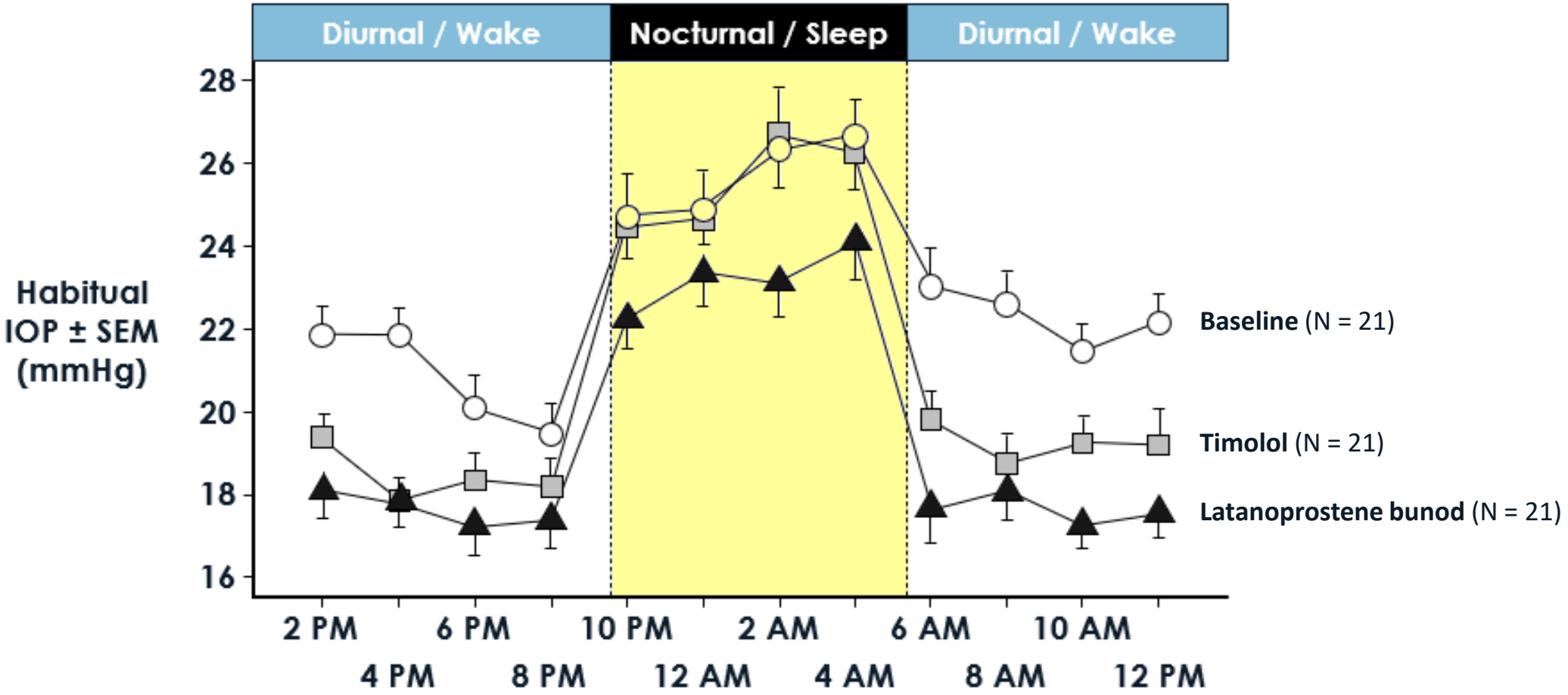


Figure adapted from Liu, 2016

Surgical Procedures Effect on Nocturnal IOP

- SLT did not impact 24-hour rhythm and did not eliminate nocturnal IOP peaks[1, 2]
- No data available for MIGS effect on nocturnal IOP
- Trabeculectomy is only procedure that can provide 24-hour control[3, 4] but is associated with surgical morbidity

1. Aptel, 2017; 2. Gazzard, 2019; 3. Klink, 2012; 4. Caprioli, 2016

Summary of Unmet Need

- IOP increases at night in most glaucoma patients, even in those with normal daytime pressure
- Nocturnal IOP increases are associated with glaucomatous progression
- Most therapies have minimal impact on nocturnal IOP elevations
- Most therapies have limited effect in patients with IOP less than 21 mmHg

We need therapies that can adjunctively reduce IOP at night in patients with normal daytime IOP

APOLLO Study Overview and ARTEMIS Study Design

Ginger Clasby, MS

Clinical and Regulatory Affairs Consultant

APOLLO: 3-Month Study Design

- Prospective, multi-center, randomized, controlled, masked pivotal study
- N=64 patients
- Patients used OPAP nightly for 90 days
- One eye randomized as treatment (NP) and other as control (no NP)
- Primary endpoint at Day 90
  - Proportion of eyes with ≥ 20% IOP reduction during NP application
- Safety assessed throughout

APOLLO: Key Inclusion/Exclusion Criteria

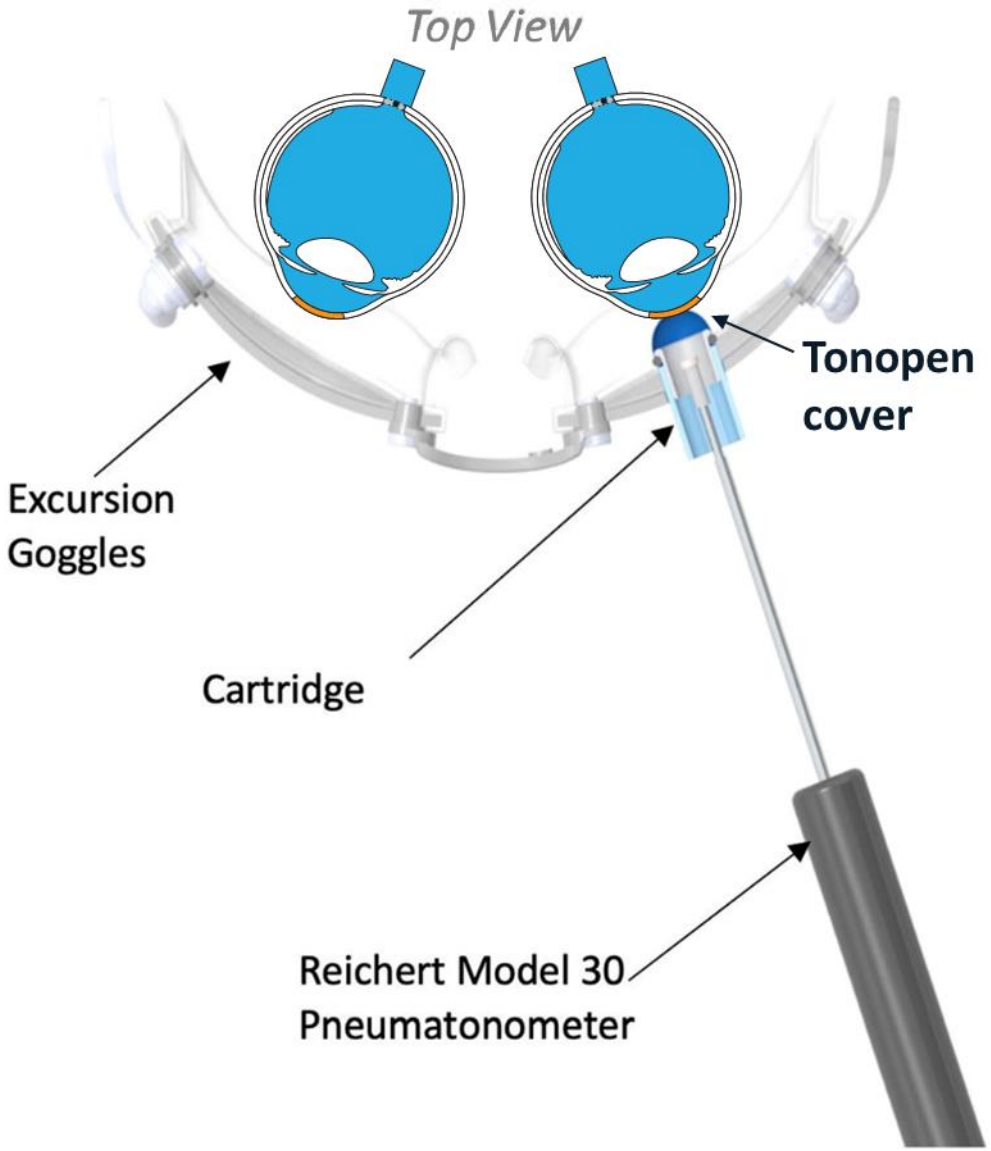
Inclusion Criteria

- Age ≥ 22
- Diagnosis of ocular hypertension, glaucoma suspect, or OAG
- IOP between 13 and 32 mmHg, inclusive
- Best corrected distance visual acuity (BCDVA) better than 20/200
- Orbital anatomy permitting proper seal

