EYLEA® (aflibercept) for the Treatment of Retinopathy of Prematurity (ROP)

January 09, 2023

Dermatologic and Ophthalmic Drugs Advisory Committee

Regeneron Pharmaceuticals, Inc.

Introduction

Boaz Hirshberg, MD, MBA

SVP, Clinical Sciences General Medicine

Regeneron Pharmaceuticals, Inc.

Aflibercept (EYLEA®): FDA and Globally Approved Anti-VEGF

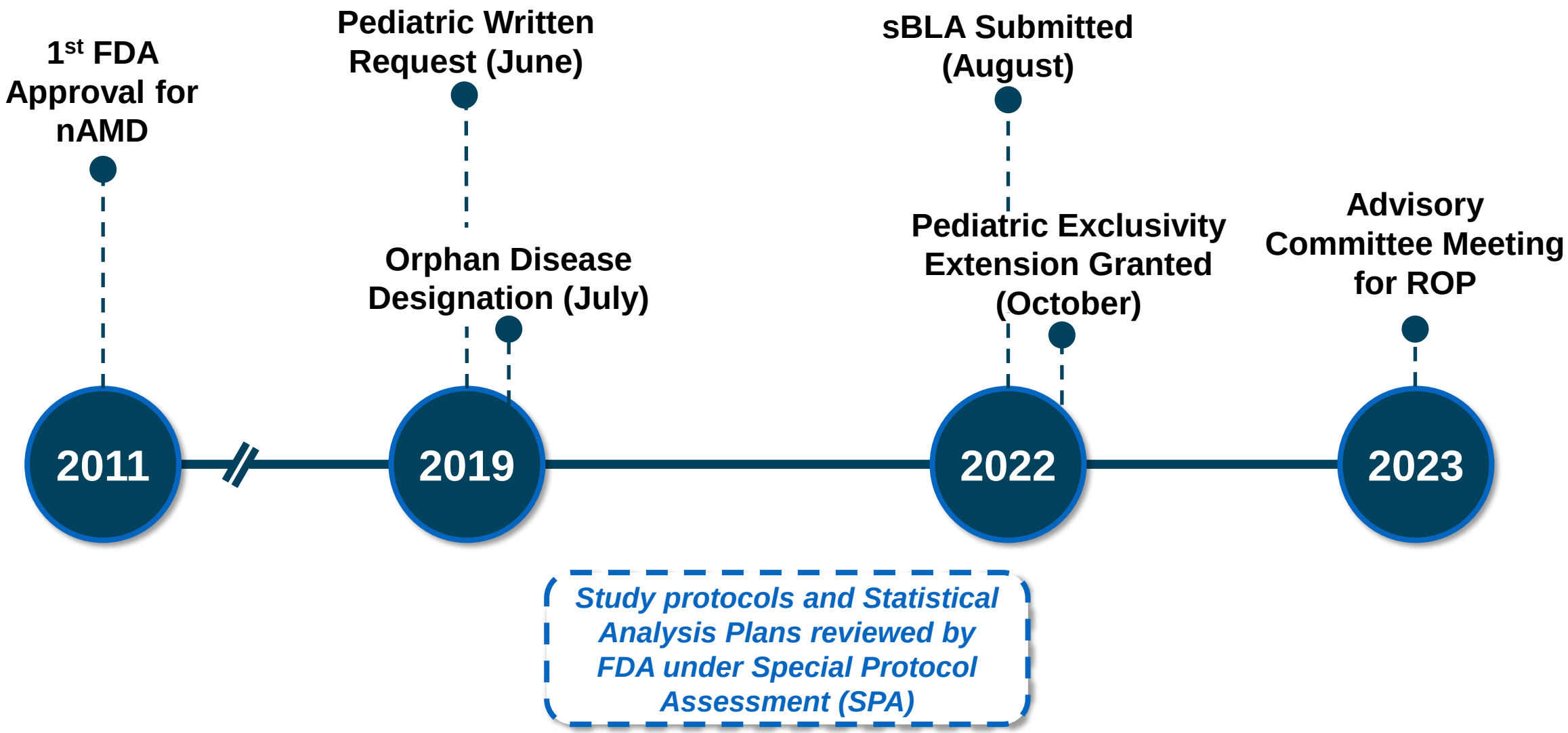
- Current US adult indications for aflibercept 2 mg
  - Neovascular (Wet) Age-Related Macular Degeneration (nAMD)
  - Macular Edema Following Retinal Vein Occlusion (MEfRVO)
  - Diabetic Macular Edema (DME)
  - Diabetic Retinopathy (DR)
- Authorized outside US in > 100 countries
- Regulatory decisions regarding EYLEA in ROP
  - Approved for ROP in Japan (2022)
  - Approved for ROP in European Union (2022)

