

**Corporate Presentation | March 2019**

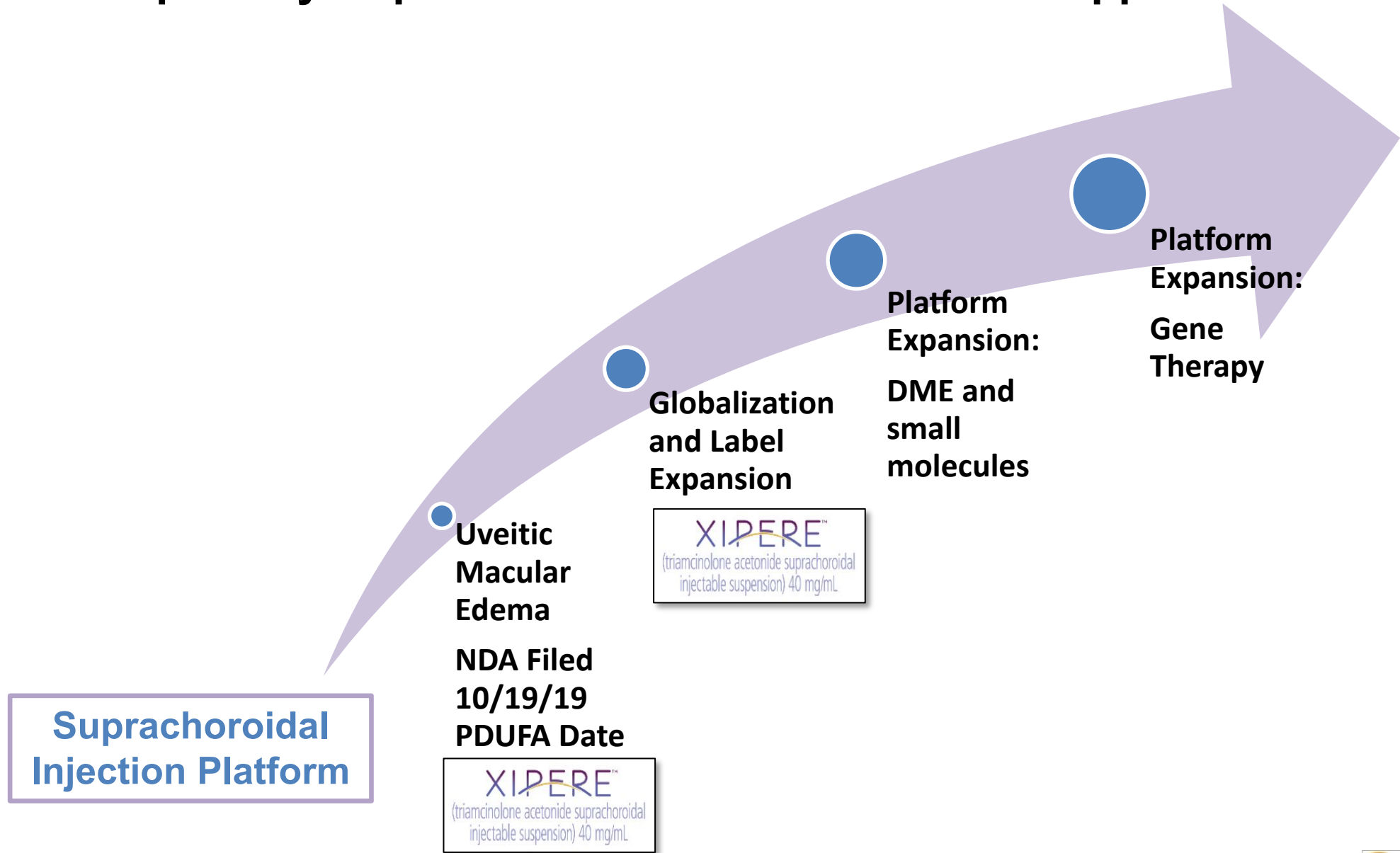
# Forward-Looking Statements

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# Proprietary Suprachoroidal "SCS" Treatment Approach



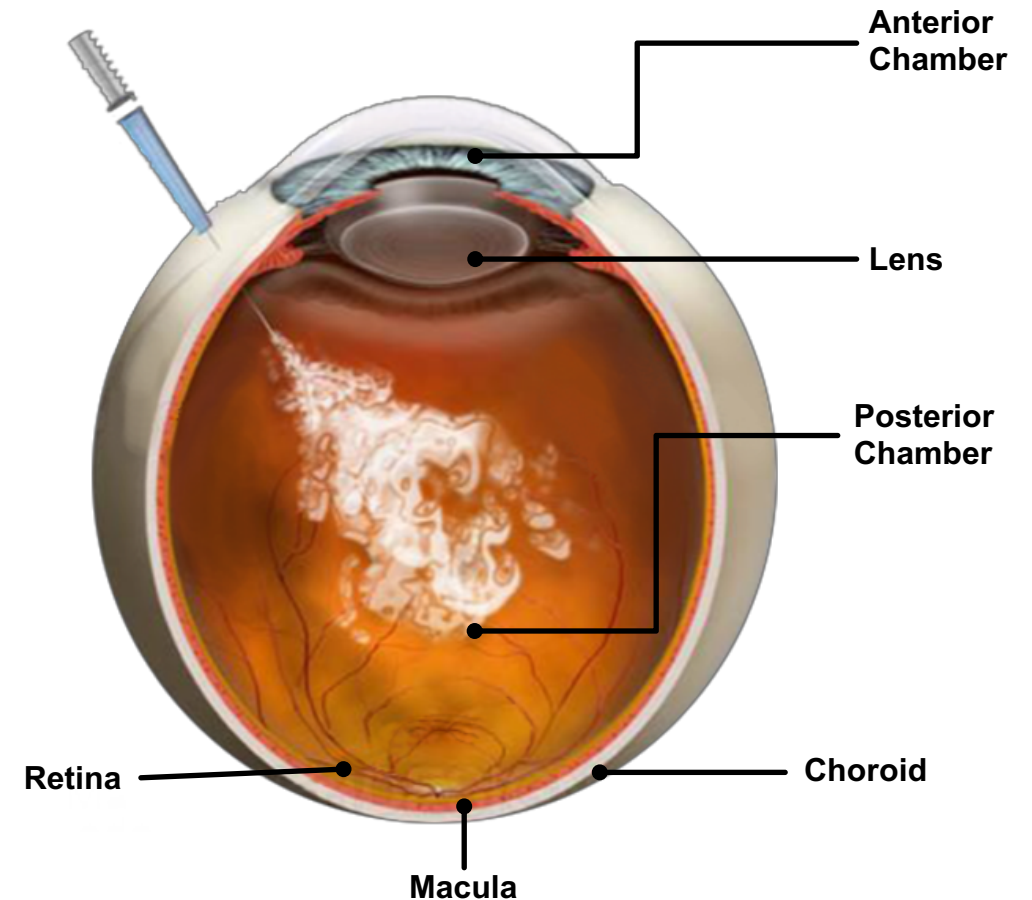
# Retinal Diseases

~5 M patients in the U.S. with target indications treated by approx. 1,900 uveitis and retinal specialists

## Privileged Organ Requiring Local Therapy

### Limitations of Current Therapy:

- **Corticosteroids** reach unintended tissues, causing cataracts and glaucoma
- **Gene therapies** require precise placement at diseased tissue
- **Multi-kinase inhibitors** and **complement inhibitors** require improved exposure to the choroid



Treatment via intravitreal injection

# Exclusive and Proprietary Access to the Back of the Eye Through the Suprachoroidal Space (“SCS”)

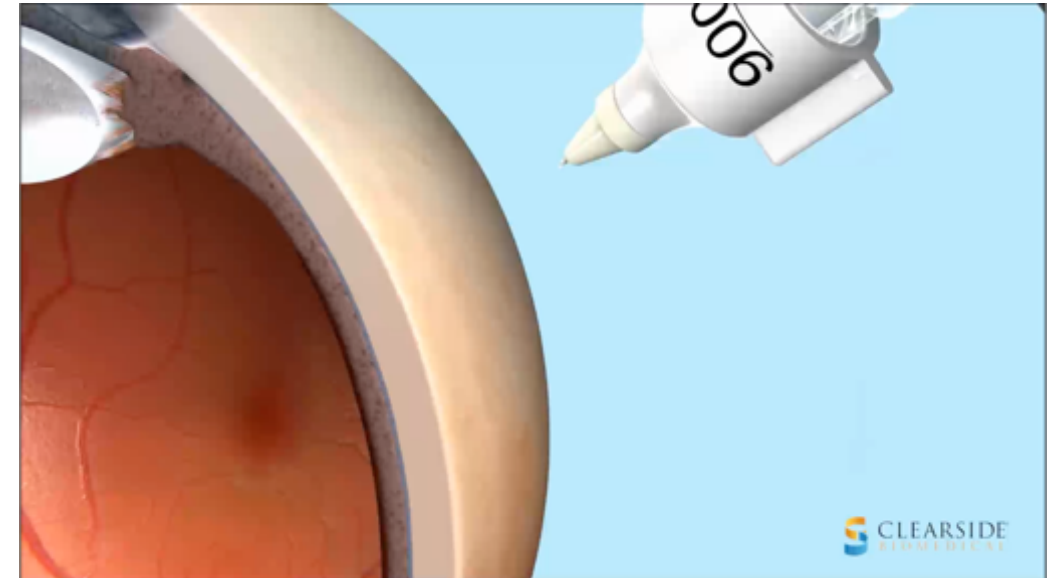
## Intravitreal & Periocular



- 0.05 mL bolus at injection site
- Drug diffuses to all areas of the eye including the anterior chamber and lens
- 0.5 mL–1 mL injected into periocular space
- Highly variable drug diffusion across the sclera into the eye

VS

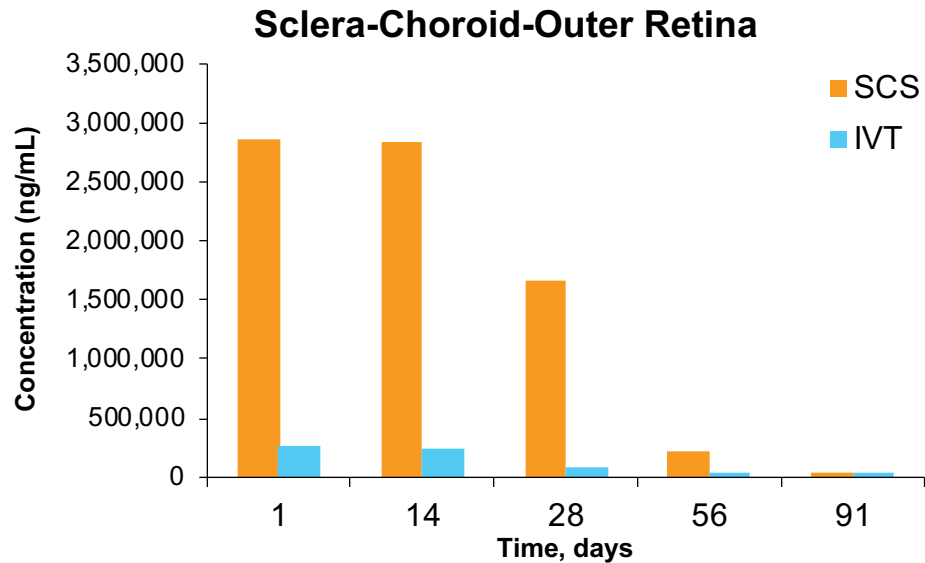
## Suprachoroidal



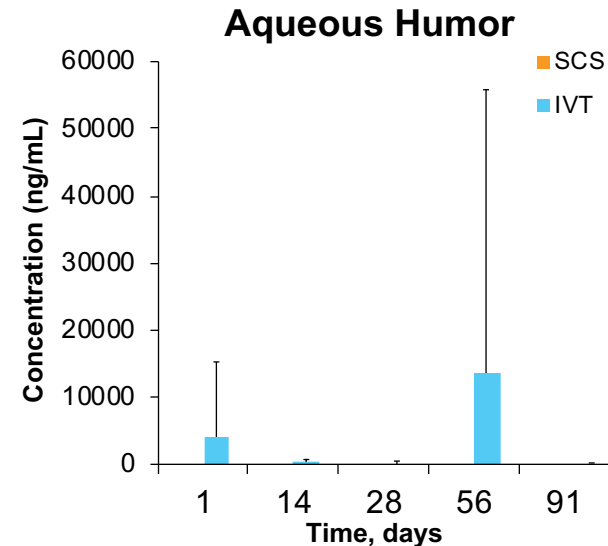
- Fluid flows instantaneously and posteriorly
- Consistent suprachoroidal injection procedure
- Fluid with drug is absorbed into the choroid, retinal pigment epithelium (RPE) and retina

# XIPERE

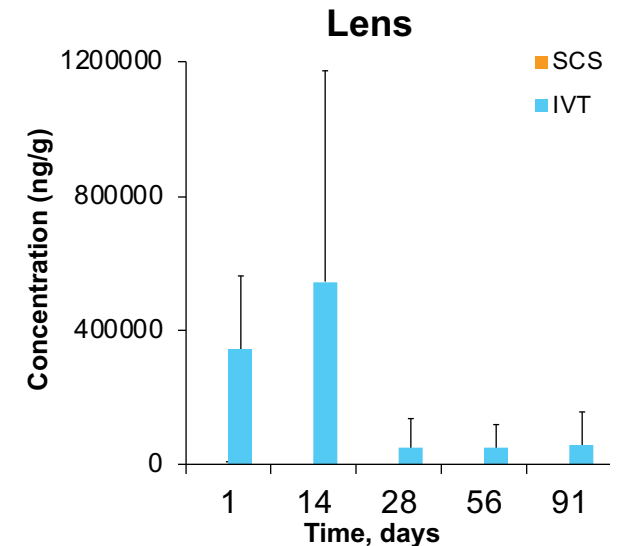
Designed to Improve Ocular Distribution of Triamcinolone Acetonide (TA)



**Over 10X the amount of TA remaining** in the choroid and RPE following suprachoroidal administration compared to intravitreal injection



**The anterior segment is relatively spared** following suprachoroidal dosing when compared to intravitreal dosing




























Potentially providing improved **visual outcomes**, increased **durability**, reduced **treatment burden** that can lead to improved **benefit to risk**