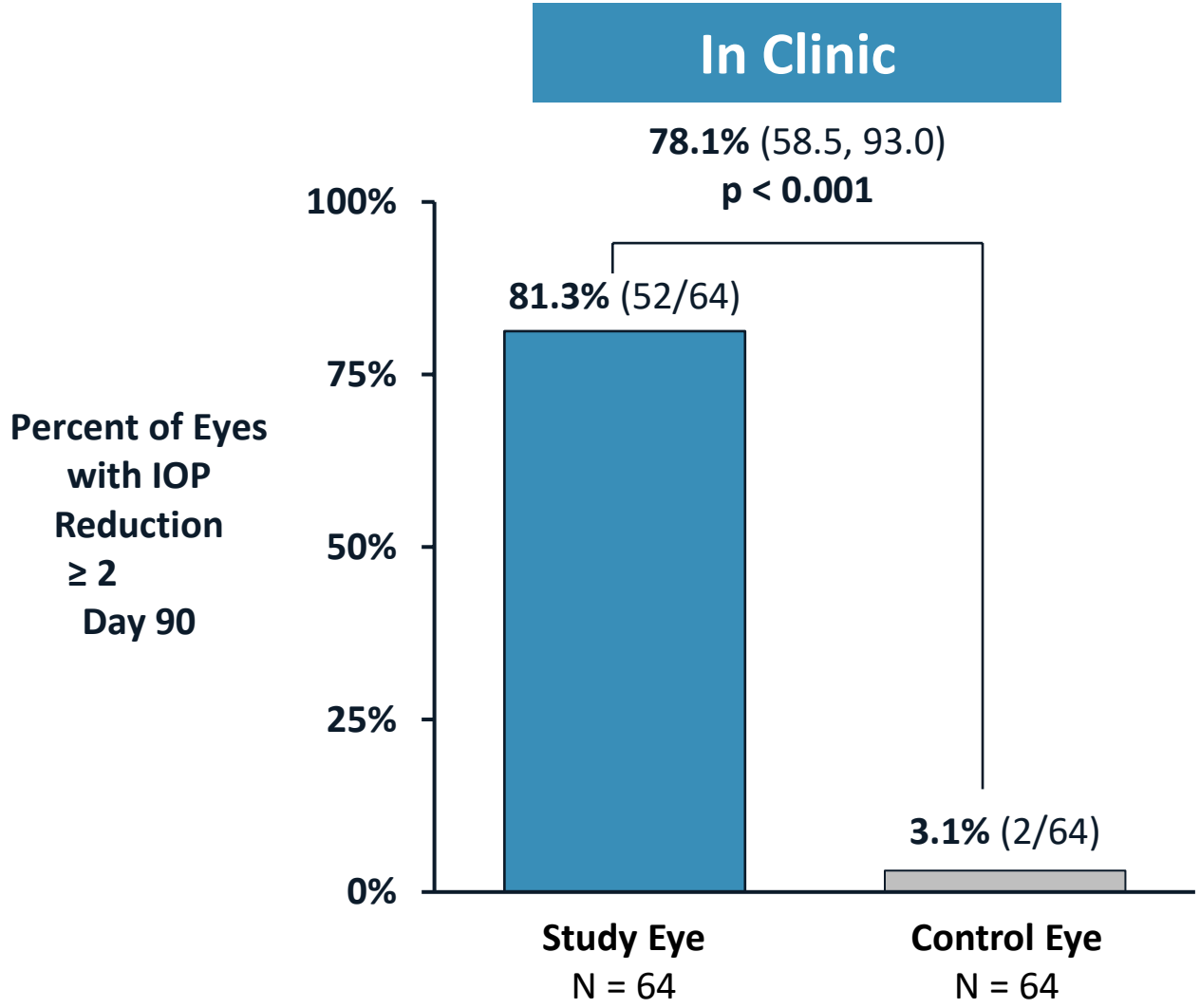
Exclusion Criteria

- Fundus findings that may prevent visualization of the retina in either eye
- Prior trabeculectomy or tube shunt
- Narrow anterior chamber angle anatomy, conjunctival chemosis, or active inflammation

Excursion Goggles Designed for IOP Measurements



APOLLO Primary Effectiveness Endpoint Achieved: Percent of Eyes with IOP Reduction ≥ 20% at Day 90 (mITT)



Missing data/discontinuations imputed as failure; IOP measured during NP application

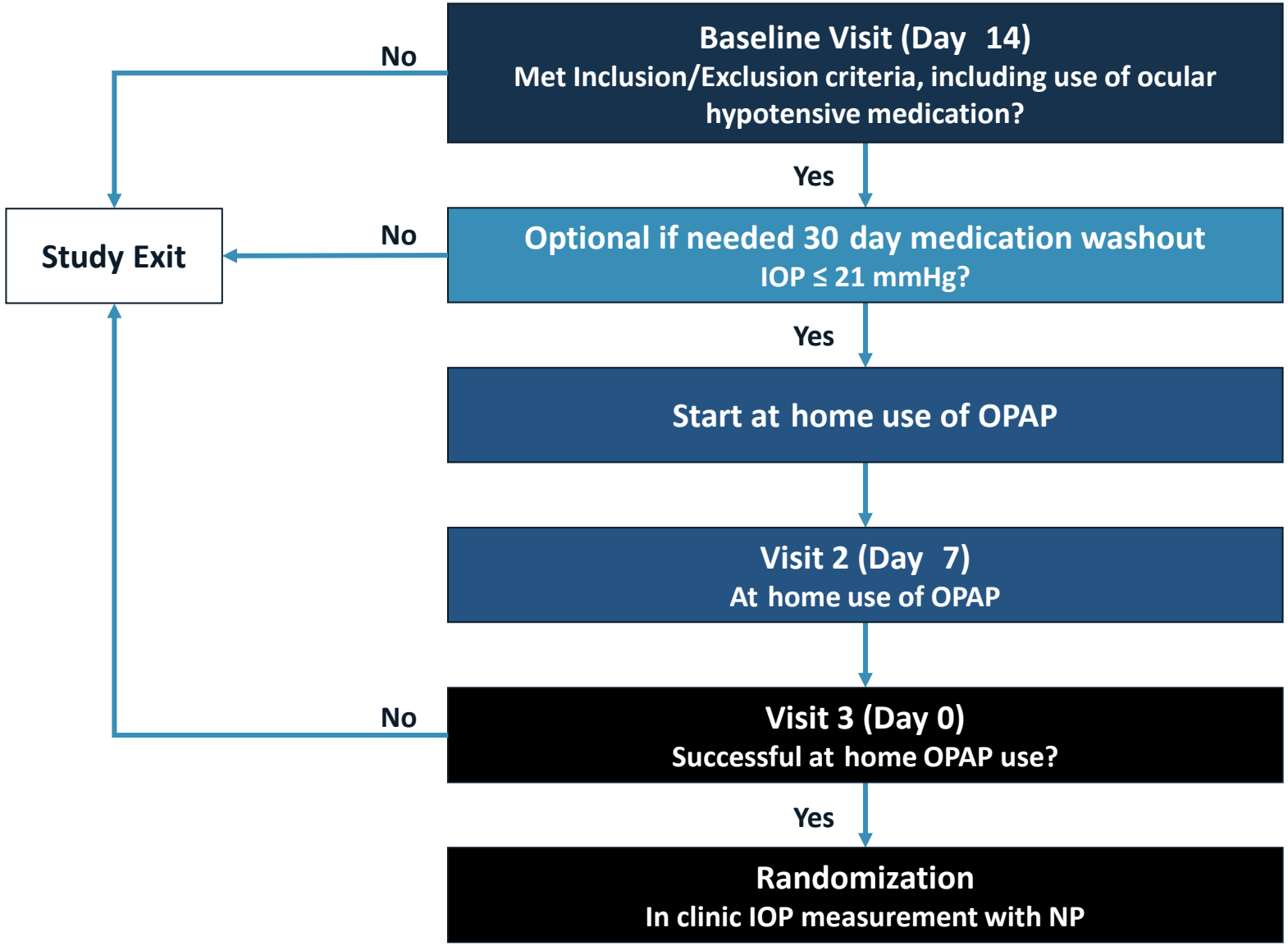
APOLLO Safety Findings Over 3-Month Study Duration

- No device-related SAEs
- All ocular and periorbital AEs were considered mild-to-moderate in nature
  - Most frequently reported events were lid or periorbital edema
- Independent, masked review performed by the University of Iowa Visual Field Reading Center (VFRC)
  - Found no evidence of glaucomatous progression

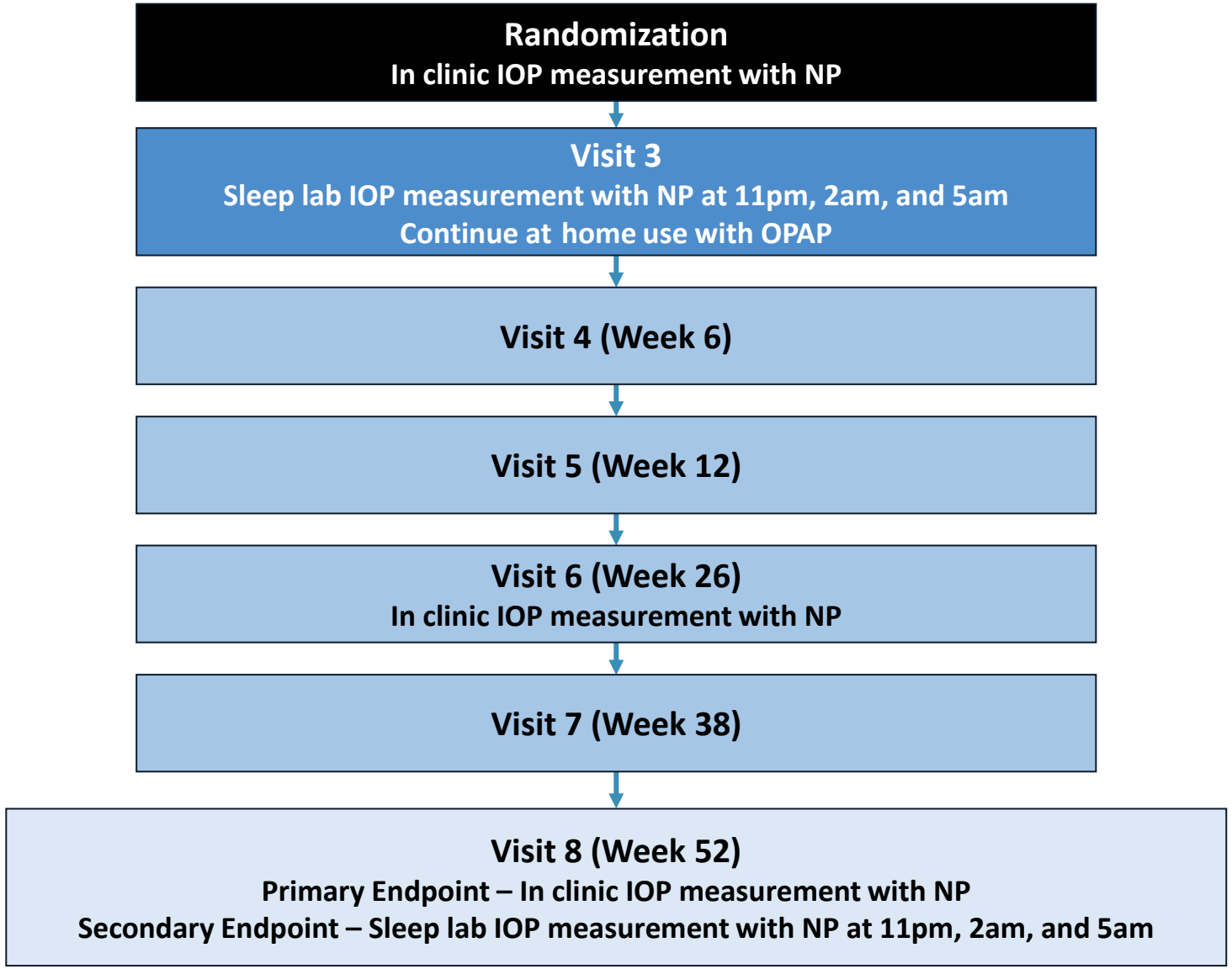
Pivotal 12-Month Study

ARTEMIS Study Design

ARTEMIS Study Clinical Design



ARTEMIS Study Clinical Design



Negative Pressure Programmed Based on Baseline IOP

- Programmed NP based on baseline IOP and reference IOP of 6 mmHg
- NP after initial sleep lab based on sleep lab IOP measurement
- Investigators given discretion to reduce NP based on patient comfort

Evaluations Performed by Masked Site Personnel

- Study eye treatment programmed by designated, trained staff who monitored patients' treatment compliance
  - Negative pressure settings could only be adjusted by this staff
- Effectiveness evaluations performed by qualified personnel masked to treatment assignment
- Visual field and optical coherence tomography images evaluated by 3 masked readers

Key Inclusion/Exclusion Criteria

Inclusion Criteria

- Age ≥ 0
- Diagnosis of NTG
- Unmedicated IOP between 12 and 21 mmHg in both eyes
- BCDVA better than 20/200
- Orbital anatomy permitting proper seal
- Ability to successfully average ≥ 3 hours of sleep wear during ≥ 3 of 7-day run-in period

Exclusion Criteria

- Fundus findings that may prevent visualization of the retina in either eye
- Prior trabeculectomy or tube shunt
- Narrow anterior chamber angle anatomy, conjunctival chemosis, or active inflammation

20% Reduction in IOP Selected as Trial Endpoint Based on FDA Guidance

GUIDANCE DOCUMENT

Premarket Studies of Implantable Minimally Invasive Glaucoma Surgical (MIGS) Devices

Guidance for Industry and Food and Drug Administration Staff

DECEMBER 2015

2. Primary effectiveness

The recommended primary effectiveness endpoint is the percentage of subjects with reduction of at least 20% (i.e., ≥20%) in mean diurnal IOP from baseline. [5-9] The proposed hypothesis test for the primary effectiveness endpoint should be described in the statistical analysis plan.