VEGF = vascular endothelial growth factor

Role of VEGF in ROP is Well Understood

- Vascularization of retina occurs late in gestation
  - Completion occurs shortly before 39 – 40 weeks
- Premature birth interrupts normal retinal development
- Avascularized, ischemic retina upregulates VEGF and other related cytokines
- Overexpression of VEGF leads to pathologic neovascularization
- Aflibercept binds to VEGF preventing activation of VEGF receptors and halting the formation of abnormal blood vessels

Aflibercept for ROP Regulatory History



Indication and Recommended Dose

Aflibercept 0.4 mg administered by intravitreal injection for the treatment of retinopathy of prematurity

Totality of Data Supports Aflibercept for Premature Infants with ROP

Unmet Need

- ✓ Severe vision impairing disease
- ✓ No approved pharmacologic agents in US
- ✓ Only FDA-cleared laser therapy

Efficacy

- ✓ Aflibercept offers meaningful clinical and practical benefits
- ✓ Clinical trial data build on data from increasing off-label anti-VEGF use

Safety

- ✓ Acceptable safety profile in pediatric population and > 10 years of FDA approved use in adult indications

Importance of Updated Eylea Labeling and Communication to Providers and Caregivers

- As part of FDA's pediatric written request, ROP clinical trial data will be included in Eylea label
  - Labeling important tool to inform physicians of proper use and dosing
- Approval allows for proactive education on appropriate patient follow-up for prescribers
- Regulated pharmacovigilance to monitor and report ongoing safety
- Long-term follow-up, through 5 years of age, underway

Agenda

Unmet Need

Faruk Örge, MD
Professor of Ophthalmology and Pediatrics
Case Western Reserve University
Director of Pediatric Ophthalmology and Adult Strabismus
Rainbow Babies and Children's Hospital

Efficacy

Robert Vitti, MD
VP, Clinical Sciences Ophthalmology
Regeneron Pharmaceuticals Inc.

Safety

Suzanne Green, MBChB
Therapeutic Area Head, Global Patient Safety
Regeneron Pharmaceuticals, Inc.

Clinical Perspective

Steven Donn, MD, FAAP, FAARC
Professor Emeritus of Pediatrics
Division of Neonatal-Perinatal Medicine
University of Michigan Medical School

Additional Experts

Thomas DiCioccio, PhD
Vice President, Pharmacometrics
Regeneron Pharmaceuticals, Inc.

Benjamin Drosman RPh, MBA
Senior Vice President, Ophthalmology Regulatory Affairs
Regeneron Pharmaceuticals, Inc.

Bret Musser, PhD
Head of Biostatistics
Regeneron Pharmaceuticals, Inc.

Disease Background and Unmet Need

Faruk H. Örge MD, FAAO, FAAP

William R. and Margaret E. Althans Chair and Professor
Director, Center for Pediatric Ophthalmology and Adult Strabismus
Rainbow Babies and Children's Hospital
Department of Ophthalmology and Visual Sciences
Professor of Ophthalmology and Pediatrics, Case Western Reserve University School of Medicine
IPOSC Immediate Past President
KTEF PEOC Editor in Chief