# Focused Pipeline of SCS Treatments

## For Multiple Blinding Eye Diseases

INDICATION	STUDY DRUG	CURRENT STATUS				
Uveitis (macular edema associated with uveitis)	XIPERE (triamcinolone acetonide ophthalmic suspension) for Suprachoroidal Injection					
		PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	NDA
DME (diabetic macular edema)	XIPERE					
		PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	NDA
Wet AMD	Proprietary Compound(s)					
		PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	NDA
DME	Proprietary Compound(s)					
		PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	NDA
Usher Syndrome	Gene Therapy					
		PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	NDA



# UVEITIS

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One of the World's Leading Causes of Blindness





## The Opportunity

First Treatment for Macular Edema Associated with Uveitis

### Primary Need

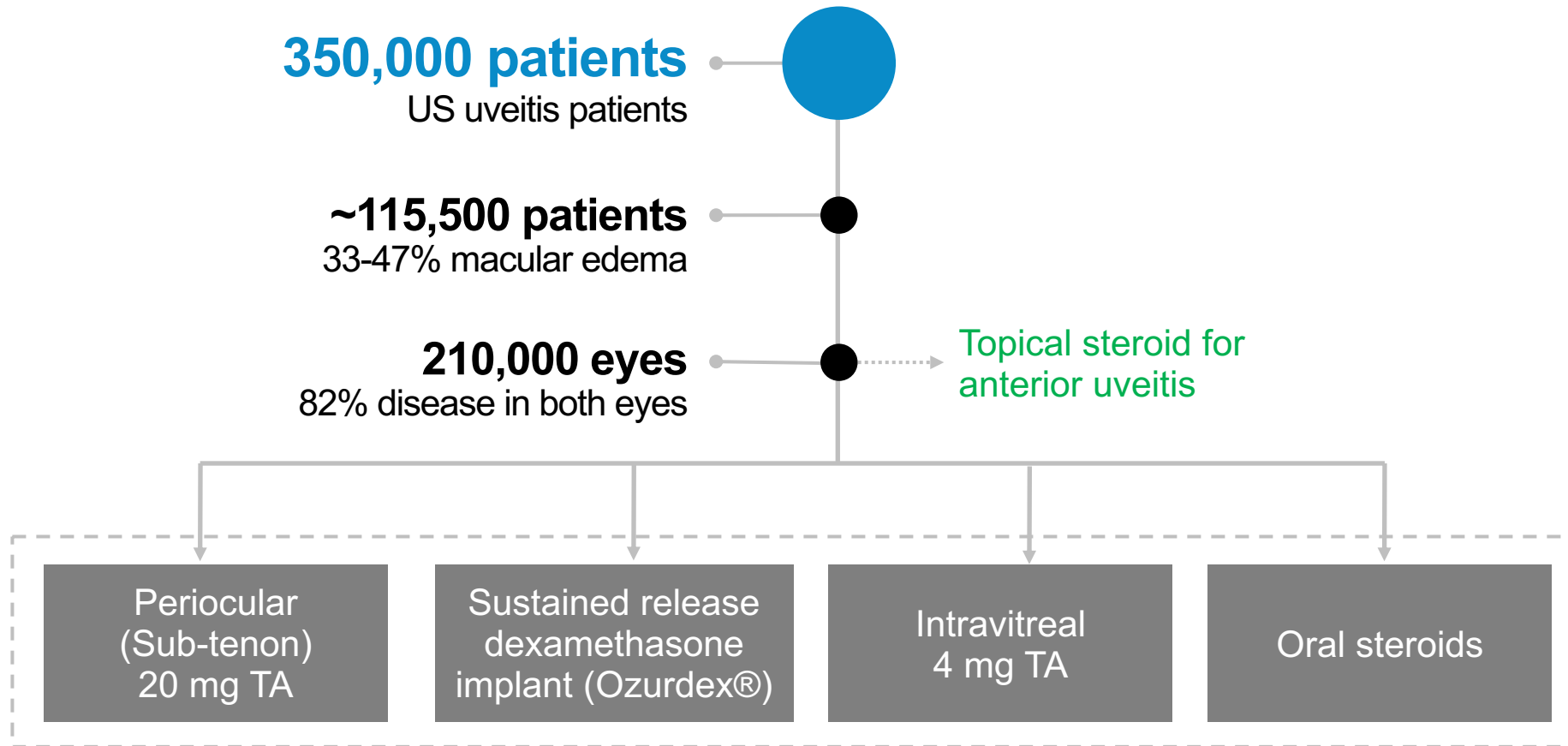
- 1) An approved therapy that targets vision impairment due to the underlying macular edema associated with all uveitis

### The Problem

- 1) Inflammation creates sight threatening macular edema
- 2) No approved treatment for macular edema associated with uveitis
- 3) No approved treatments for all anatomic locations of uveitis
- 4) Oral corticosteroids often prescribed when disease is local to the eye

# Current Treatment Paradigm for Uveitis

**Corticosteroids = most common treatment**  
for uveitis complications



## Current treatments

Note: TA = triamcinolone acetonide

\* Ophthalmologists with uveitis / retina fellowship who see  $\geq 5$  patients with macular edema secondary to NIU

Sources: 1) Target Ophthalmologist ATU, May 2018; 2) Lardenoye, C. et al. Ophthalmology 113.8 (2006): 1446-1449.

# Status of Current Therapy in Macular Edema Associated with Uveitis

## The POINT Study<sup>1,3</sup>

	Periocular (Sub-tenon or orbital floor) 40 mg TA (Kenalog®)	Sustained release dexamethasone implant (Ozurdex®)	Intravitreal 4 mg TA (TRIESENCE®)
Macular Edema	23%	46%	39%
Mean Visual Acuity	4.27	9.5	9.7
Rescue (2 <sup>nd</sup> steroid dose given by week 8 or 12) <sup>2, 4</sup>	49%	56%	49%
IOP lowering meds initiated	24%	33%	31%

**POINT Study Conclusion:** Intravitreal TA and intravitreal dexamethasone implant were superior to Periocular TA in visual acuity improvements in uveitic macular edema subjects

1. Thorne, 2018; study was conducted and funded by the NEI

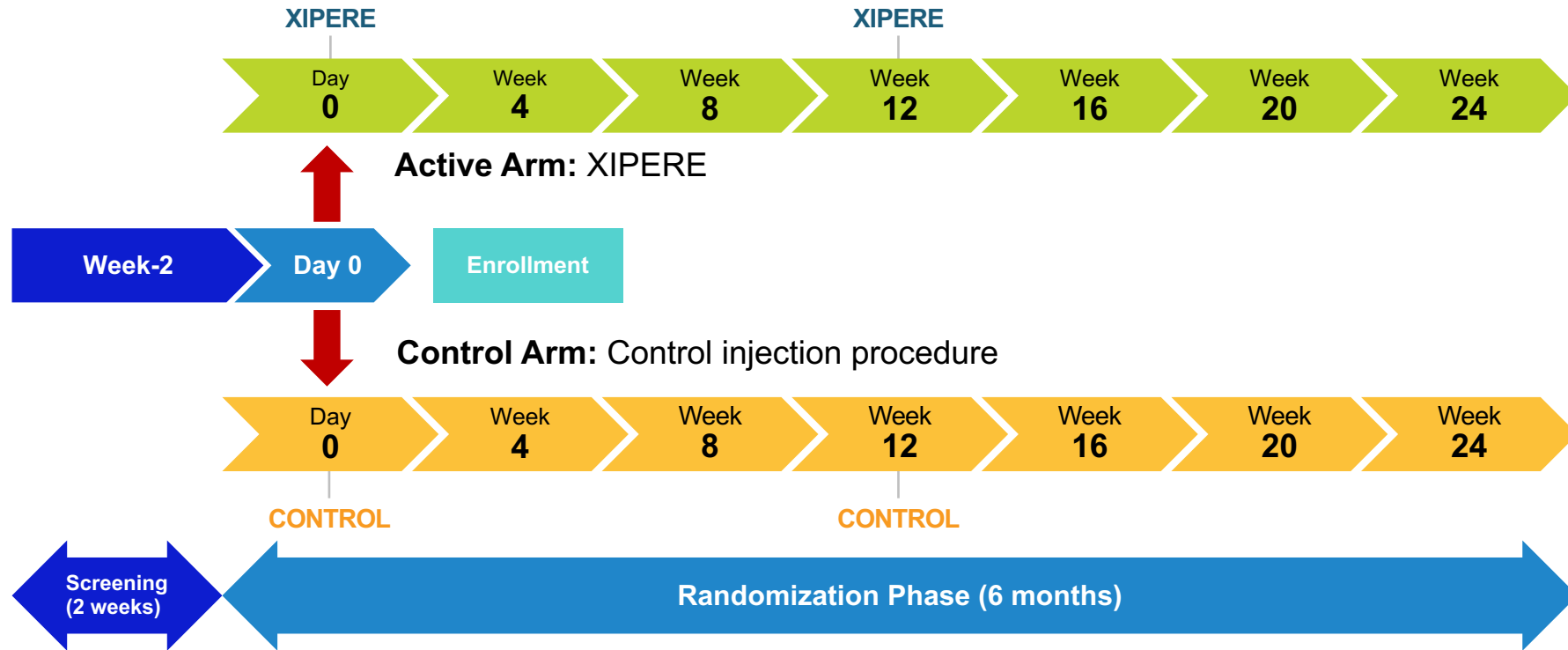
2. 2nd injections were based on macular edema criteria, either because of not improving or worsening edema

3. Clearside does not make any comparative claims regarding any products included in the POINT study

4. Protocol allowed week 8 for intravitreal and subtenon TA but suggested week 12 in the case of intravitreal Ozurdex

# PEACHTREE

## Pivotal Phase 3 Clinical Trial Testing XIPIRE in CME Involved Uveitis



Two-arm, randomized, controlled, double-masked, multi-center trial at ~60 clinical sites

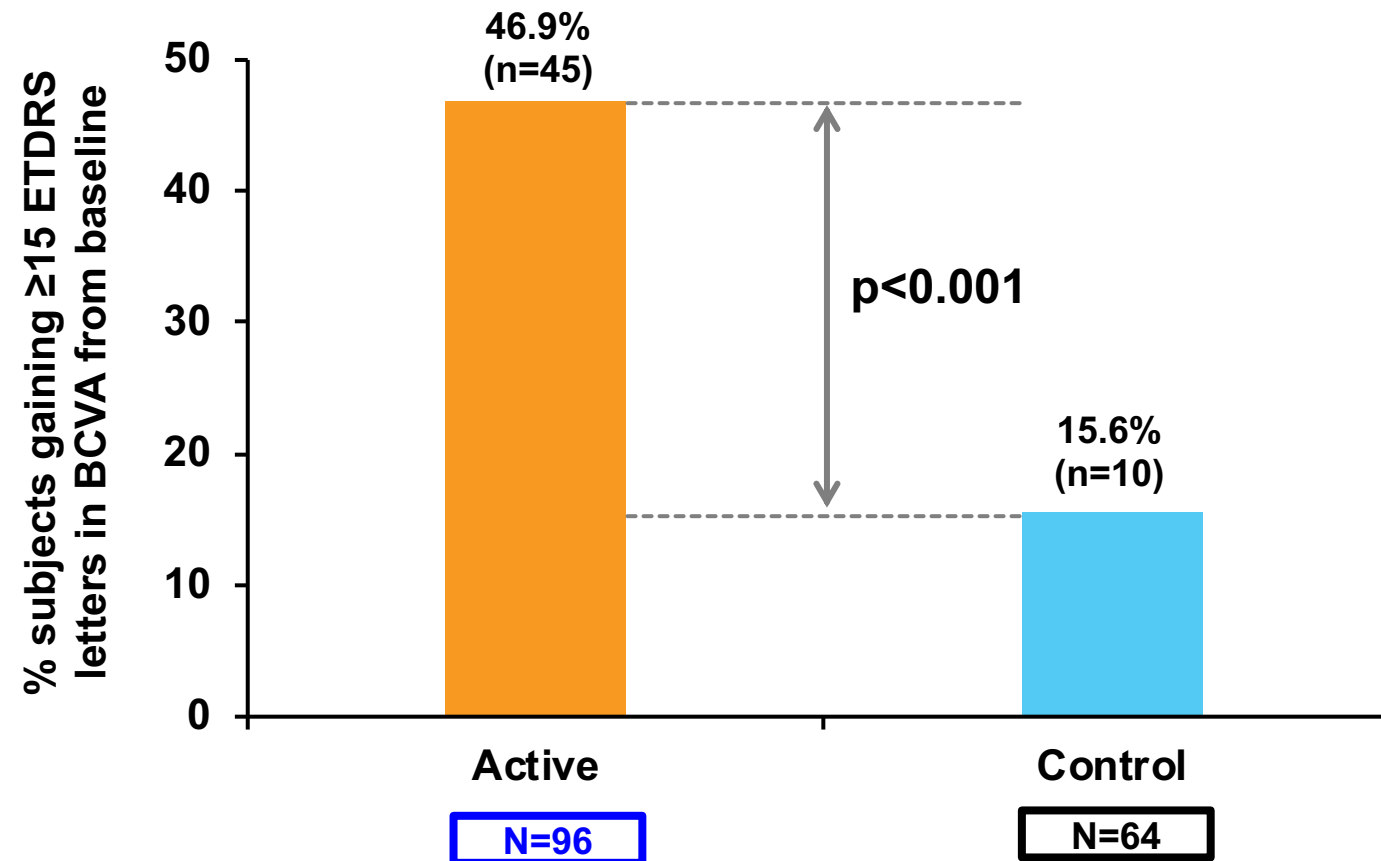
3:2 randomization of XIPIRE vs. sham injection; 160 subjects total

Primary endpoint at 6 months; superiority of best corrected visual acuity outcome from treatment