FDA, 2015

Pre-specified Primary and Secondary Effectiveness Endpoints

- Primary effectiveness endpoint
  - Proportion of study eyes with Week 52 **in clinic** IOP reduction ≥ 20% during NP application as compared with baseline
- Secondary effectiveness endpoint
  - Proportion of study eyes with Week 52 **sleep lab** IOP reduction ≥ 20% during NP application as compared with baseline
- Eyes of patients with missing IOP data at Week 52 in clinic or sleep lab considered "failures"

Baseline defined as IOP measurement prior to negative pressure application at specific visit

Safety Outcomes

- Ocular and periorbital AEs
- Non-ocular AEs
- Visual acuity changes
- Clinically significant slit lamp and fundus exam findings
- Changes in
  - Visual field mean deviation (MD)
  - Optical coherence tomography (OCT) imaging

Sample Size Calculation Based on Primary and Secondary Effectiveness Endpoints

- McNemar's exact conditional test
  - Two-sided significance level of 0.05
  - Sample size needed for power: minimum 50 patients at 52 weeks
    - Primary Effectiveness Endpoint: ≥ 92% power
    - Secondary Effectiveness Endpoint: > 80% power

Analysis Populations

Population	Definition	n (%)
ITT	**All randomized patients**	94 **(100%)**
Safety	**All randomized patients who had at least one application (of any duration) of NP to study eye after randomization**	93 **(98.9%)**
mITT	**All randomized patients who had at least one full application of NP to study eye after randomization**	93 **(98.9%)**
Per Protocol (PP)	**All patients in mITT who met all entry criteria, had no major protocol deviations, and completed their Week 52 visits**	60 **(63.8%)**

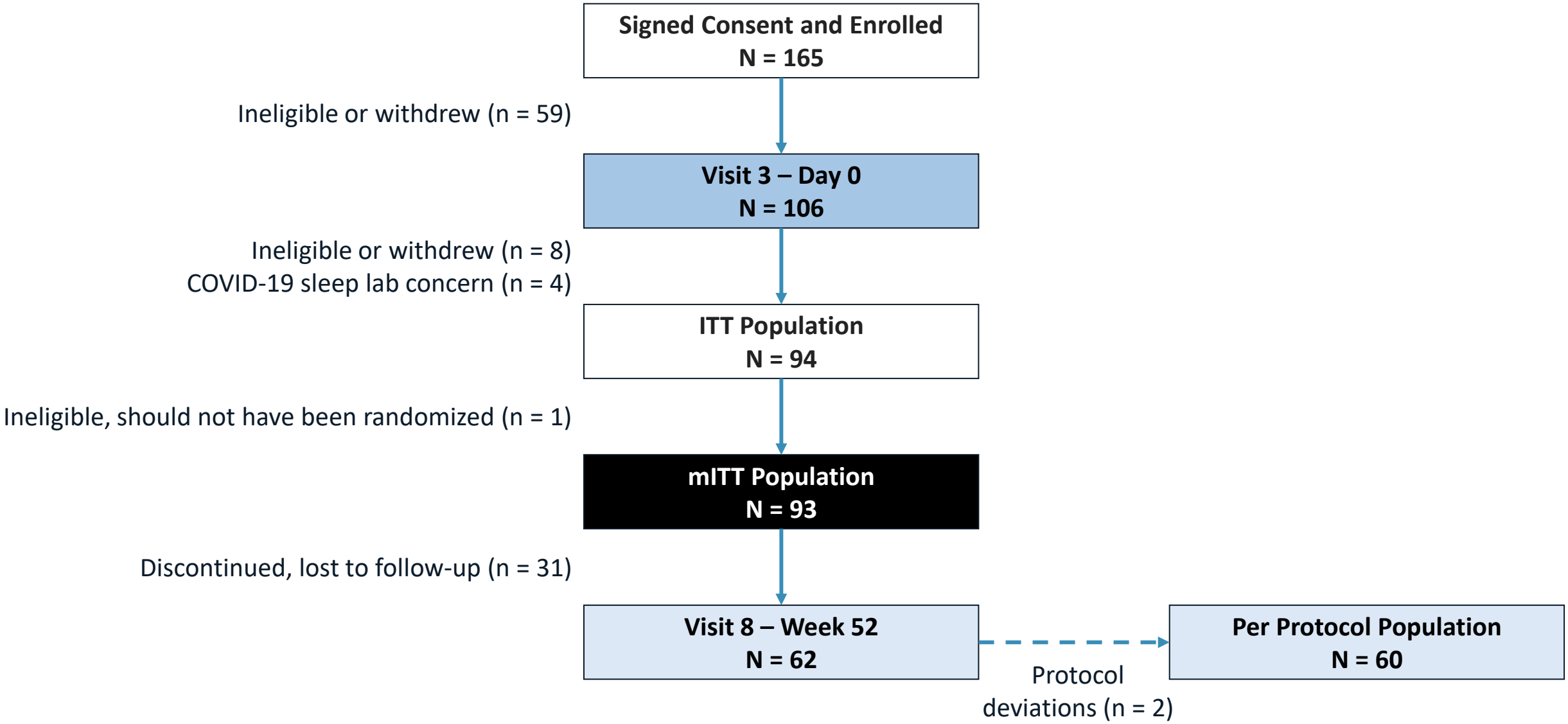
ARTEMIS Trial Results

Thomas W. Samuelson, MD

Adjunct Professor of Ophthalmology

University of Minnesota

Disposition



Demographics

	N = 93
Age, median (min, max)	**61** (40, 85)
Female	**68%**
Race	
White	**69%**
Black or African American	**14%**
Asian	**16%**
Other	**1%**
Ethnicity	
Hispanic or Latino	**19%**
Not Hispanic or Latino	**81%**
Study Eye	
Right	**49%**
Left	**51%**

Baseline Characteristics

	Study Eye N = 93	Control Eye N = 93
Mean IOP, mmHg (SD) (GAT)	**14.7** (2.0)	**14.8** (2.2)
Topical ocular hypotensive medications		
0	**44%**	**46%**
1+	**56%**	**54%**
Previous surgical procedure*		
Minimally invasive glaucoma surgery (MIGS)	**5%**	**5%**
Glaucoma laser procedure	**15%**	**19%**
Cataract surgery	**20%**	**19%**
Mean BCDVA, LogMAR (SD)	**0.06** (0.12)	**0.08** (0.14)
Mean central corneal thickness, µm (SD)	**536.2** (38.2)	**538.1** (37.5)
Gonioscopy Shaffer Grade III-IV	**100%**	**100%**
Mean vertical cup to disc (SD)	**0.67** (0.15)	**0.66** (0.16)
Visual field mean deviation, dB (SD)	**-4.03** (4.86)	**-3.67** (4.65)

*** Data in category not previously reviewed by FDA**

Key Topics FDA is Asking Panel to Discuss

1 Clinical Benefit

Do you believe there is clinical benefit to the lowering of this alternative IOP parameter and increasing of TCPD on a daily basis for several hours?

2 Effectiveness

Do you believe the IOP lowering as measured by excursion tonometry during use of the device, in combination with data from the other supportive studies demonstrates a reasonable assurance of effectiveness?

3 Safety

Do you believe the available data demonstrates reasonable assurance of safety at 1 year / long-term safety?

4/5 Labeling

Do you believe the available data supports the proposed range of programmable NP / wear time?

Does the proposed IFU statement use the appropriate nomenclature and language to accurately describe the function of the device with regard to IOP?

6 Benefit-Risk

Do the probable benefits of the FSYX OPAP device outweigh the probable risks for use in patients who meet the criteria specified in the proposed IFU?

OPAP Use Metrics

	Day 0 to Week 6 N = 91	Week 6 to Week 12 N = 81	Week 12 to Week 26 N = 74	Week 26 to Week 38 N = 68	Week 38 to Week 52 N = 65
Mean study eye programmed NP (± SD; mmHg) (min, max)	**10.0 ± 2.4 (5.0, 16.0)**	**12.0 ± 3.1 (6.0, 20.0)**	**12.1 ± 3.0 (6.0, 20.0)**	**11.7 ± 3.1 (5.0, 20.0)**	**11.9 ± 3.8 (5.0, 20.0)**
% of nights with OPAP Use	**87%**	**86%**	**82%**	**78%**	**79%**
Average nightly wear (hours)*	**5.5**	**5.4**	**5.5**	**5.5**	**5.6**

Baseline programmed NP = 10 ± 2.4 (N = 93)

*** Includes wear time only from nights where usage is > 20 minutes**

Mean Nightly Wear Stable over Course of Study

Average nightly wear*	Day 0 to Week 6 N = 81	Week 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
0 – 4 hours	11 **(13.6%)**	13 **(17.6%)**	13 **(19.1%)**	11 **(16.9%)**	6 **(9.7%)**
> 4 – 6 hours	36 **(44.4%)**	31 **(41.9%)**	24 **(35.3%)**	22 **(33.9%)**	30 **(48.4%)**
> 6 – 8 hours	34 **(42.0%)**	30 **(40.5%)**	30 **(44.1%)**	31 **(47.7%)**	24 **(38.7%)**
> 8 hours	0	**0**	1 **(1.5%)**	1 **(1.5%)**	2 **(3.2%)**