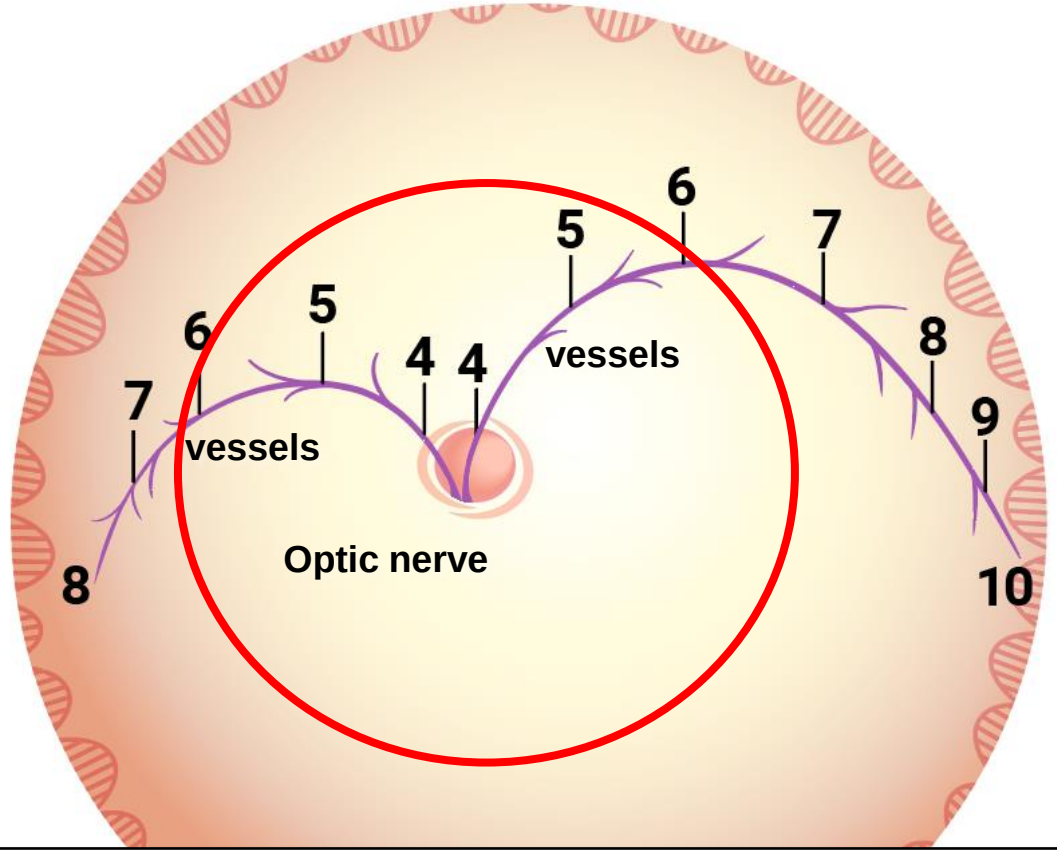
Retinopathy of Prematurity: A Rare, Vision-Impairing, and Potentially Blinding Retinal Disease

- A leading cause of preventable childhood blindness worldwide
  - Incidence increasing due to improved survival of extremely premature newborns
- Incomplete development of peripheral retina vascularization leads to ischemia and production of VEGF
  - Neovascularization
  - Potential retinal detachment
- ~1500 babies per year require treatment
  - Born < 32 weeks' gestational age
  - Weighing < 1500 grams (3.3 lbs)