# PEACHTREE Met Its Primary Endpoint

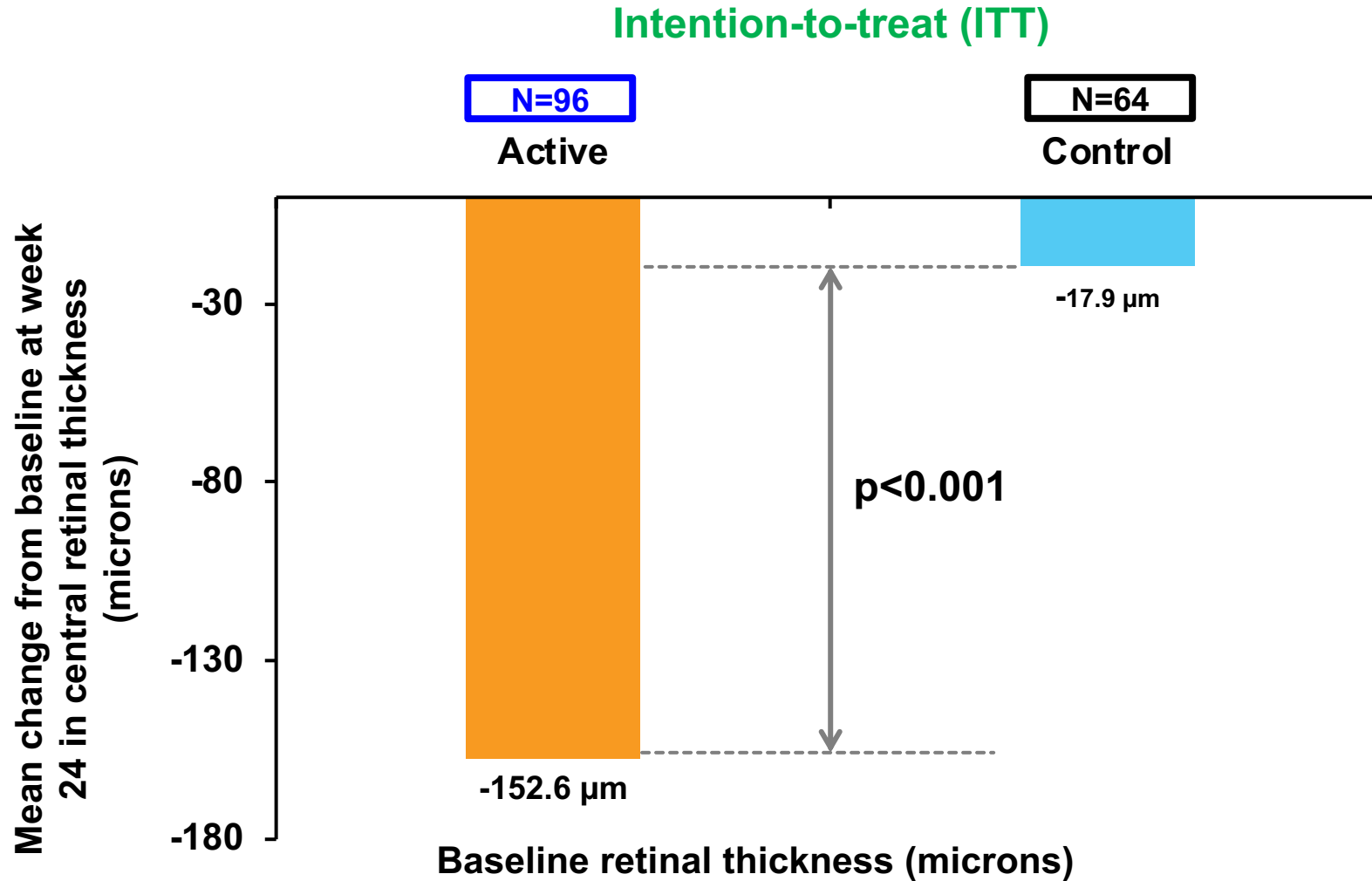
## ETDRS BCVA

Proportion of subjects in each arm gaining  $\geq 15$  ETDRS letters in BCVA from baseline at Week 24



# PEACHTREE Met Its Secondary Endpoint

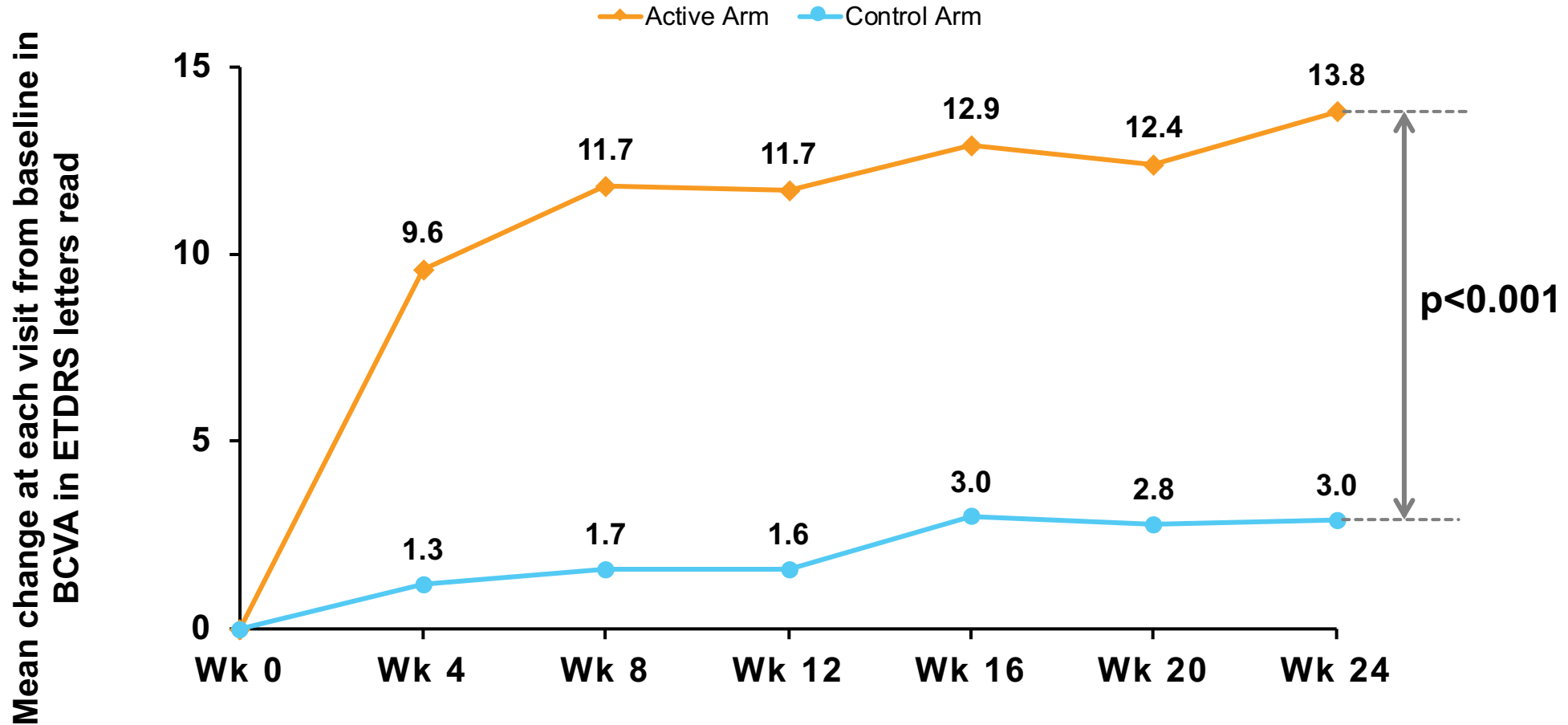
Mean Change from Baseline in CST at Week 24 in Microns



480.9  $\mu\text{m}$ : active arm; 525.4  $\mu\text{m}$ : control arm

# Vision Gained Rapidly and Sustained Through Week 24

Mean Change in BCVA in ETDRS Letters by Visit

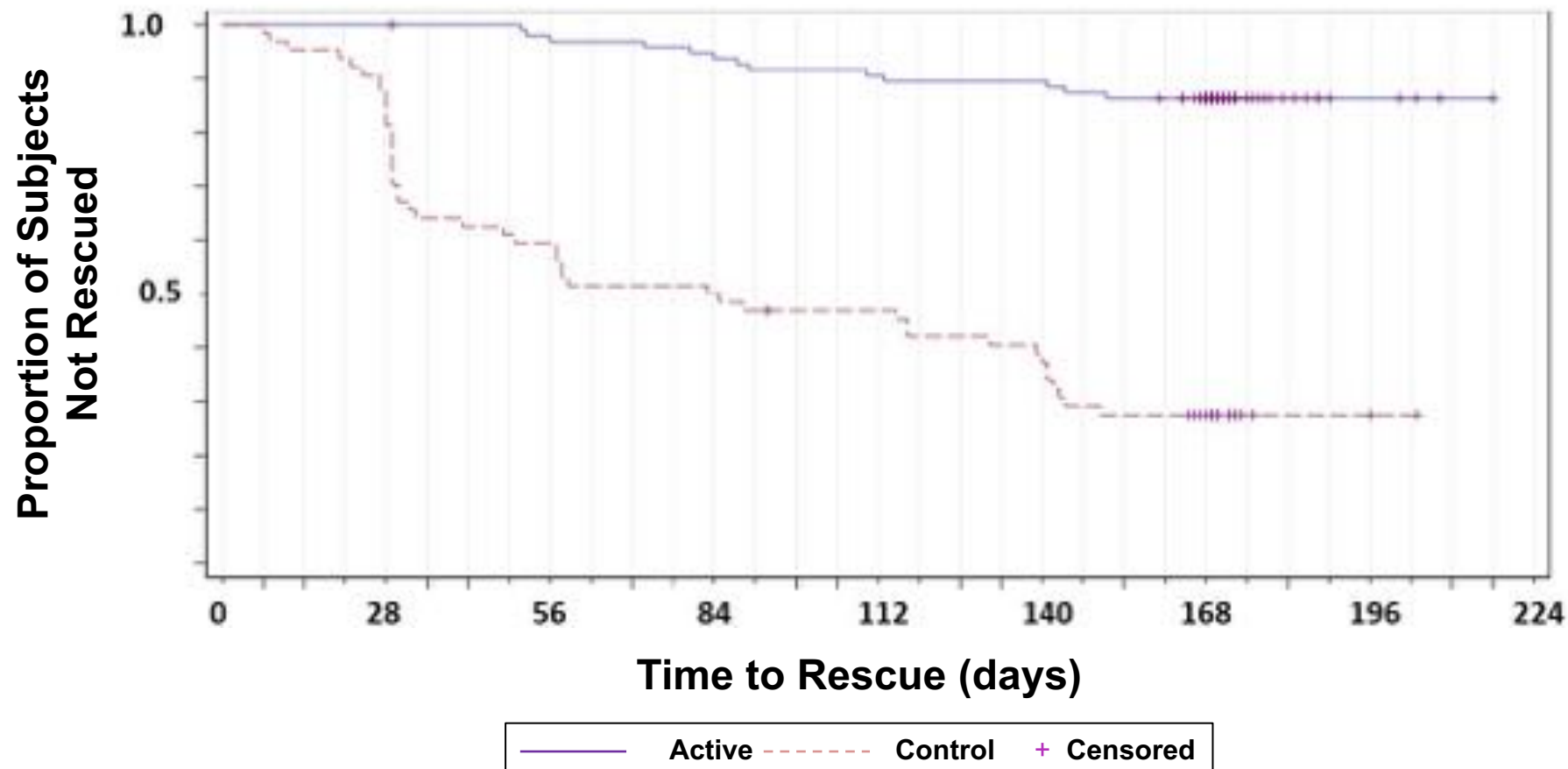


Baseline ETDRS letters read  
54.7: active arm; 53.5: control arm



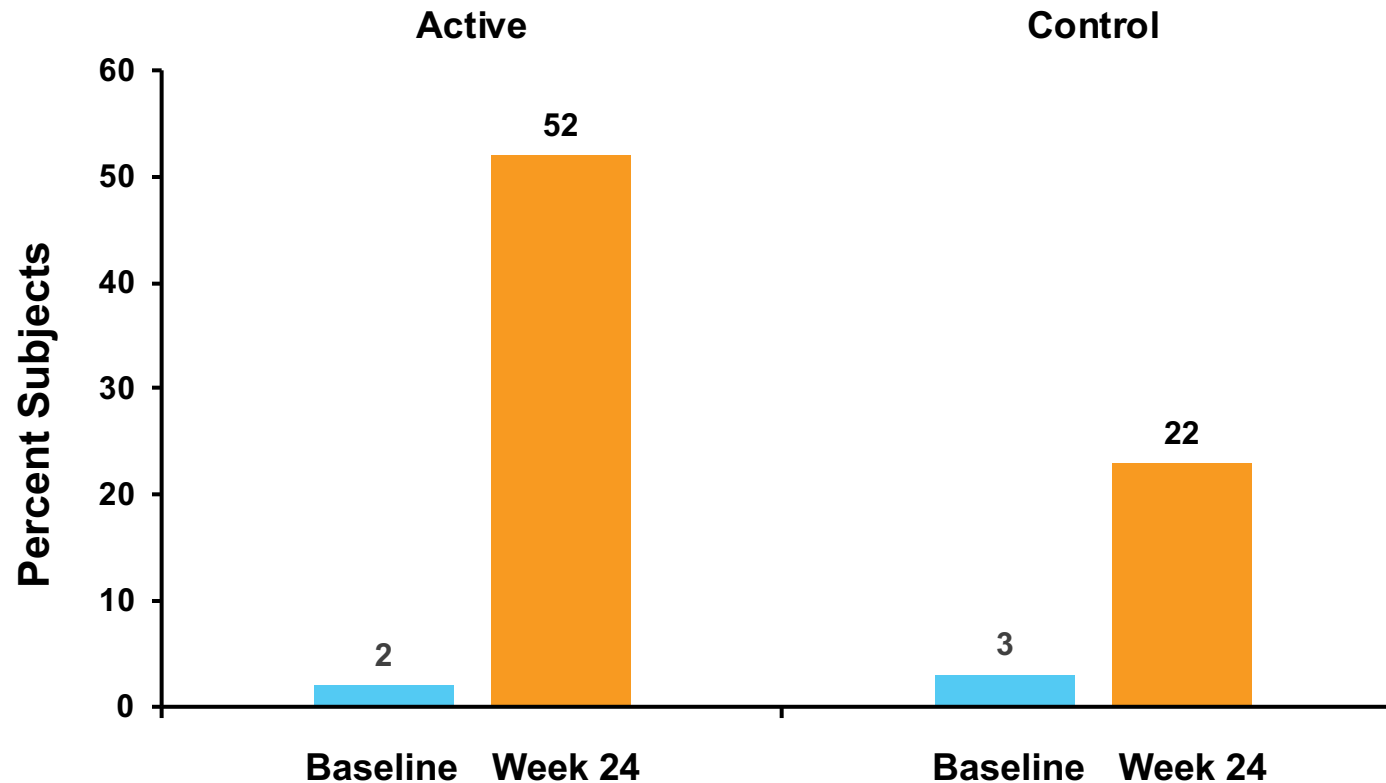
# Subject Rescue: Kaplan-Meier

Over **85%** of subjects in the **Active** arm did not require rescue therapy, compared to **28%** of subjects in the **Control** arm