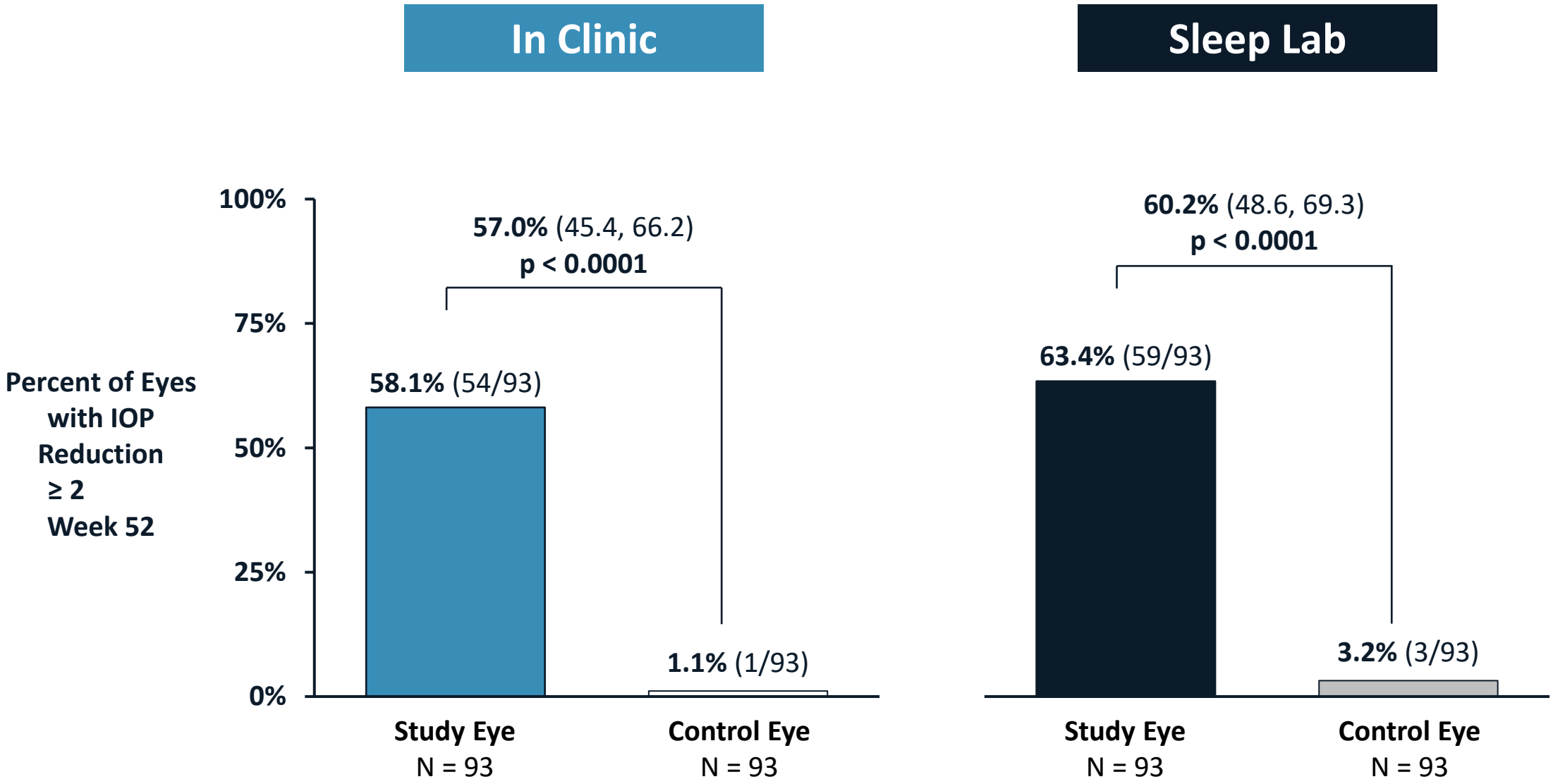
*** Includes wear time only from nights where OPAP usage is > 20 minutes**

Current Labeling on OPAP Use

- Instructions for Use:
  - **Right Eye**: Enter NP value for right eye. Values can be 0, -5mmHg to -20mmHg in 1mmHg increments. The – sign is automatically added.
  - **Left Eye**: Enter NP value for left eye. Values can be 0, -5mmHg to -20mmHg in 1mmHg increments. The – sign is automatically added.
  - **Duration**: Enter the amount of time planned for treatment. Treatment duration can range from 1 to 8 hours. If not programmed to stop earlier, the OPAP will automatically stop treatment after 8 hours.

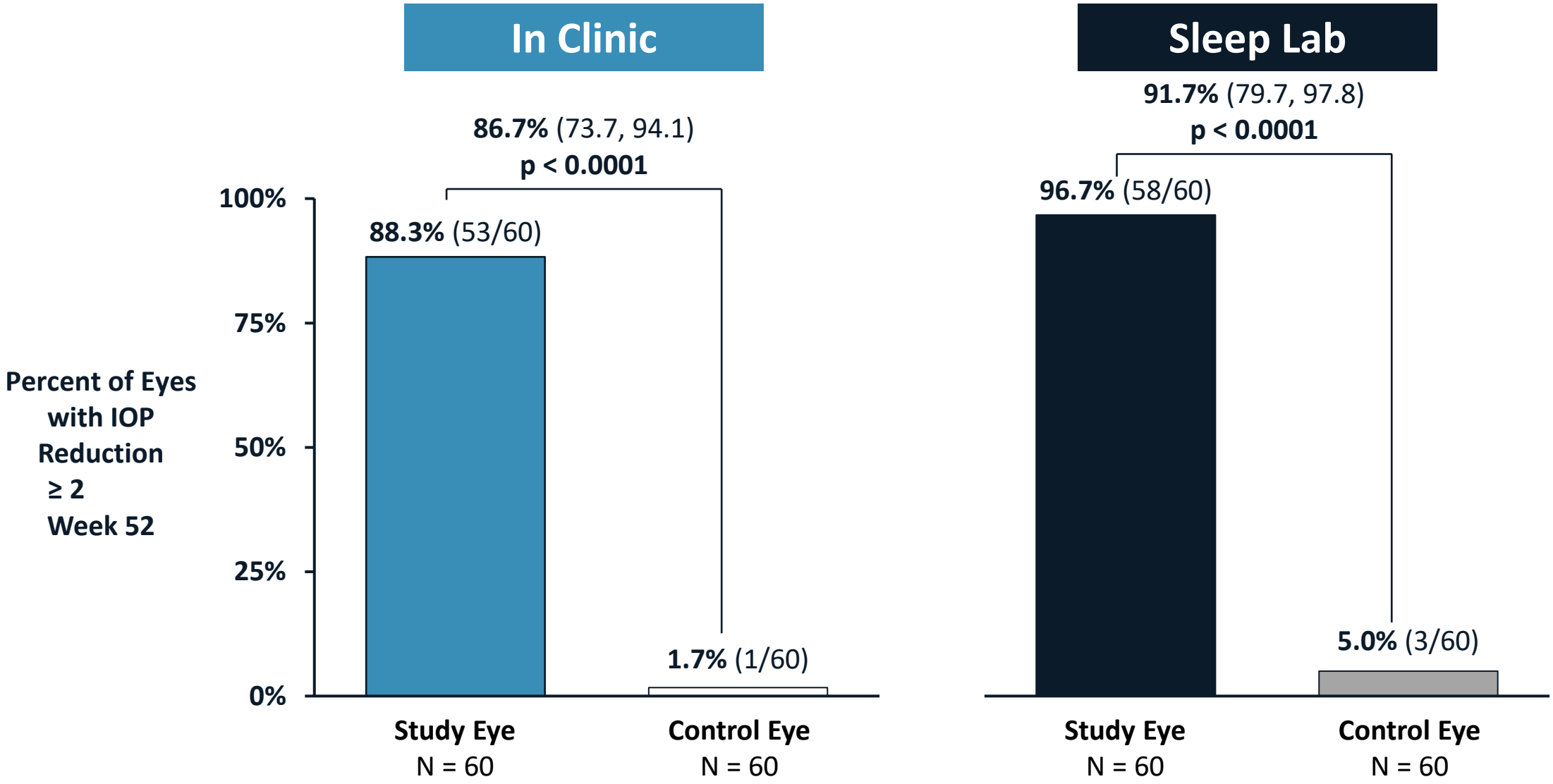
Effectiveness

Primary and Secondary Effectiveness Endpoints Achieved: Percent of Eyes with IOP Reduction ≥ 20% at Week 52 (mITT)