Retinal Vascular Development Begins at 16 Weeks Gestation

Nasal retina

Vessels complete in 32 – 34 weeks



Temporal retina

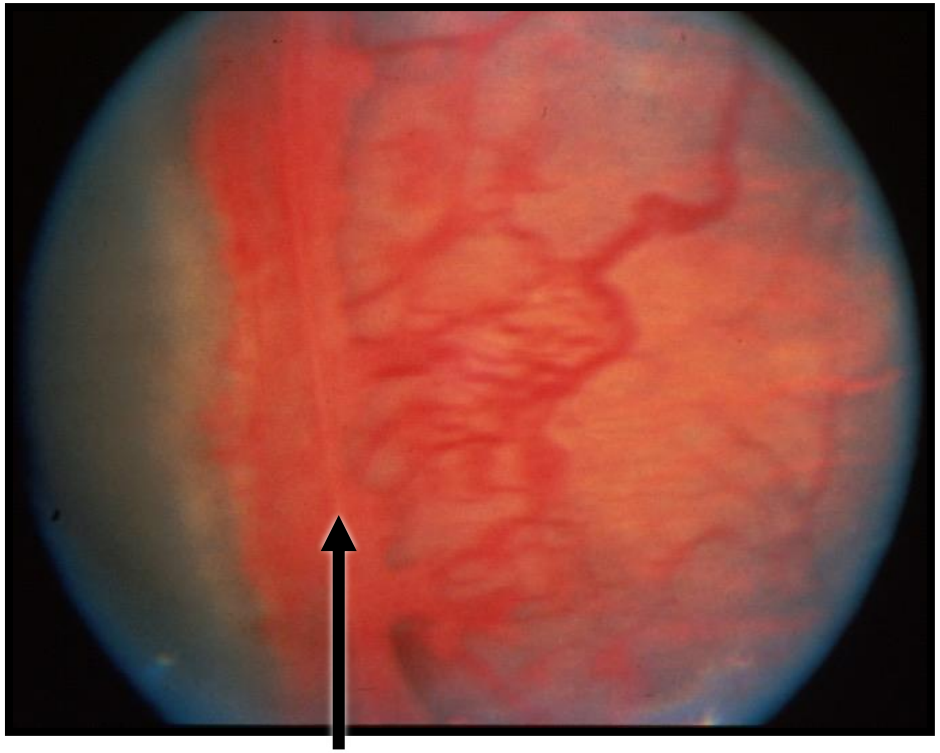
Vessels complete in 38 – 40 weeks

Blood vessel growth by month from optic nerve toward periphery

Treatment is Needed if ROP is Severe