# % Subjects Reading 20/40 or Better

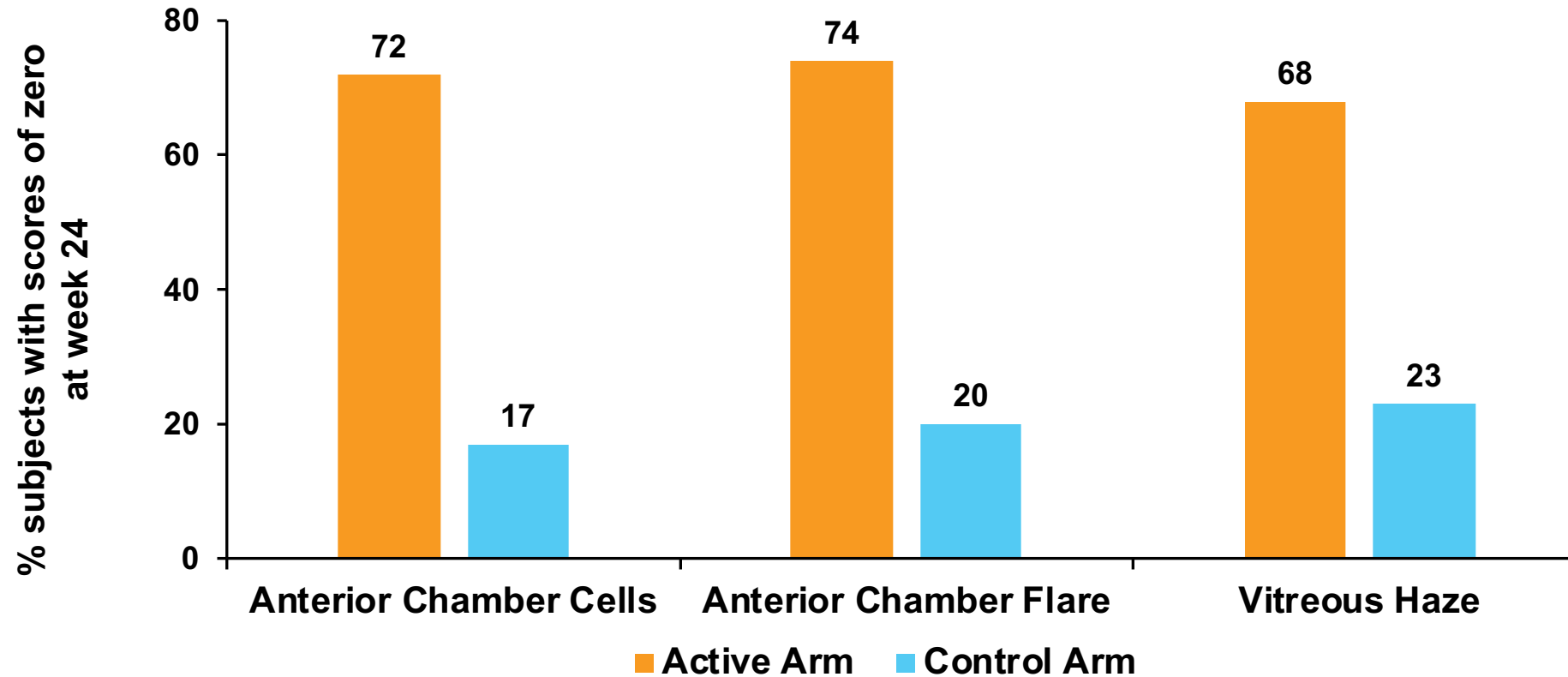
Legal Driving Vision in Most States



- Starting at week 8, approx. 50% of the Active subjects could read 70 or more ETDRS letters (20/40)
- This improvement was sustained through the 24 weeks of the trial

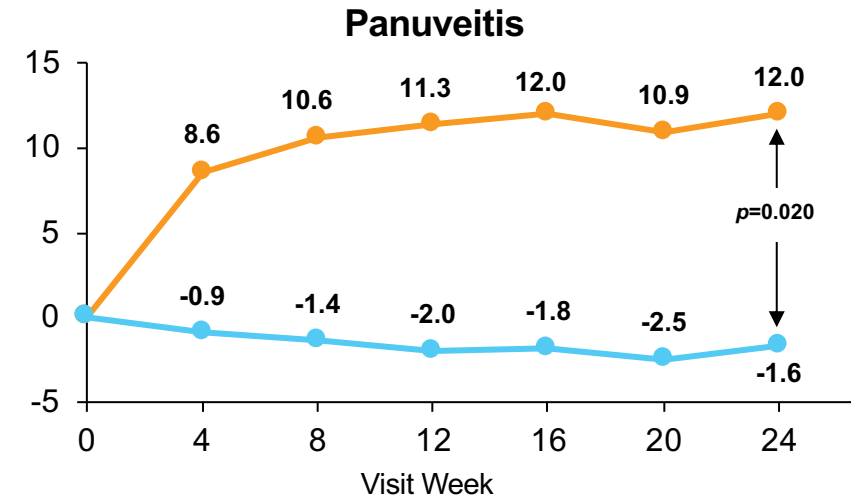
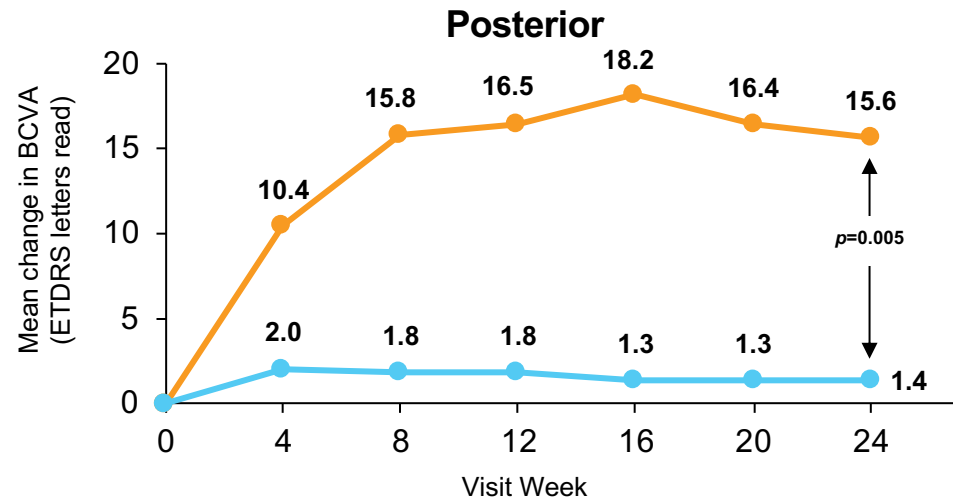
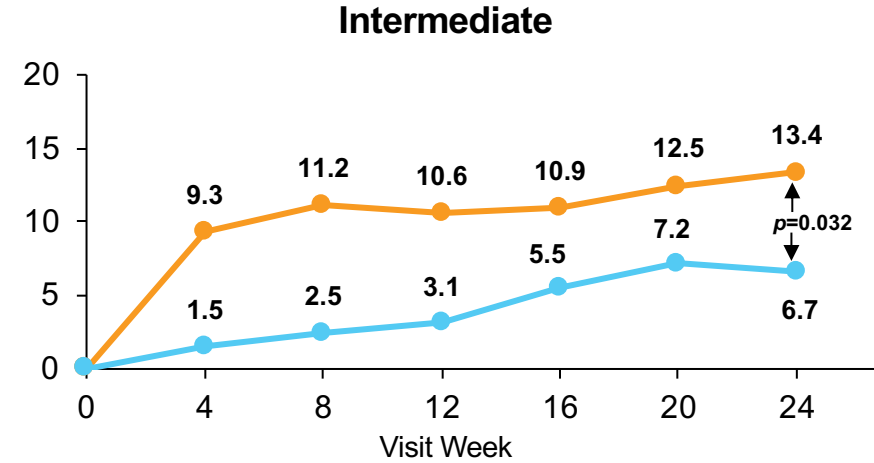
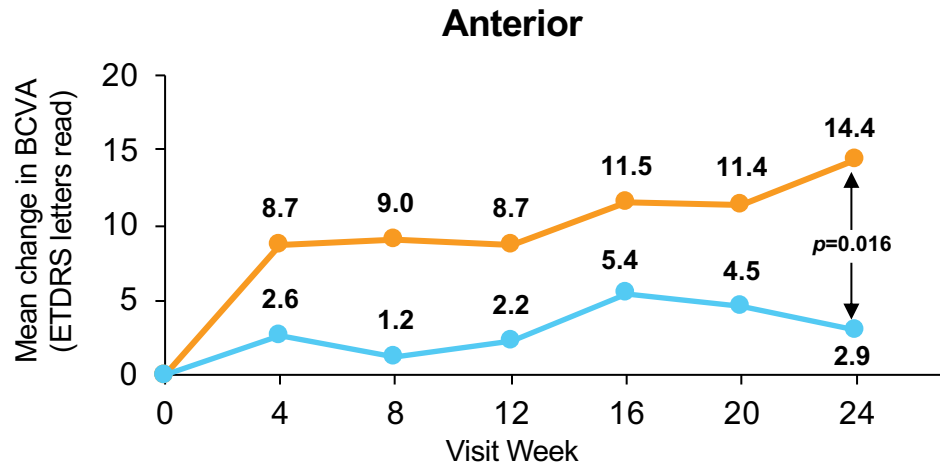
# XIPERE

Resolved Inflammation in 2 of 3 Subjects in PEACHTREE



- Resolution of each of these three signs of inflammation on the SUN\* scales is clinically and statistically significant
- In subjects with scores of 2 or greater in vitreous haze, 40.9% experienced resolution in the active arm, compared to 0% of subjects in the control arm

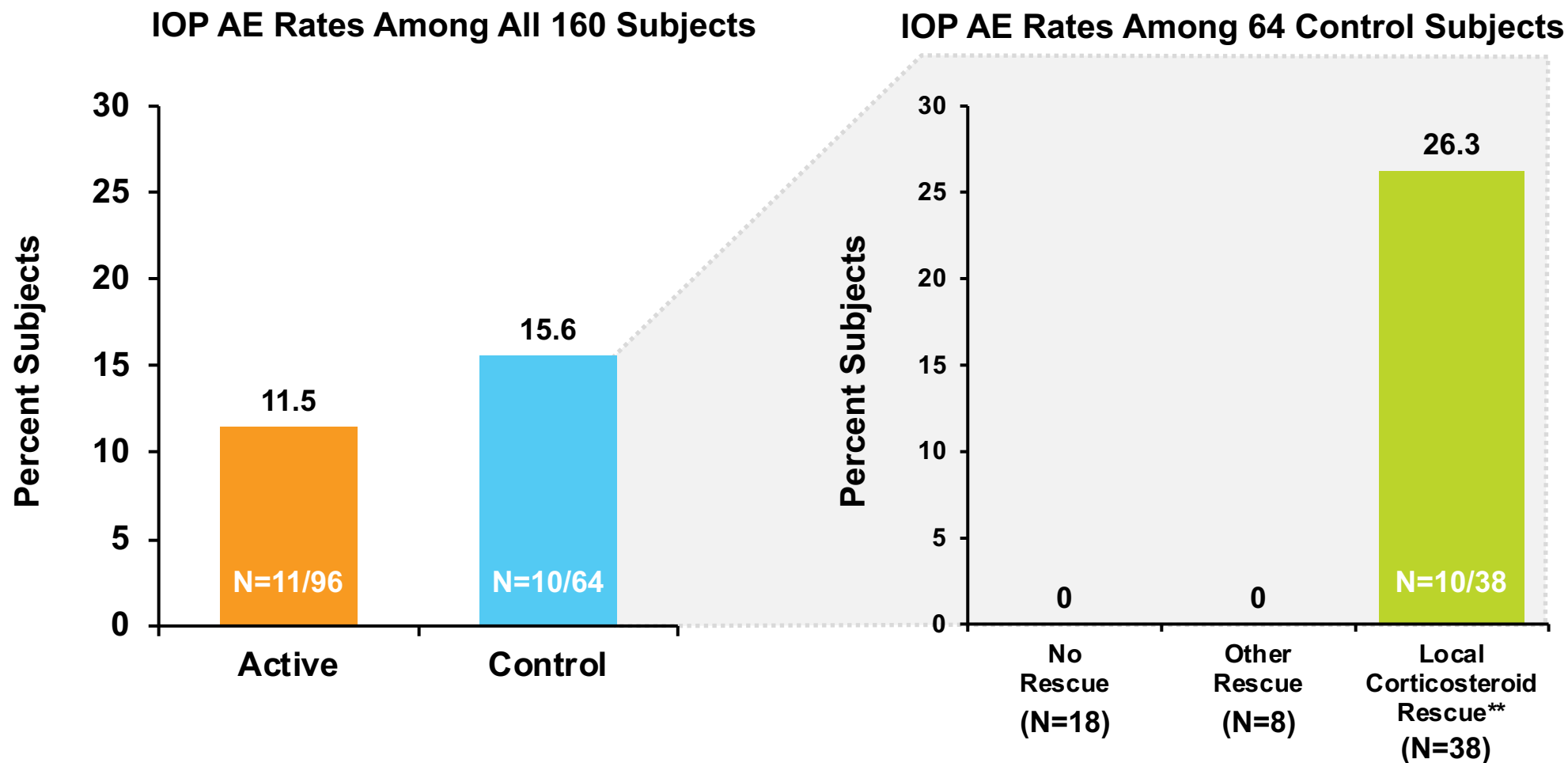
# Subjects From Each of the Four Anatomic Subtypes of Uveitis Treated with XIPEERE Achieved Significant Visual Improvement