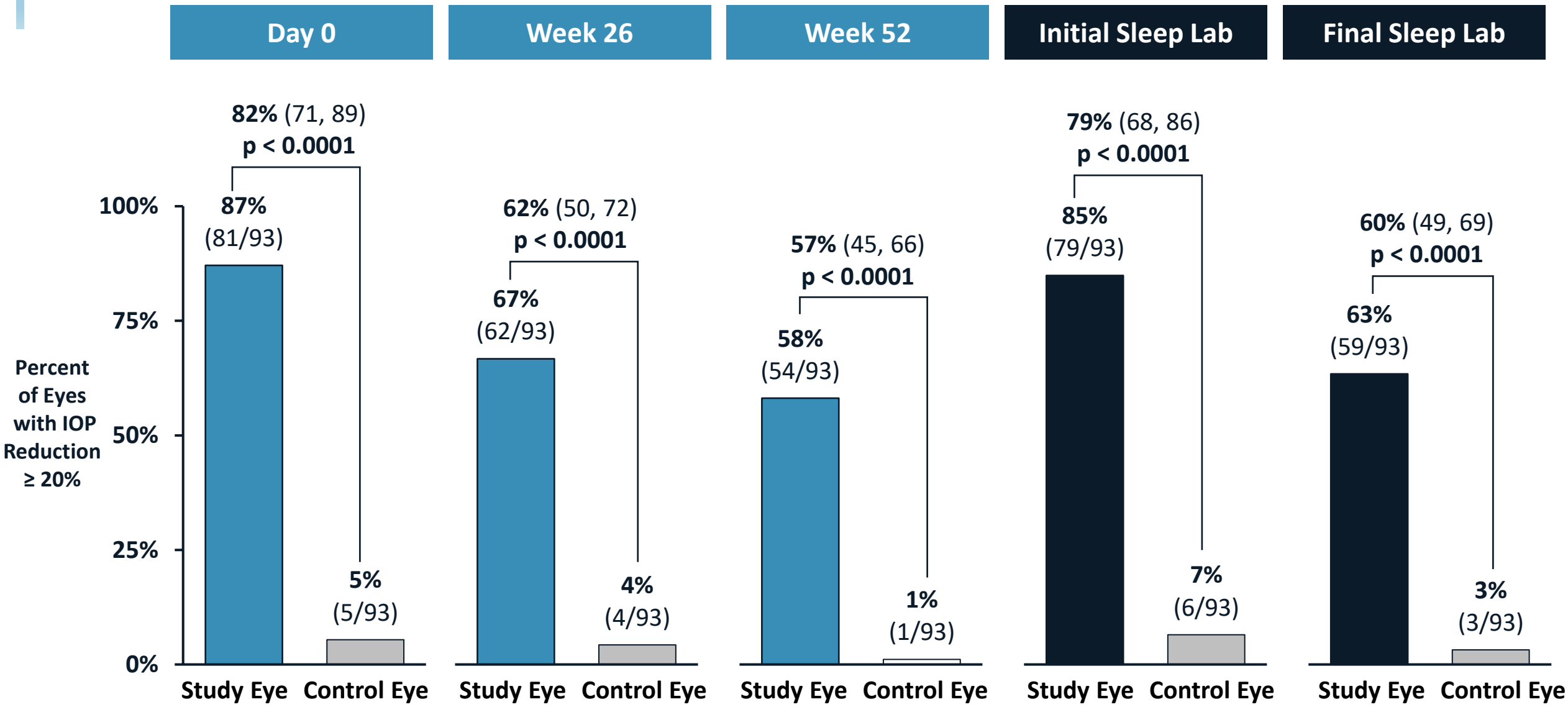


Missing data/discontinuations imputed as failure

Per Protocol Analysis Demonstrates Robustness of Findings

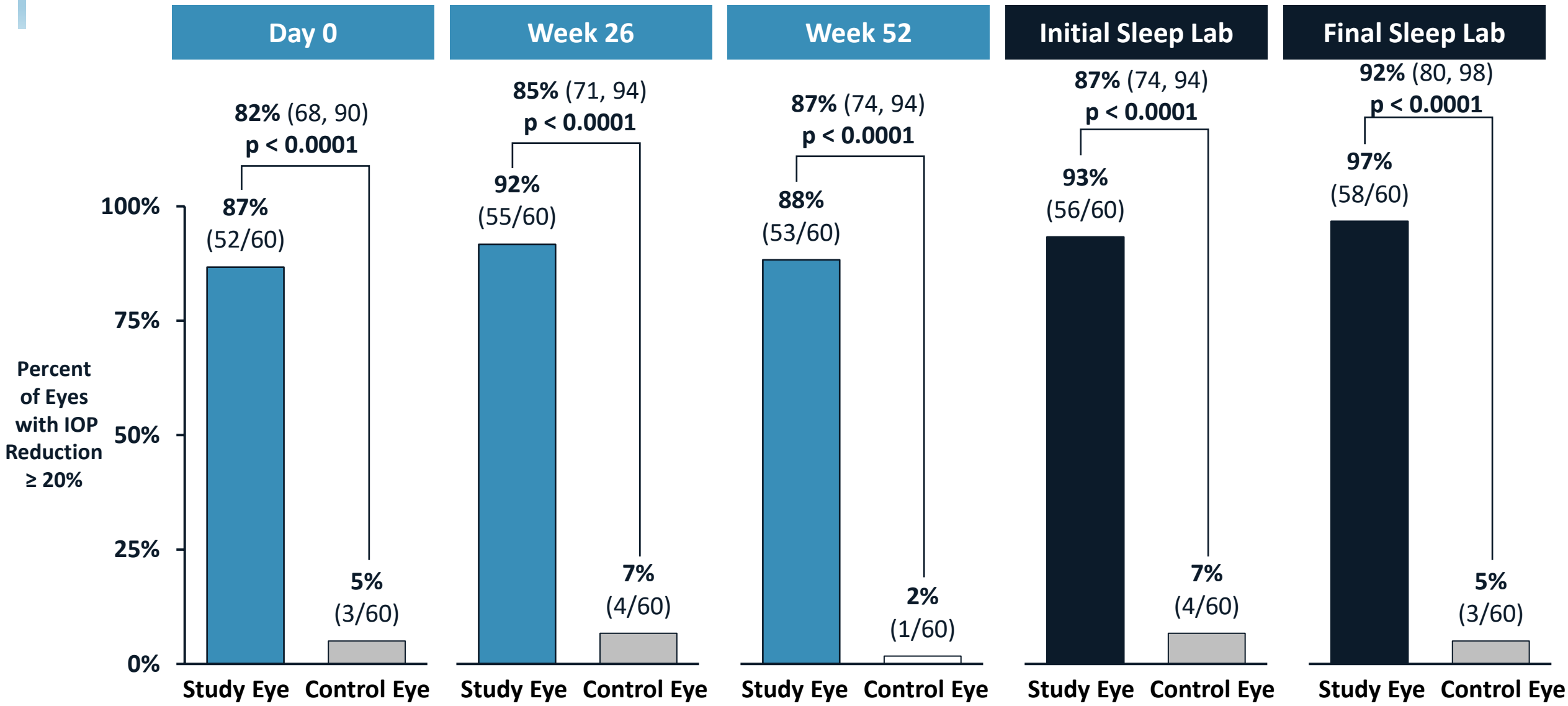


Secondary Analysis: Results Demonstrate Robustness of Effect (mITT – Missing Data / Discontinuations Imputed as Failure)



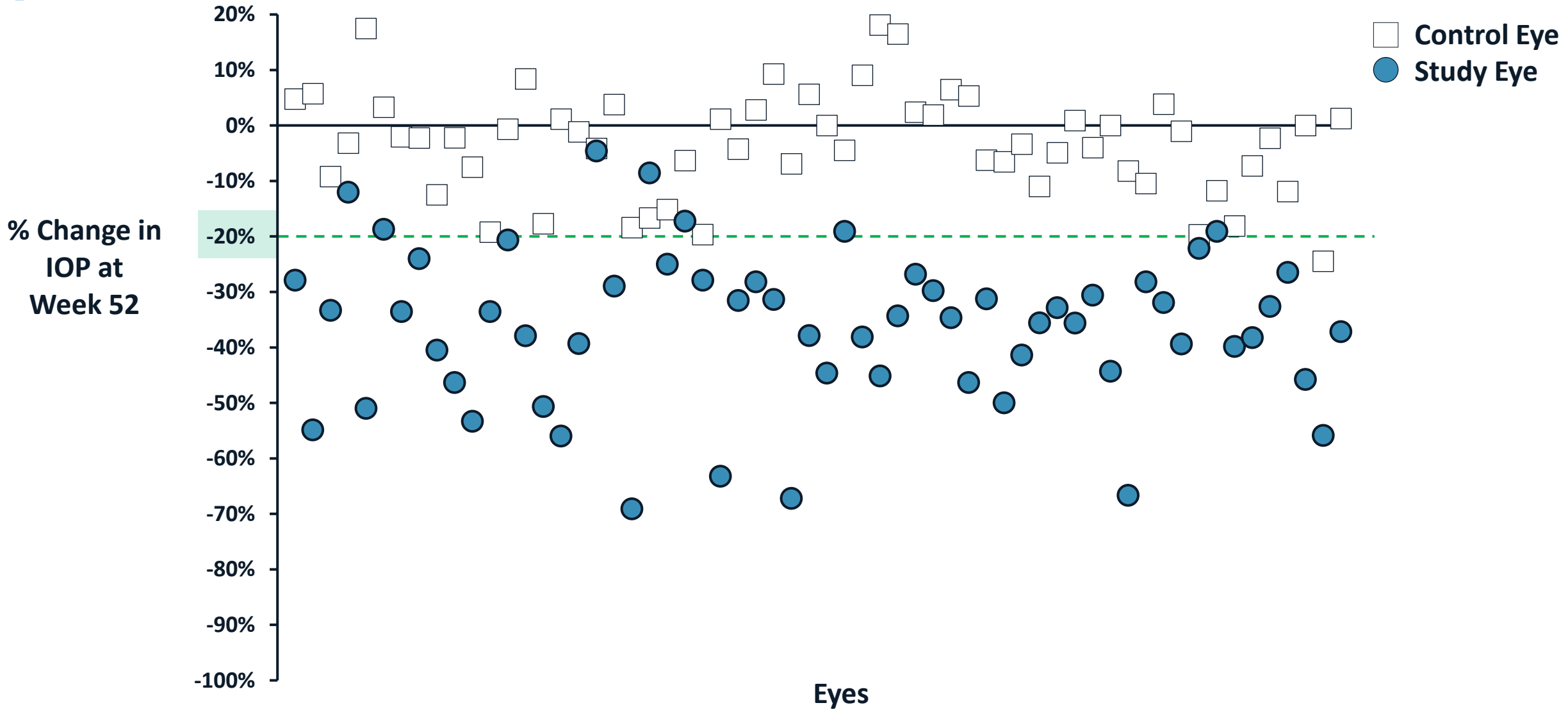
P-values/CIs at Day 0, Week 26 and initial sleep lab were not pre-specified or adjusted for multiple comparisons

Secondary Analysis of Primary and Secondary Effectiveness Endpoints Demonstrate Consistency Over Time (Per Protocol)



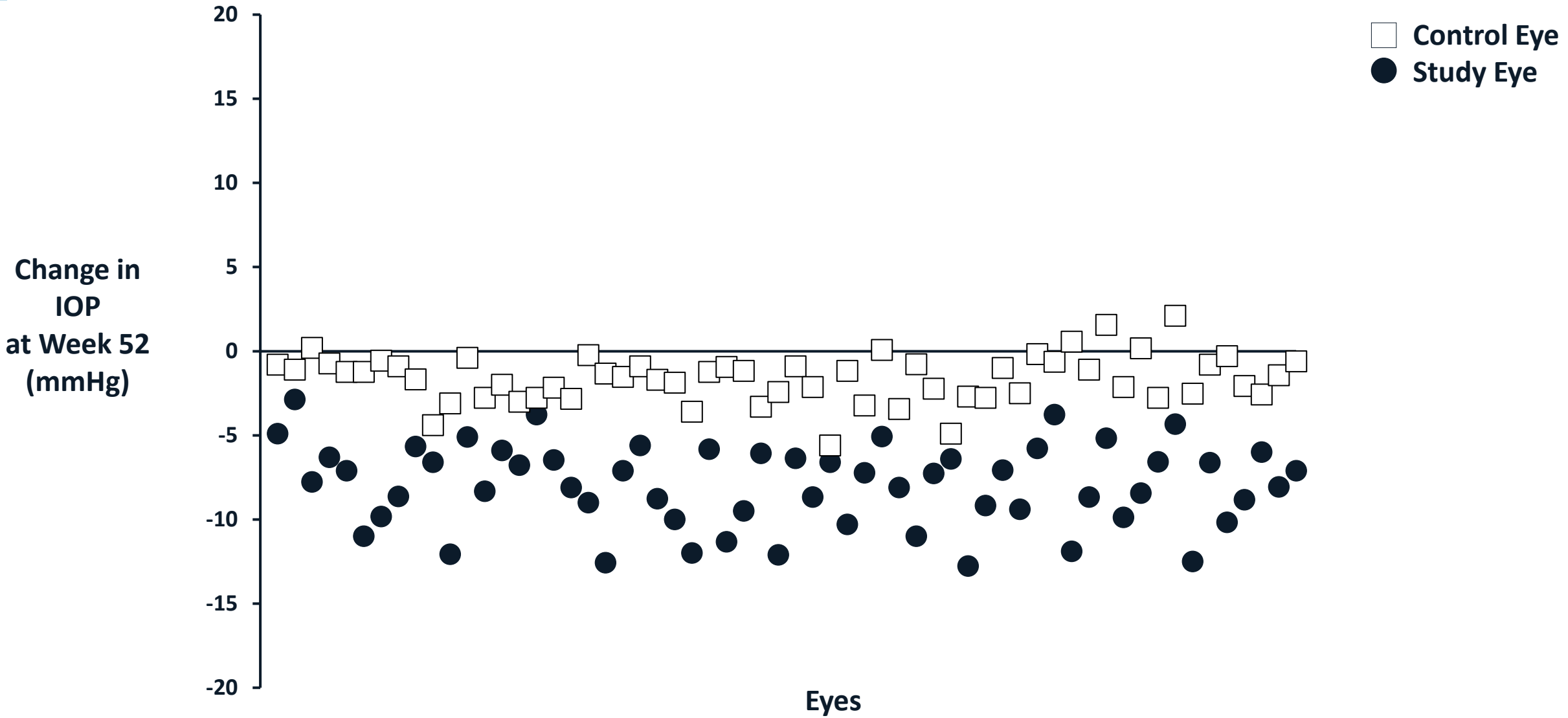
Day 0 and Week 26 In Clinic and initial sleep lab data have not been reviewed by FDA. P-values/CIs at these timepoints were not pre-specified or adjusted for multiple comparisons.