● Active Arm

● Control Arm

# Safety: Elevated IOP



- IOP lowering medications were initiated in 7.3% and 9.4% subjects in the XIPERE and control arms respectively

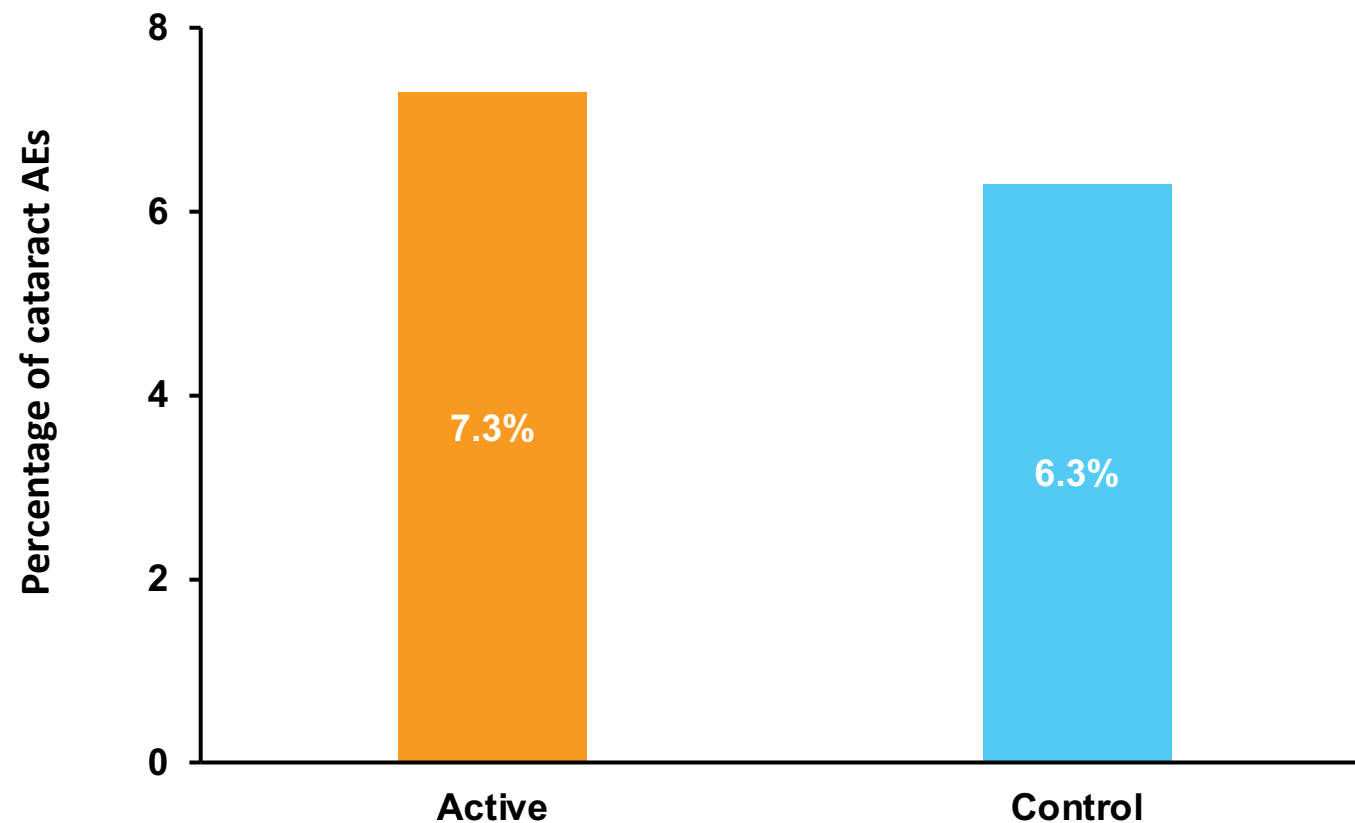
“Elevated IOP” includes (a) increased IOP, (b) ocular hypertension, and (c) glaucoma

AE = adverse event; IOP, intraocular pressure.

\*\* intravitreal OZURDEX® (dexamethasone intravitreal implant) and subtenon and intravitreal triamcinolone acetate

# Safety: Cataracts in XIPERE and Control Arms

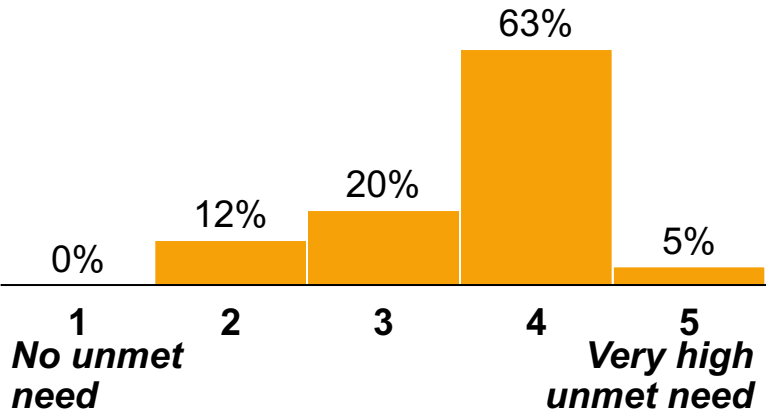
% Cataract AEs in Each Arm



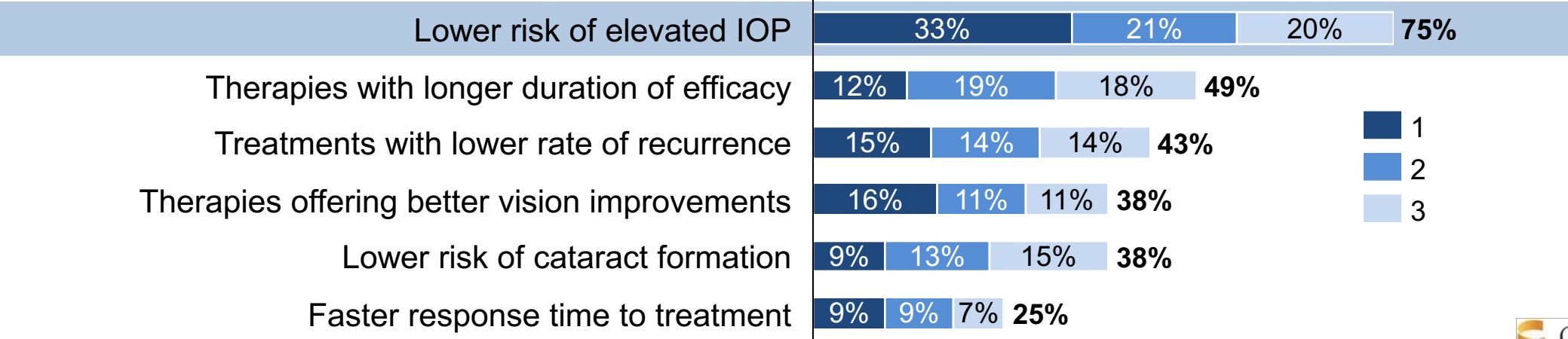
**No cataract surgeries in this trial**

# Specialists Perceive High Unmet Need Among Current Therapies, with Greatest Concern Over Elevated IOP

## Perceived Unmet Need for treating ME Secondary to NIU



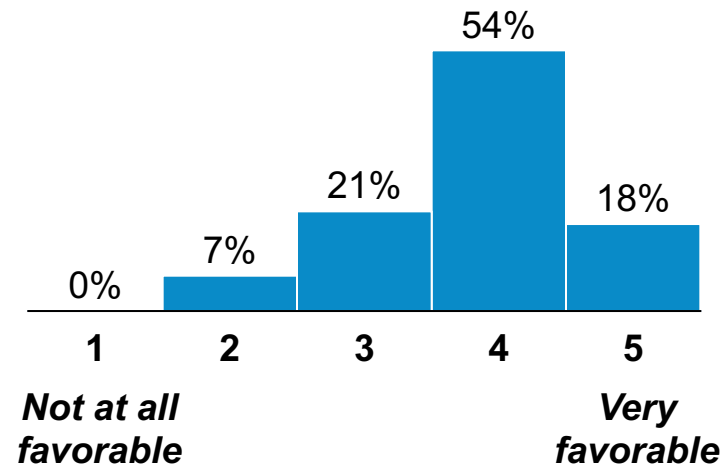
## Top Unmet Needs in Treating ME Secondary to NIU



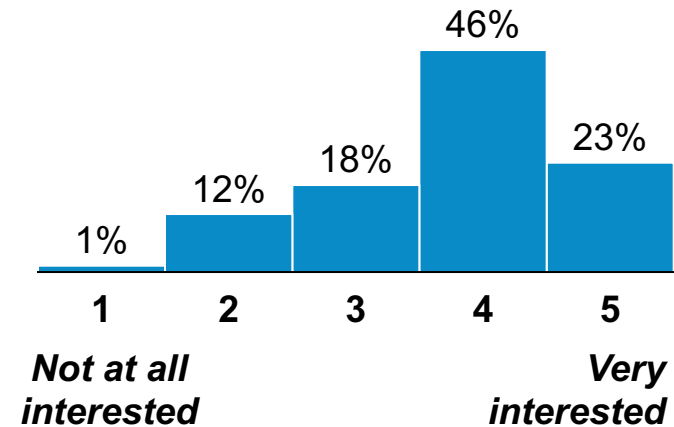


# When Introduced to XIPERE Profile, ~70% of Specialists React Favorably and Are Interested in Using

## Overall Reaction to XIPERE



## Interest in Using XIPERE



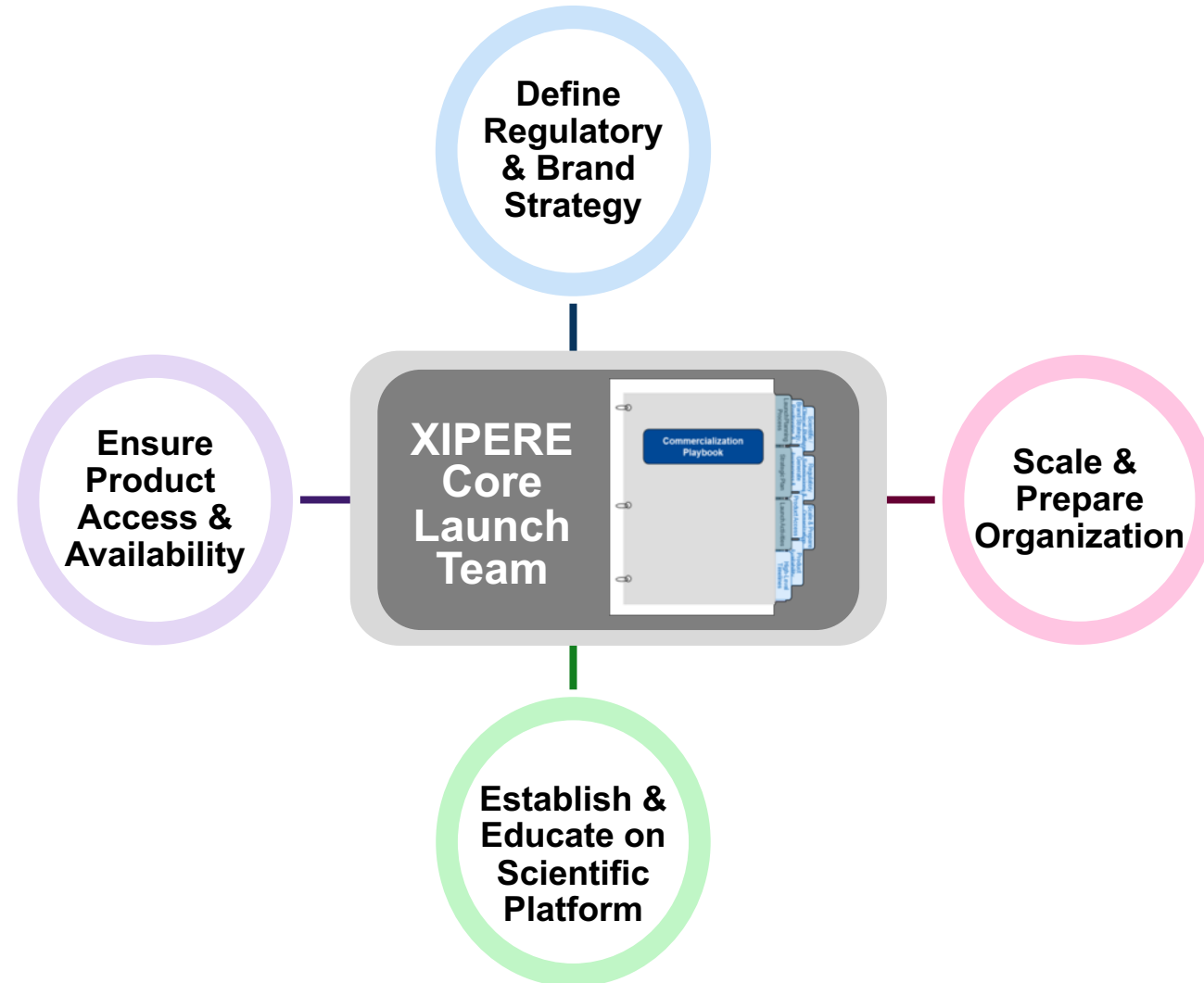
***“When you’ve got a drug that is that same you’ve been using all along but you can deliver more efficiently and comfortably – that’s a winner”***

**-Academic uveitis specialist**

# Preparing for Launch

## Key Focus Areas:

- Physician and patient education
- Injection training for the physicians
- Reimbursement support



# DME

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Potential Path Forward for  
XIPERE as a Monotherapy



## The Opportunity In Treating DME

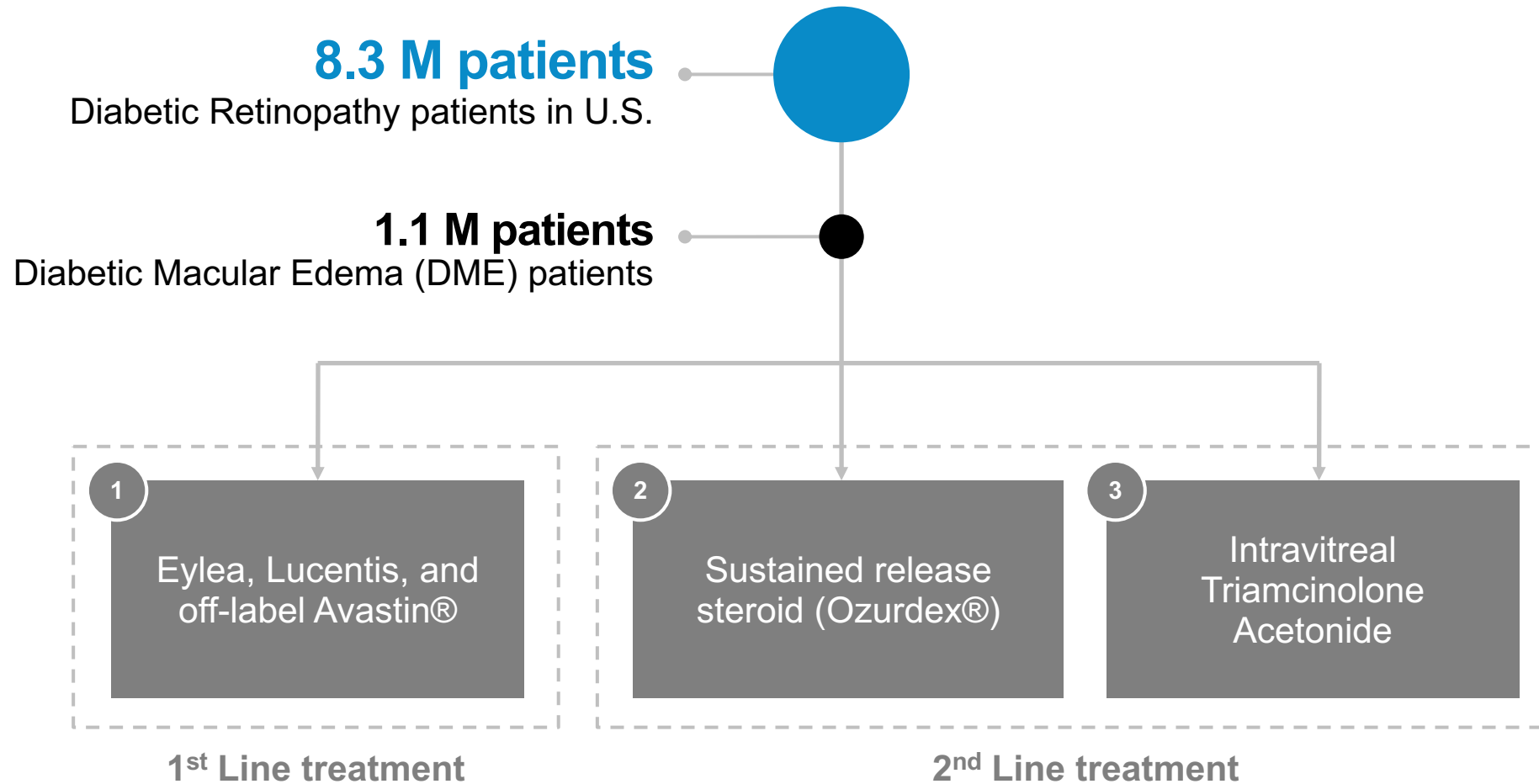
### Primary Need

- 1) Improved resolution of edema and lower burden of care for diabetic patients

### The Problem

- 1) DME course and response to anti-VEGF injection is largely variable
- 2) 40% and 55% of patients have continued macular edema in years 2 and 3, respectively, even after monthly intravitreal anti-VEGF injections
- 3) High burden for DME patients leading to poor compliance

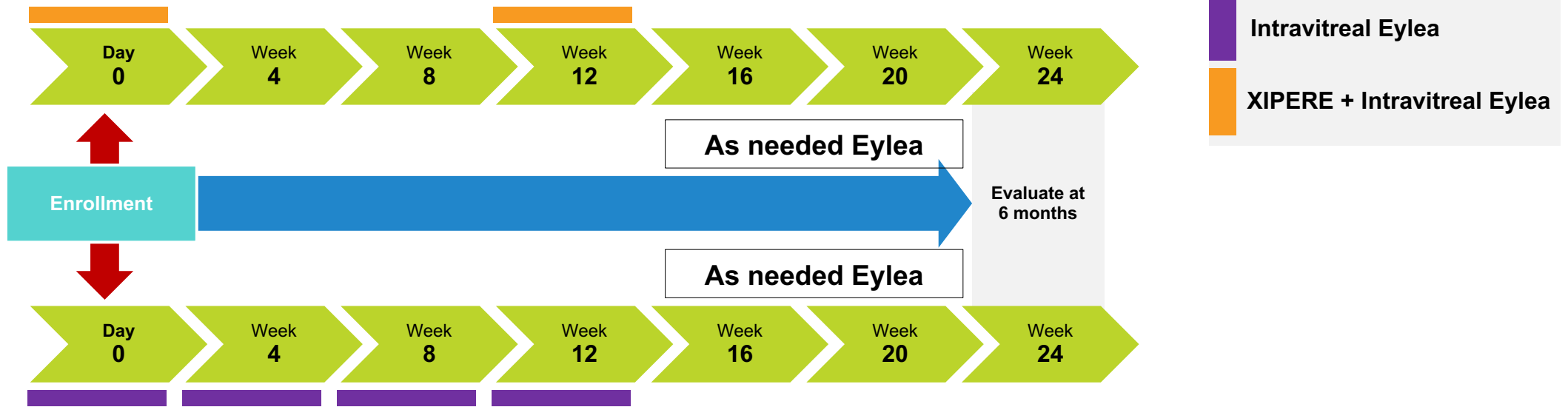
# Current Treatment Paradigm for DME



# TYBEE

## Design for Phase 2 DME Clinical Trial

### Combination arm: Intravitreal Eylea + XIPERE (n=36)

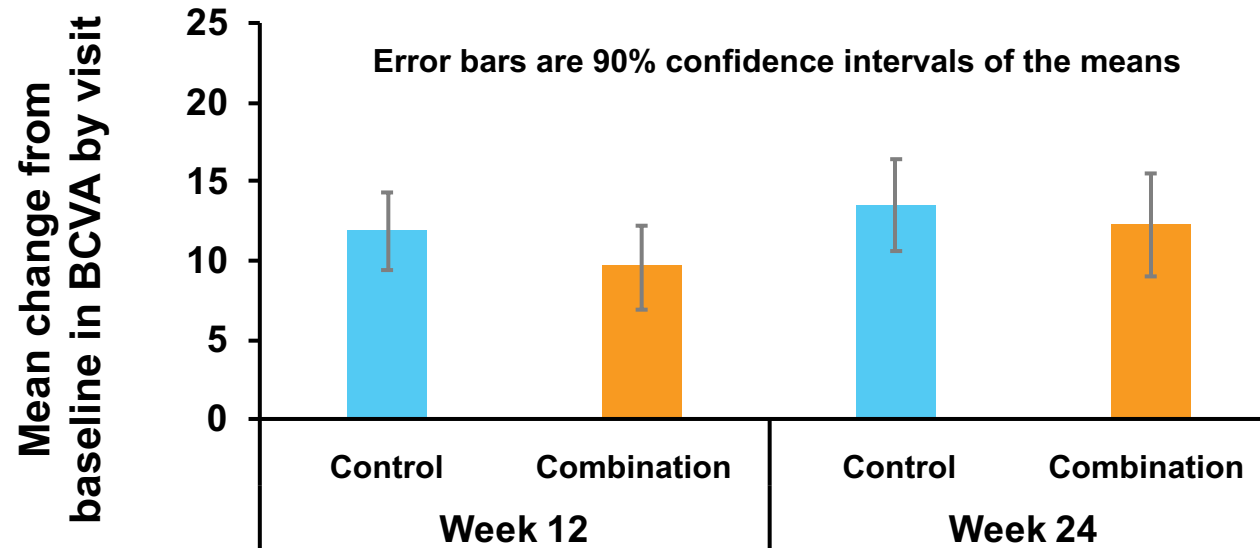


### Control arm: Intravitreal Eylea only (n=35)

Any additional treatment based on **as needed** criteria at Week 16 and Week 20 will be intravitreal Eylea

- Controlled, masked, randomized study of combination XIPERE + intravitreal Eylea vs. intravitreal Eylea alone
- Evaluation at Month 6; treatment is based on PRN criteria from Month 3
- Primary outcome measure is comparison of mean change from baseline in BCVA at 24 weeks between the combination arm and the control arm. The study was powered and designed to show that the mean change in BCVA is not different between the two arms.

# Quarterly Treatments with XIPIRE and Anti-VEGF Showed Similar Outcomes to Anti-VEGF Given Monthly



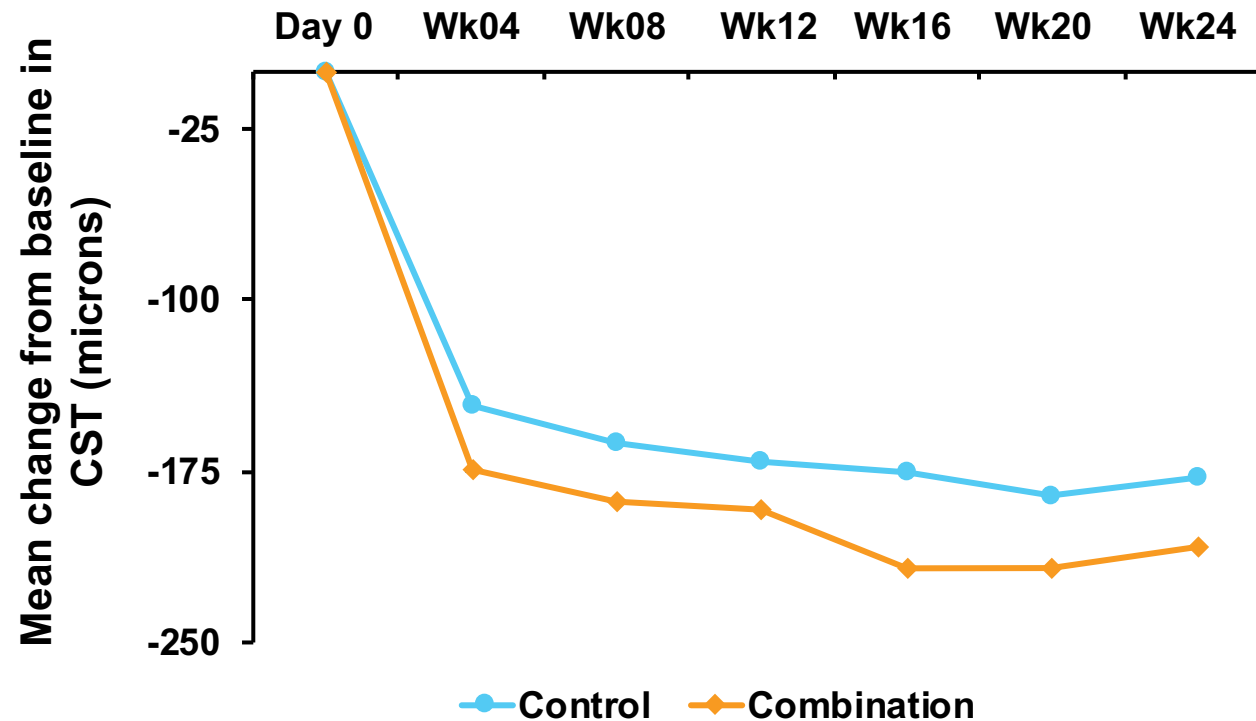
**Baseline BCVA in ETDRS letters:**  
58: control arm; 57: active arm

- XIPIRE appears to be able to extend visual gains: data from XIPIRE and anti-VEGF at week 12 and week 24 show similar outcomes compared to anti-VEGF alone given monthly

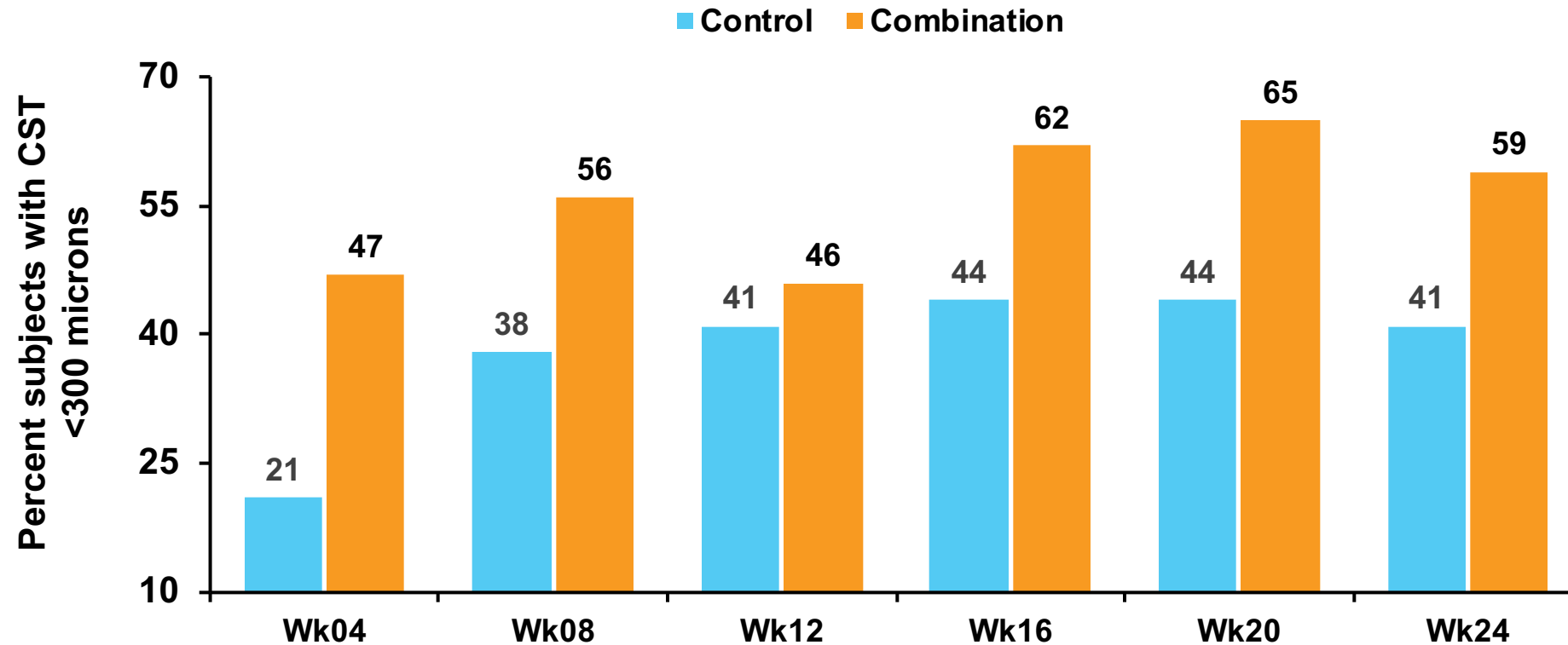


# Lesson 1: Improved Central Subfield Thickness (CST)

Each arm shows a **statistically significant improvement in CST** from baseline at week 24 (\*p<0.001)