All Study Eyes Showed IOP Lowering at Week 52 (In Clinic, Per Protocol)



Data have been provided to FDA but have not been reviewed

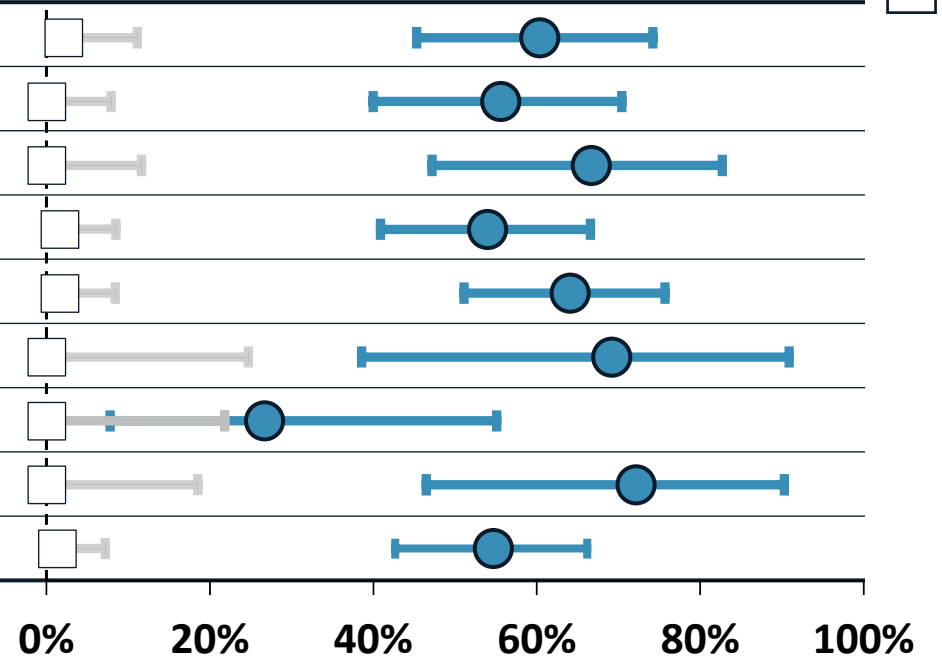
All Study Eyes Showed IOP Lowering at Week 52 (Sleep Lab, Per Protocol)



This figure has not been reviewed by FDA

Effectiveness in Subgroups (mITT)

Patient level		N	Percent Achieving IOP R uction ≥ 20%
Age	≤ 1	48	
	> 61	45	
Sex	Male	30	
	Female	63	
Race*	White	64	
	Black / African American	13	
	Asian	15	
Ethnicity*	Hispanic	18	
	Non-Hispanic	75	

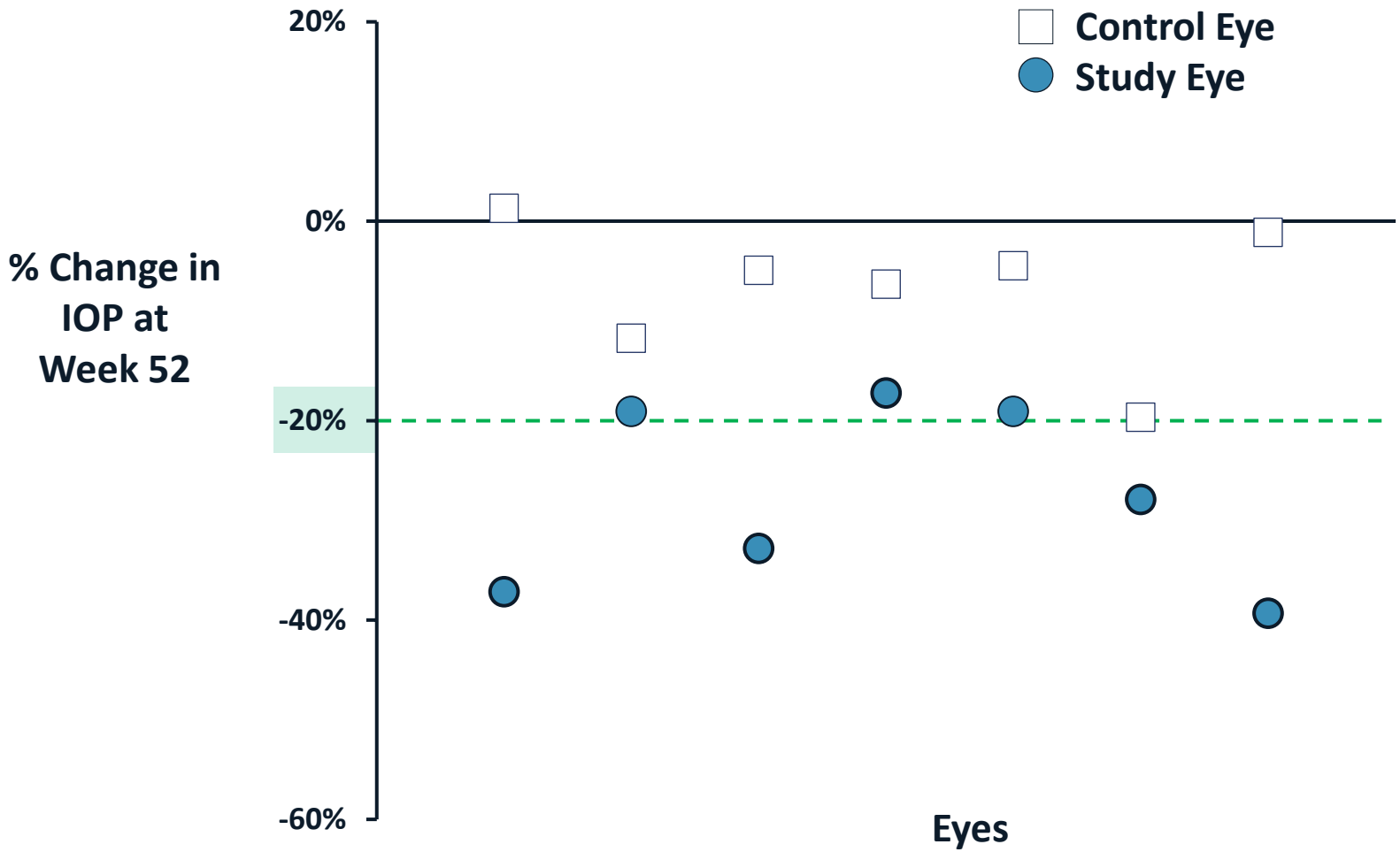


*Analyses not previously reviewed by FDA; CIs not pre-specified

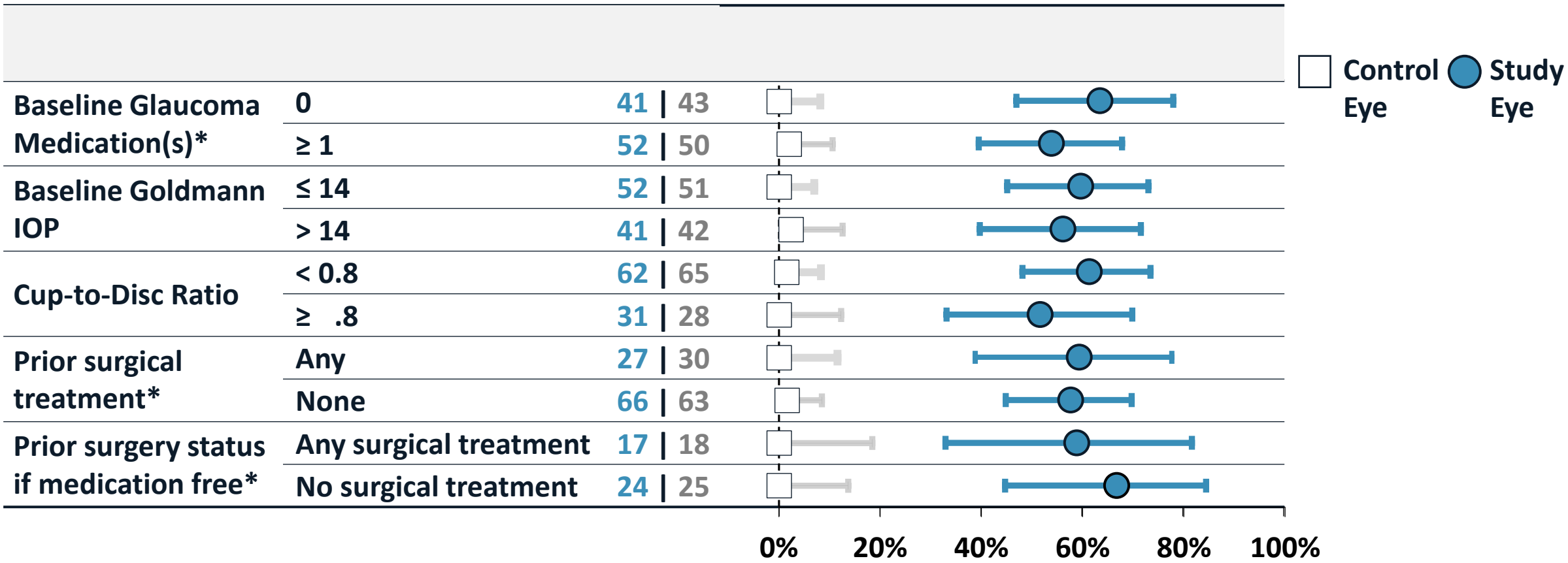
Effectiveness in Asian Subgroup (In Clinic, mITT)

- 8 patients discontinued
  - Voluntary withdrawal = 3
  - Site closed for COVID = 2
  - Reaction to goggles material (AE) = 1
  - Non-compliance = 1
  - SAE (panc. cancer) = 1

- 7 patients completed
- For study eyes, mean 27.5% reduction
  - 4 had reductions ≥ 20%
  - 2 had a 19% reduction
  - 1 had a 17% reduction



Effectiveness in Subgroups (mITT)



*Analyses not previously reviewed by FDA; CIs not pre-specified

Key Topics FDA is Asking Panel to Discuss

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Does the proposed IFU statement use the appropriate nomenclature and language to accurately describe the function of the device with regard to IOP?