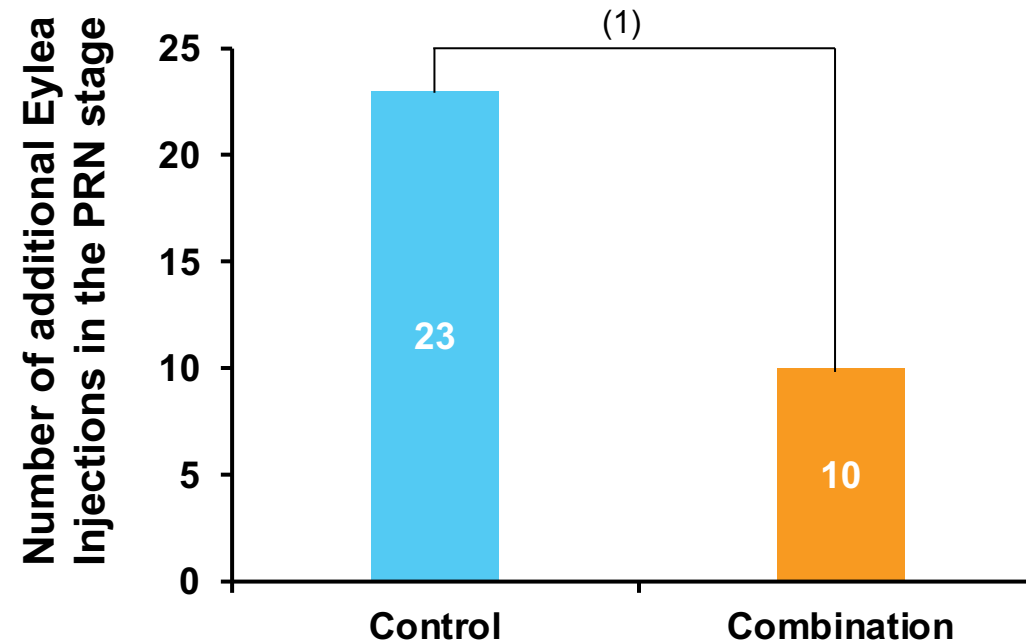


## Lesson 2: Resolution\* of CST By Visit



- A significantly greater percentage of subjects in the Combination arm showed resolution\* in their CST at the week 4 visit ( $p < 0.01$ ) compared to those in the Control arm
- The greater resolution in CST appeared to be sustained through each visit through week 24 in the trial

## Lesson 3: Combination Arm Achieved Equivalent Vision with Fewer Treatments



- ~50% fewer treatments through week 12
- ~57% fewer treatments in the PRN period (p=0.03)

# Path Forward in DME

Treatment burden and patient compliance are significant barriers to optimal treatment in DME

## Real world data demonstrates patients missing out on visual gains

- DME subjects receive 3-7 anti-VEGF injections and gain ~5 letters in vision
- Phase 3 trials demonstrate that compliant subjects have the potential to gain ~10 to 12 letters\*

## Current anti-VEGFs require retreatment every 4 to 8 weeks

- Subjects gained approximately 10 letters and were maintained for 12 weeks with XIPIRE + intravitreal Eylea in TYBEE
- XIPIRE has the potential to maintain visual gains on a quarterly dosing regimen and could address treatment burden in DME patients

## Plan to advance clinical development of XIPIRE monotherapy into the therapeutic rotation with anti-VEGF for DME

\* Lucentis PI, 2018; Eylea PI, 2018  
Holekamp AJO July 2018  
Ciulla AAO 2018 <https://doi.org/10.1016/j.oret.2018.06.004>

# The SCS Platform

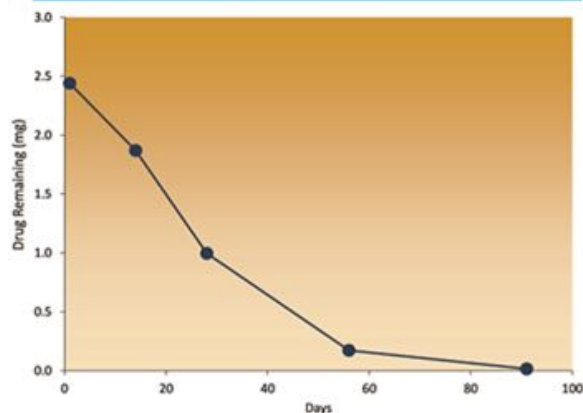
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Nonclinical

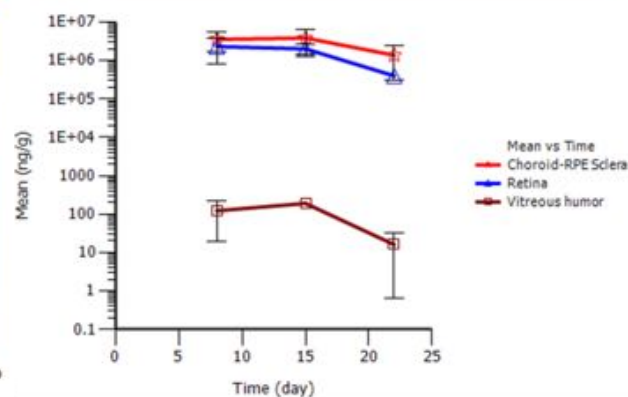
# Like TA, Small Molecules offer Unique Distribution and Durability

Small molecule compounds evaluated exhibiting lower solubility result in favorable pharmacokinetic and ocular distribution profiles.

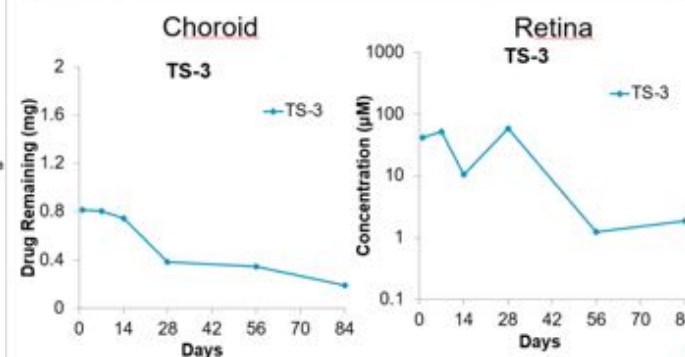
Compound A: Drug Remaining RPE/Sclera/Choroid



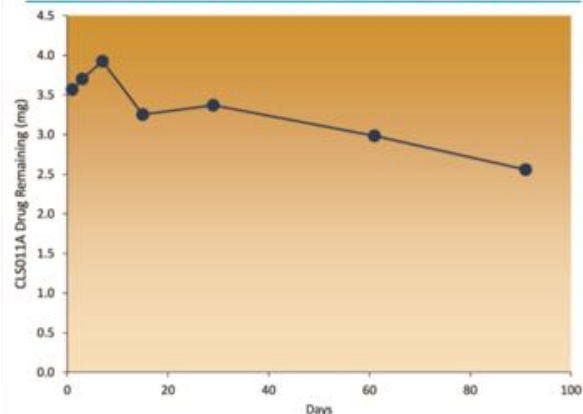
Compound C: Tissue Concentration Profile



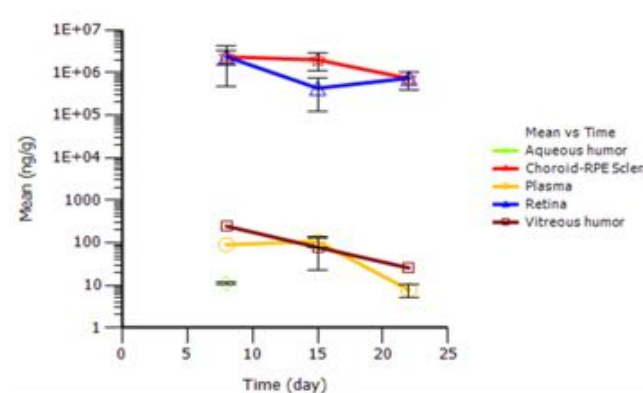
Compound E Tissue Concentration



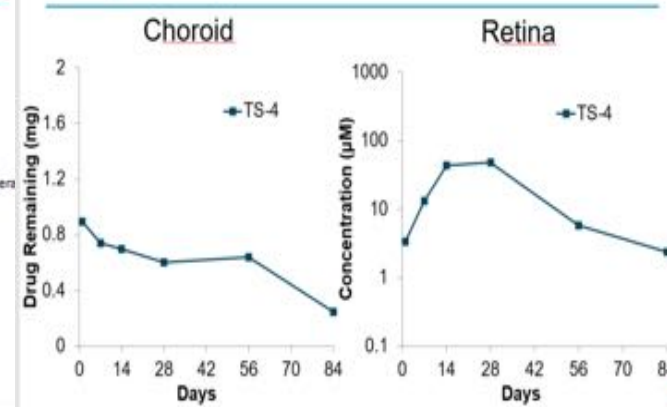
Compound B: Drug Remaining RPE/Sclera/Choroid



Compound D: Tissue Concentration Profile



Compound F Tissue Concentration



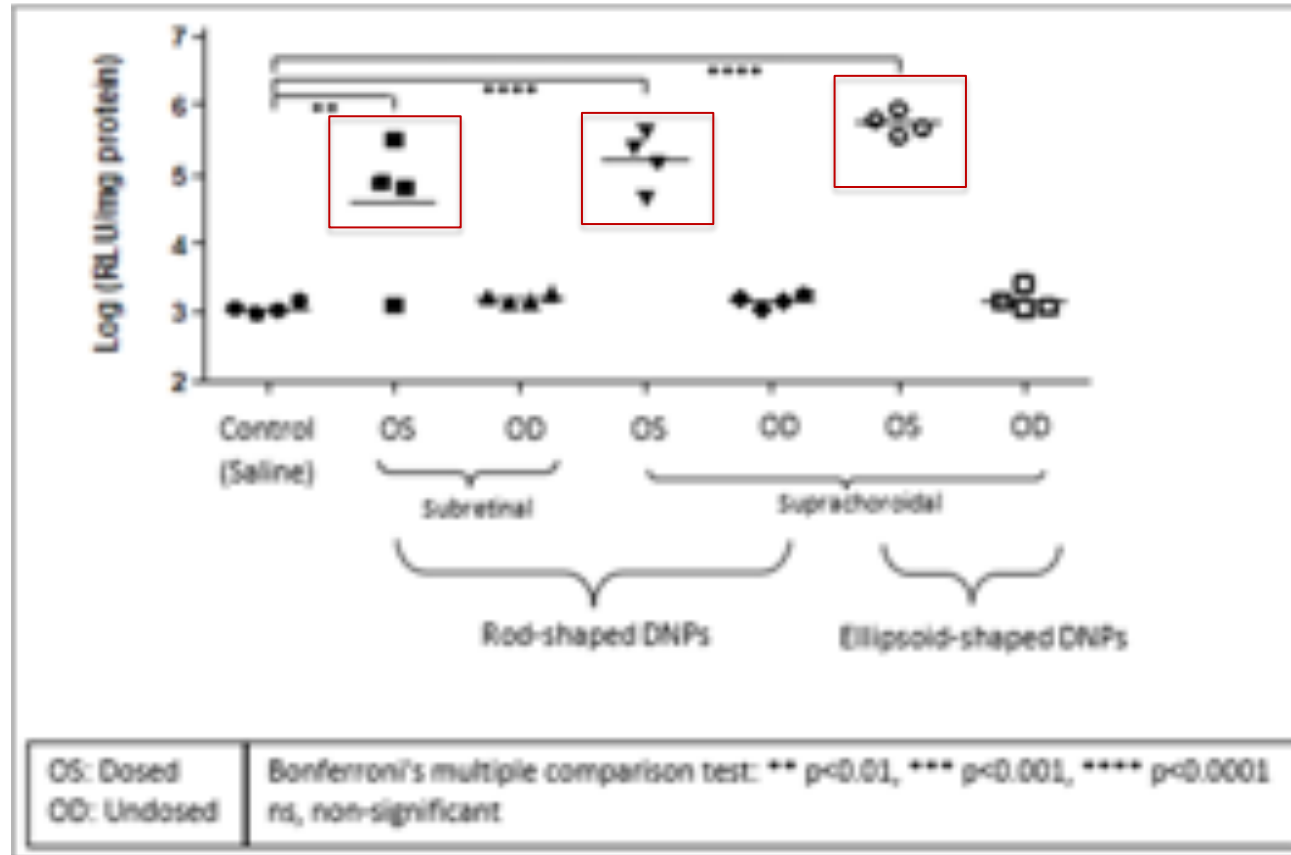
# Suprachoroidal (SC) Injection Offers Potential for Safe, Targeted, and Efficient Ocular Gene Therapy

- Targeted treatment of posterior tissues possible via SC injection
  - Spread of injectate flows circumferentially and posteriorly
- Safety
  - Avoids the risks of sub-retinal surgery
  - Does not require detachment of the photoreceptors from the RPEs, without associated risk of iatrogenic injection to already compromised disordered retina
  - SC injection procedure training is minimal
- Access to care
  - Does not require specialized gene therapy surgery treatment centers
  - In-office SC injection procedure is less expensive than surgical procedures
  - Procedure time is significantly less than standard sub-retinal procedure

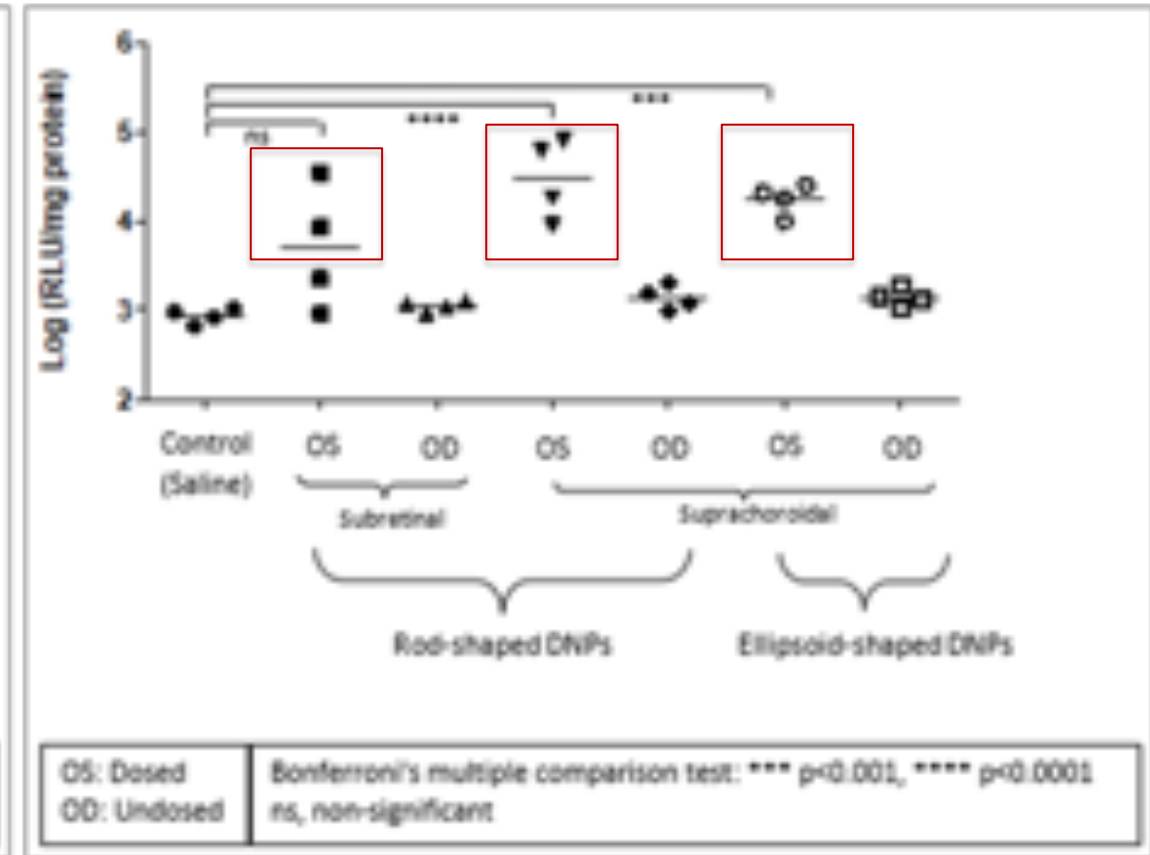


# DNA Nanoparticles Transfect the Retina and Choroid

Non Viral-Luciferase, Rabbit  
CHOROID



Non Viral-Luciferase, Rabbit  
RETINA



# DNA Nanoparticles Offer Potential for Safe, Efficacious, and Repeat Dosing Ocular Gene Therapy

- Potential advantages: DNA nanoparticles versus viral vector-mediated gene therapy
  - Unlike AAV (payload capacity of 5 kb), can transfer large genes (up to ~20 kb)
  - Safety: non-immunogenic, without viral capsid proteins or pre-existing immunity
    - Potential for repeat and greater dosing
  - Efficacy in numerous ocular animal models
    - Higher doses may be used to enhance transfection
  - Manufacturing: simpler than viral-based gene therapy
- Potential disadvantages: DNA nanoparticles versus viral vector-mediated gene therapy
  - Durability: may not represent one time therapy

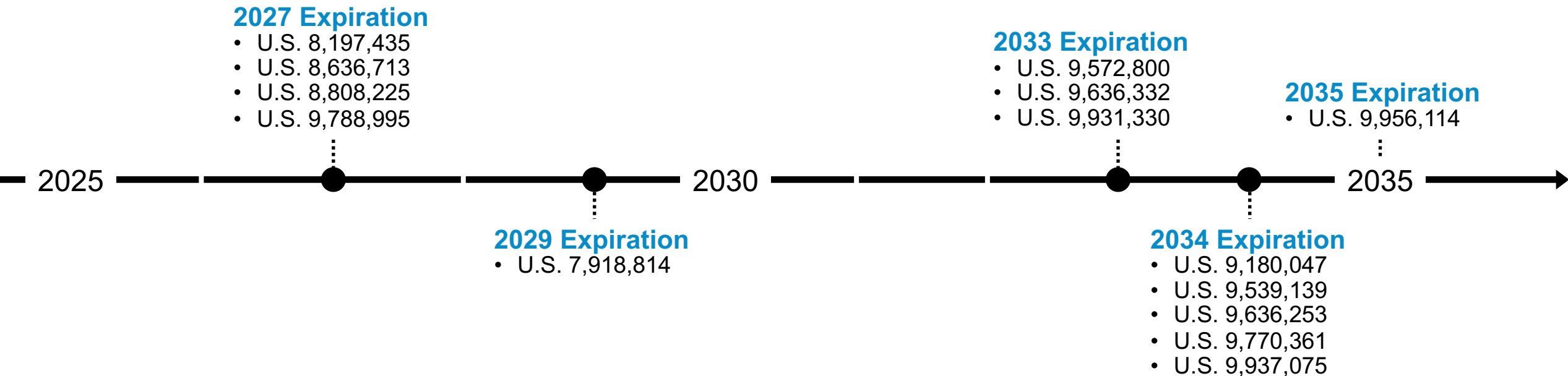


# **A WORLD WITHOUT BLINDNESS**

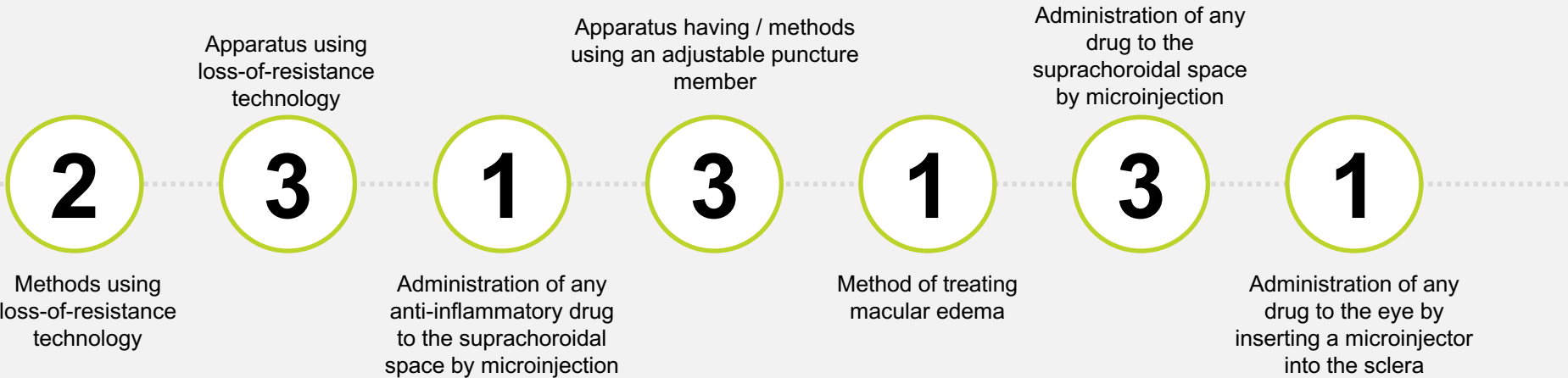
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In Summary

# Opportunity is Well Protected



**14**  
U.S. Patents  
Total



# Accomplished Leadership Team With Deep Ophthalmic Experience

	Experience	Years
<b>Daniel White</b> President, CEO and Director	GSK, Stiefel, CIBA Vision, Alimera	25
<b>Thomas Ciulla, M.D., MBA</b> Chief Medical Officer	Spark Therapeutics, Indiana University School of Medicine	27
<b>Charles Deignan</b> Chief Financial Officer	AtheroGenics, AAI Pharma, Schering-Plough	27
<b>Brion Raymond</b> Chief Commercial Officer	Genentech, Carl Zeiss Meditec, Xoma	14
<b>Leslie Zacks</b> General Counsel and Chief Compliance Officer	Arbor, Shionogi	24
<b>Rafael Andino</b> VP, Engineering & Manufacturing	CR Bard, CIBA Vision, Dupont, GE, IBM	26
<b>Carol Hoang, Pharm.D.</b> VP, Medical Affairs	DigiSight, Novartis, Genentech, BMS	17
<b>Viral Kansara, Ph.D.</b> VP, Discovery	Novartis, Merck, Alcon	12
<b>Jennifer Kissner, Ph.D.</b> VP, Clinical Development	Alcon, Acucela	17
<b>Rick McElheny</b> VP, Business Development	Sanofi, MEDA, Vidara	18
<b>Lester Rodríguez</b> VP, Quality	Pharma Tech, Ciba Vision, Novartis, Shionogi	30

## Ophthalmic Experience

**Alcon**

**ALIMERA  
SCIENCES**

**CIBA VISION**

**Genentech**

**MERCK**

**NOVARTIS**

**SHIONOGI**

**Spark**  
THERAPEUTICS

# Multiple Upcoming Milestones

2019 & 2020

## Uveitis



FDA acceptance of NDA



PDUFA date – Oct. 19, 2019



U.S. Launch – Q1 2020



EMA application

## Other Pipeline



Presentation of data on suprachoroidal platform at medical meetings



DME program next steps



Additional nonclinical results from preclinical gene therapy programs

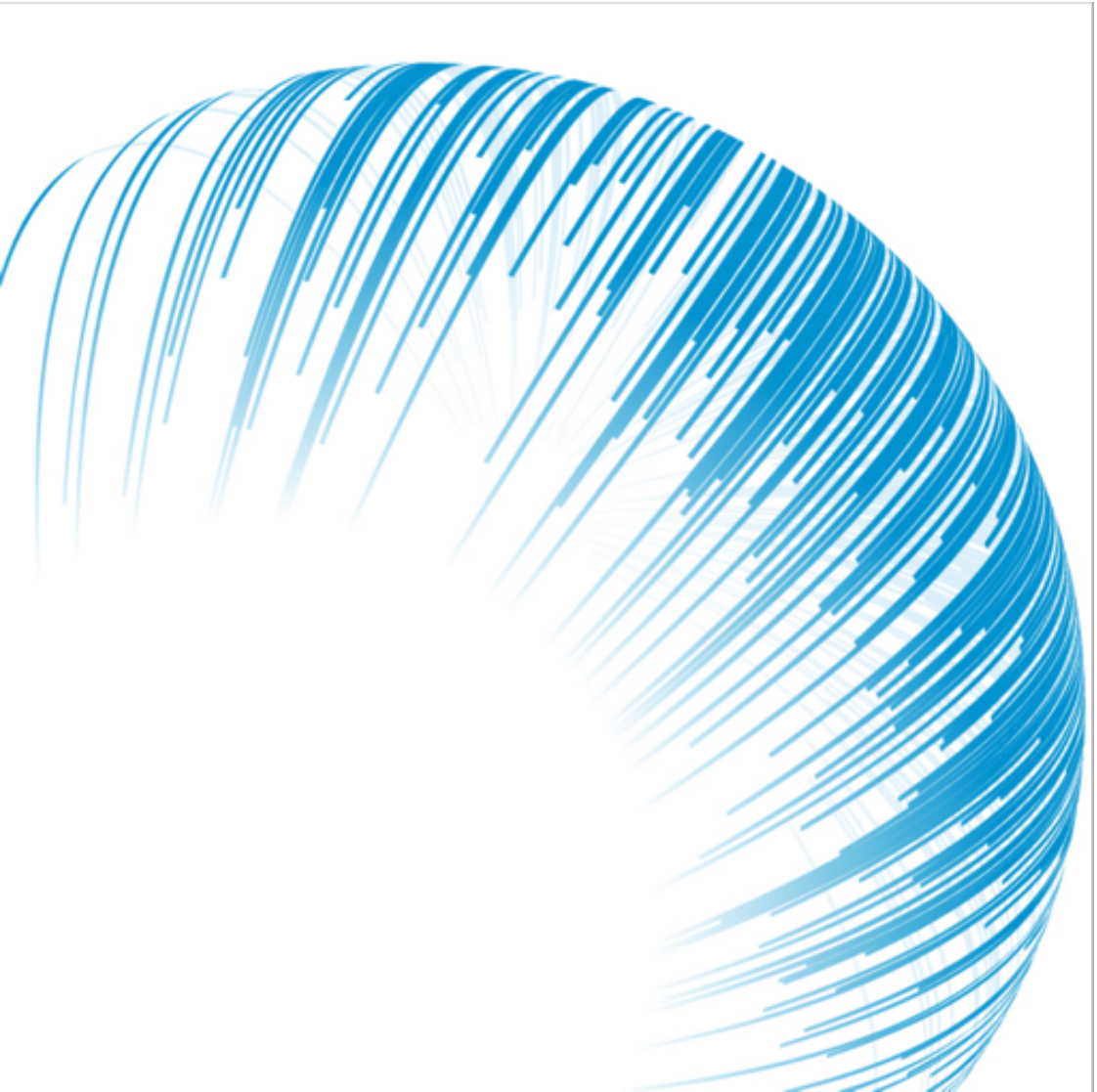


Additional preclinical data on small molecule programs



## Investment Summary

- Lead product candidate, XIPERE, for the treatment of macular edema associated with uveitis
  - Pivotal Phase 3 PEACHTREE trial success
  - NDA submitted in Q4 2018 with October 19, 2019 PDUFA
  - If approved, XIPERE would be the first therapy with this indication
  - If approved, formal launch for XIPERE anticipated in Q1 2020
- Exclusive and proprietary access to the back of the eye through the SCS
  - Technology and approach well protected with 14 patents
- Suprachoroidal platform includes late-stage and nonclinical product candidates targeting multiple blinding eye diseases
- Large and growing retinal market opportunity: ~5 million patients in U.S. treated by approx. 1,900 uveitis and retina specialists



# THANK YOU!



*We see a world without blindness;  
relentlessly pursuing transformative,  
elegant, precise solutions to restore  
and preserve vision.*