6 Benefit-Risk

Do the probable benefits of the FSYX OPAP device outweigh the probable risks for use in patients who meet the criteria specified in the proposed IFU?

ARTEMIS Shows Consistent Clinically Meaningful Reductions in IOP During Use

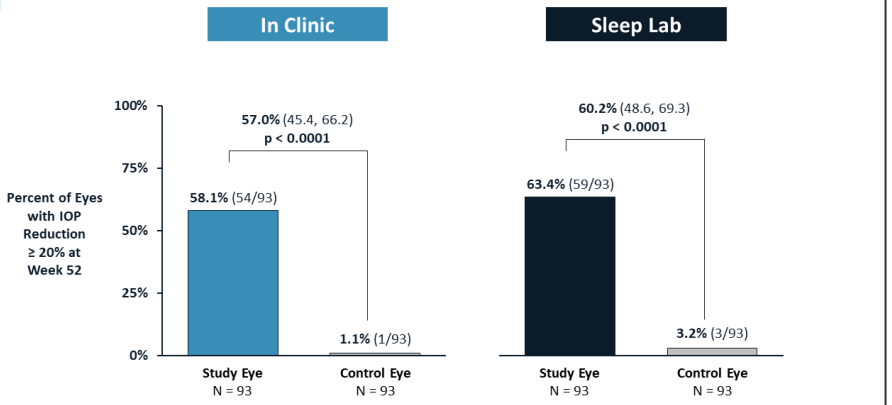
- OPAP effectively lowers IOP
  - Mean daytime, in clinic IOP reduction = **36% and 6.6 mmHg (18.0 → 11.4)**
  - Mean nighttime, sleep lab IOP reduction = **39% and 8.0 mmHg (20.4 → 12.4)**
- All measurements in study eyes showed IOP lowering
- All study populations and imputation analyses support effectiveness of treatment and consistency of results

FDA Question 2

Studies Demonstrate OPAP Effectiveness

CO-70

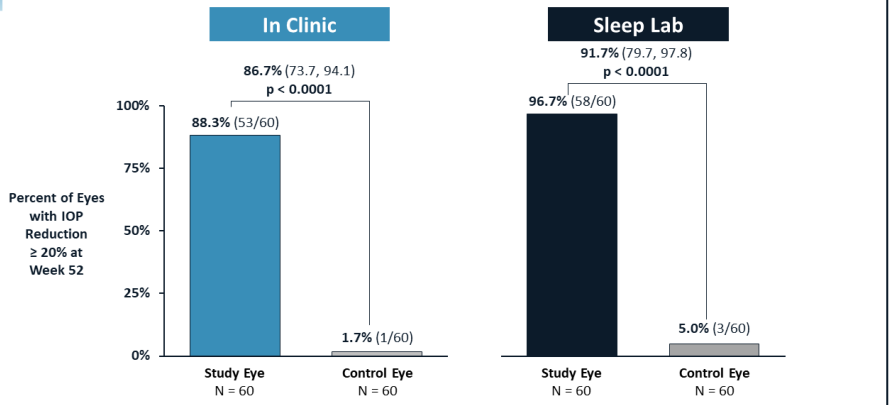
Primary and Secondary Effectiveness Endpoints Achieved: Percent of Eyes with IOP Reduction ≥ 20% at Week 52 (mITT)



Missing data/discontinuations imputed as failure

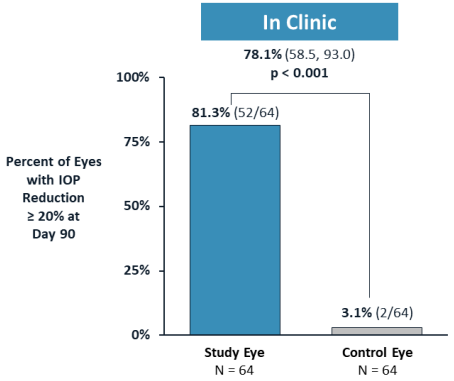
CO-71

Per Protocol Analysis Demonstrates Robustness of Findings



CO-48

APOLLO Primary Effectiveness Endpoint Achieved: Percent of Eyes with IOP Reduction ≥ 20% at Day 90 (mITT)



Missing data/discontinuations imputed as failure; IOP measured during NP application

APOLLO

Clinical Safety

Safety Overview

- No device-related SAEs
- No AEs reflective of damage to structure and function of optic nerve or anterior segment
- Safety assessments do not reflect any worsening in clinical outcomes or unanticipated adverse device effects
- All device-related AEs resolved without sequelae
- No hypotony
- No clinically significant elevations in mean IOP after removing OPAP

All Ocular AEs Resolved Without Sequalae

> 1 patient in either arm	Study Eyes N 93		Control Eyes N 93	
	n	%	n	%
Any reported ocular AE	25	27%	13	14%
Lid edema	11	12%	1	1%
Symptoms and signs of dry eyes	5	5%	5	5%
Conjunctival hyperemia	4	4%	2	2%
Eye pain	3	3%	0	0%
Lid erythema	2	2%	1	1%
Lo f CDV ≥ 2 fr m	2	2%	2	2%
Posterior vitreous detachment	2	2%	0	0%

- 1 lid edema AE in study eye was severe
  - Resolved within a week, but patient terminated study participation

Patients may have had more than one AE reported

All Periorbital AEs Resolved Prior to Study Completion or Discontinuation

	Study Eyes N 93		Control Eyes N 93	
> 1 patient in either arm	n	%	n	%
Any reported periorbital AEs	17	18%	7	8%
Periorbital edema	12	13%	1	1%
Periorbital contact dermatitis	4	4%	3	3%
Periorbital pain	2	2%	1	1%

- 80% mild in nature, no severe AEs
- Headache reported in 2 patients (2%)
- All of these cases resolved

No Device-related SAEs

Patients may have had more than one AE reported

Ocular Hypotensive Medication Use Remained Stable

	Week 52 N = 62			
	Study Eye		Control Eye	
	n	%	n	%
D cr ≥ 1 me c	1	2%	1	2%
No change	59	95%	59	95%
Inc ≥ 1 me c	2	3%	2	3%

Other Findings Not Considered to be Adverse Events

- Slit Lamp
  - No cases of corneal edema, no changes in anterior chamber angle, and no synechiae
  - 1 patient observed with 1+ corneal endothelial guttata in both eyes at Week 52
- Fundus
  - No clinically significant fundoscopic differences between study and control eyes
  - No macular abnormalities at Week 52 that had not been reported at baseline
  - 1 eye with 1+ lattice degeneration
- Cup-to-Disc Ratio
  - No differences between study and control eyes

Independent Assessment of Glaucomatous Progression

University of Iowa Visual Field Reading Center

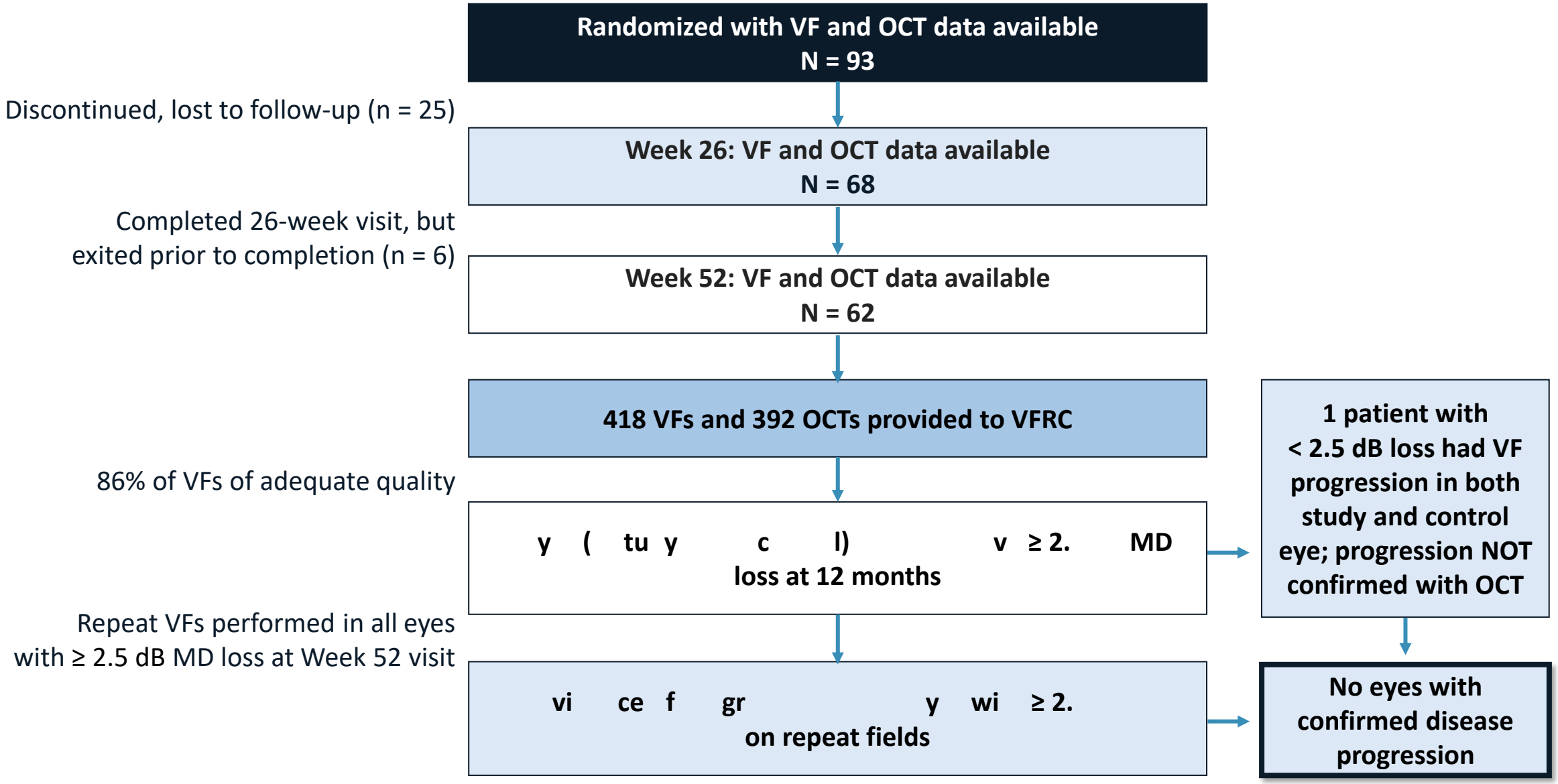
3 readers

- Michael Wall, MD
- Chris Johnson, PhD
- Michael Patella, OD

Methodology for Independent Assessments

- 2 readers reviewed each VF and flagged any eyes with worsening
- Analysis repeated with addition of all OCT data
- Any discrepancies between reads was adjudicated by third reader

VFRC Concluded No Eyes had OCT Confirmed VF Progression



Favorable Safety Experience with OPAP

- 12-Month data from ARTEMIS consistent with 3-Month data from APOLLO, further supporting positive safety profile of OPAP
- No device-related SAEs observed in any eye in ARTEMIS or APOLLO studies
  - Consistent with previous studies
- No AEs reflective of damage to structure and function of optic nerve head or anterior segment

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4/5 Labeling

Do you believe the available data supports the proposed range of programmable NP / wear time?

Does the proposed IFU statement use the appropriate nomenclature and language to accurately describe the function of the device with regard to IOP?

6 Benefit-Risk

Do the probable benefits of the FSYX OPAP device outweigh the probable risks for use in patients who meet the criteria specified in the proposed IFU?

Available Data Support Device Safety

- Data clearly support 1 year safety of OPAP
- Data also not suggestive of any longer-term issue
- Balance to continue to monitor for any safety signal based on exposure to greater patient numbers

FDA Question 3

Clinical Perspective

Leon Herndon, MD

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6 Benefit-Risk

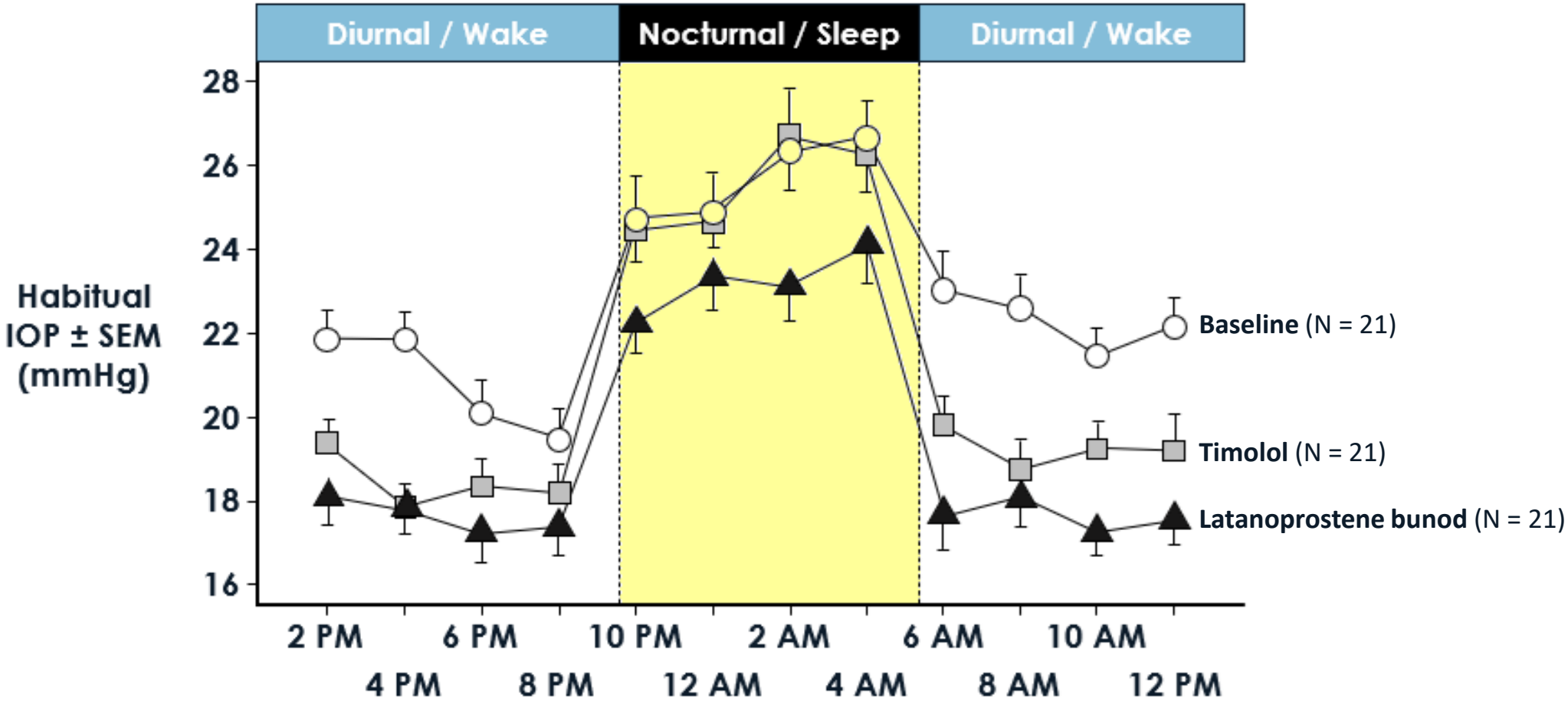
Do the probable benefits of the FSYX OPAP device outweigh the probable risks for use in patients who meet the criteria specified in the proposed IFU?

Proposed IFU Statement, Current Nomenclature, and Language are Accurate and Appropriate

The FSYX™ Ocular Pressure Adjusting Pump (FSYX 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

FDA Question 5

Patients with OAG and an IOP ≤ 21 mmHg Need Options

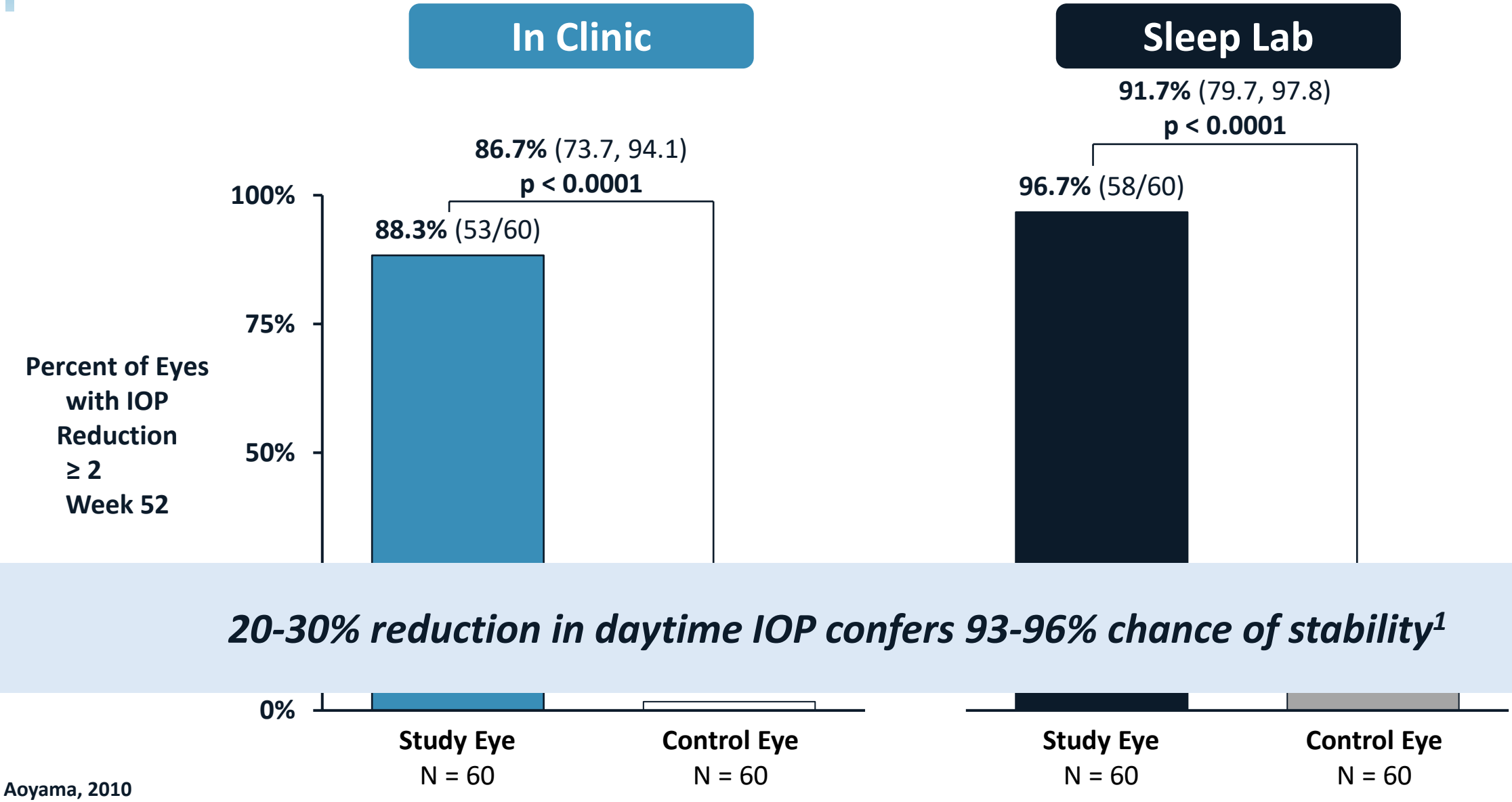


Most treatments are less effective at reducing nocturnal elevations that put patients at risk of disease progression[1-5]

Figure adapted from Liu, 2016

1. Dubey, 2020; 2. Liu, 2004; 3. Liu, 2010; 4. Orzalesi, 2000; 5. Orzalesi, 2006

Per Protocol Analysis Demonstrates Robustness of Findings



20-30% reduction in daytime IOP confers 93-96% chance of stability[1]

1. Aoyama, 2010

Favorable Safety Experience with OPAP

- No device-related SAEs
- No AEs of damage to the structure and function of the optic nerve head or anterior segment
- OPAP would provide a noninvasive treatment option to specifically address nocturnal IOP elevations

FDA Question 6

FSYX™ Ocular Pressure Adjusting Pump (OPAP) as an Adjunct Therapy for Lowering Intraocular Pressure During Nightly Use in Patients with Open Angle Glaucoma and Intraocular Pressure ≤ 21 mmHg

Ophthalmic Devices Panel

March 21, 2024