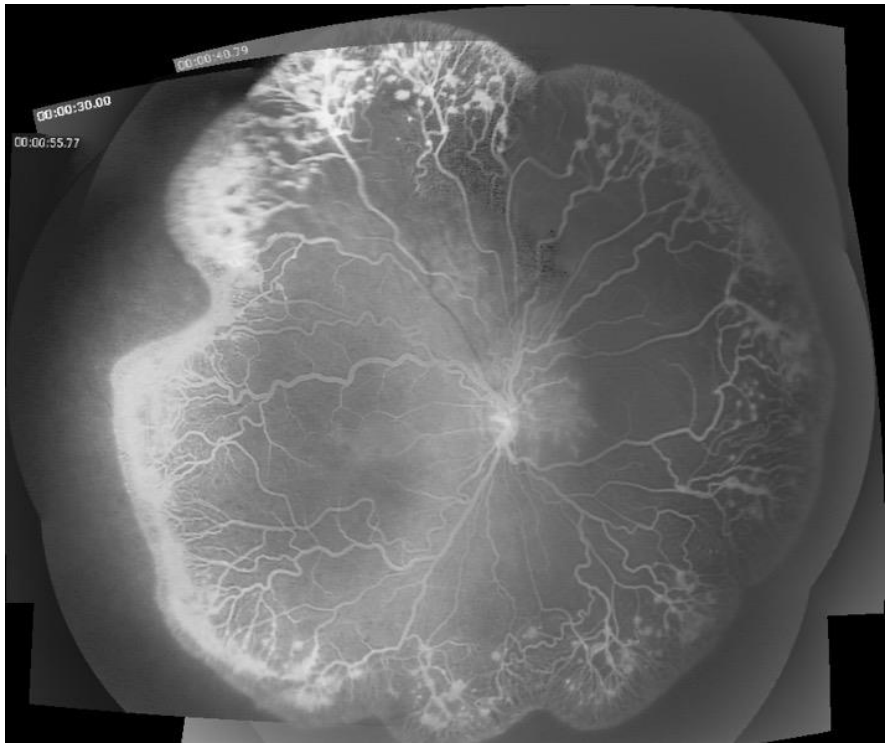
Retinas with ROP

Photography

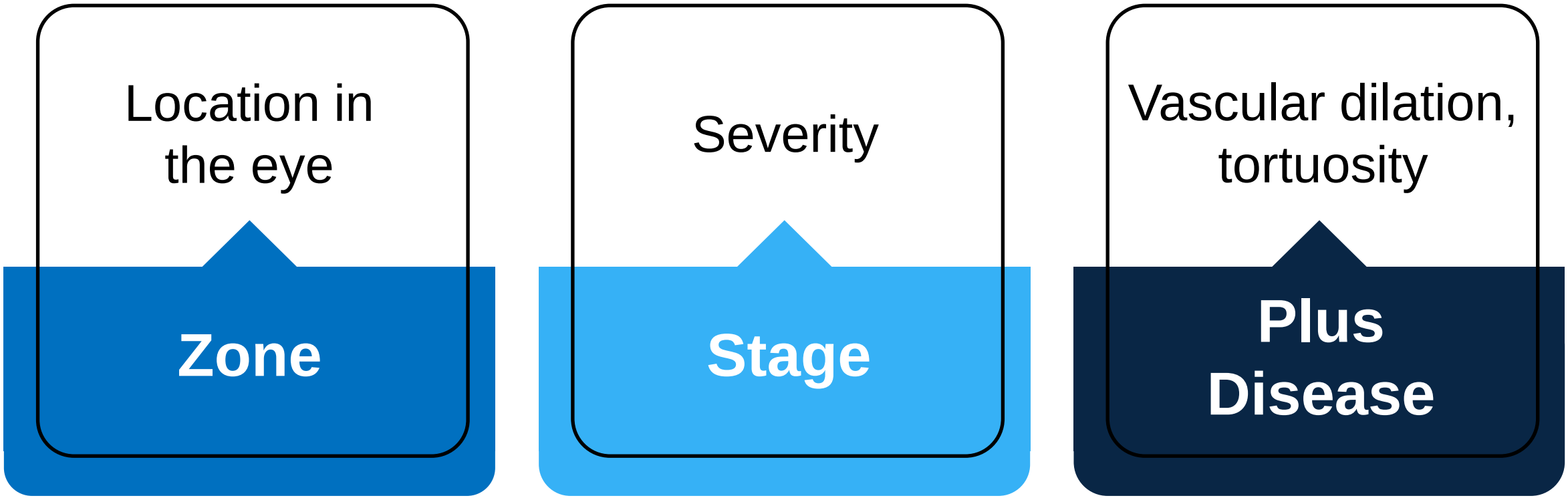


Blood vessel growth stimulated by VEGF

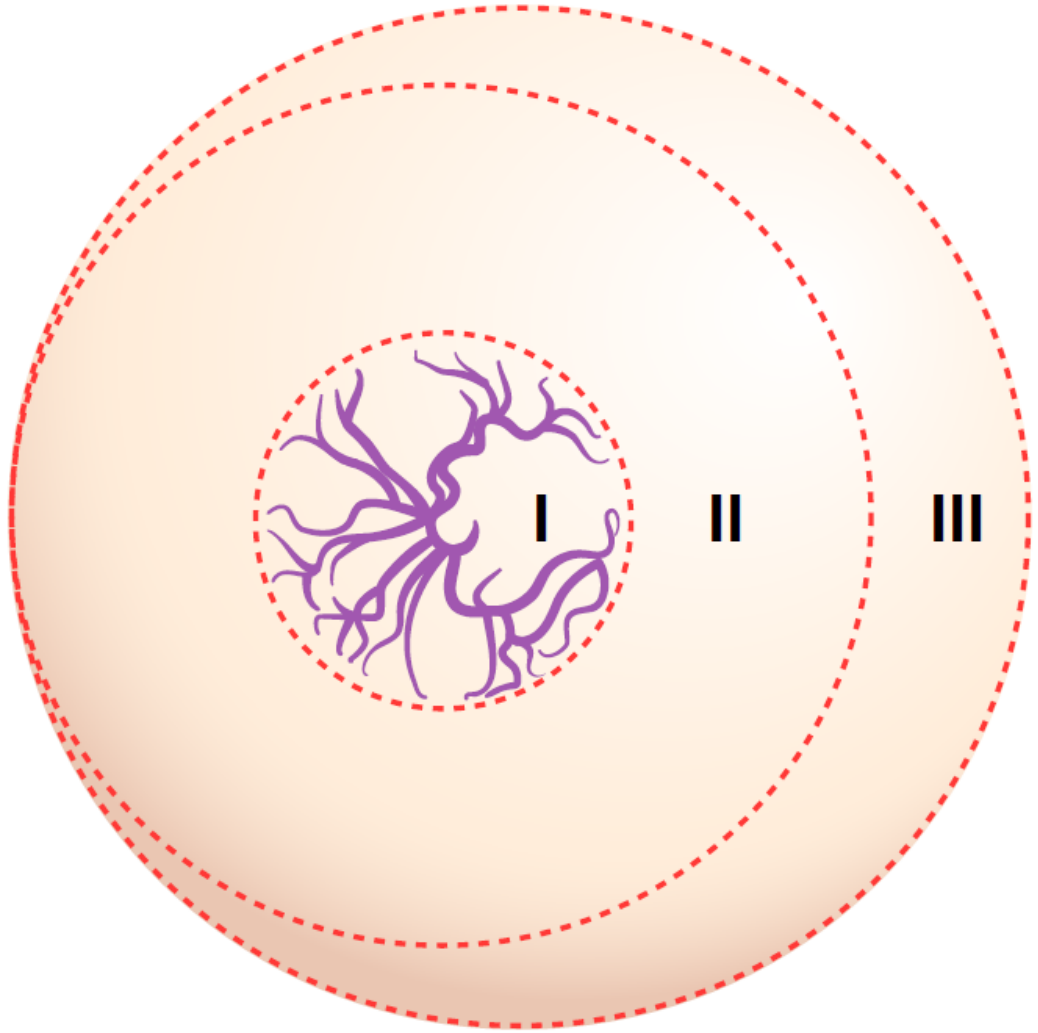
Angiography



Classification of ROP: International Classification of Retinopathy of Prematurity (ICROP)



Classification of ROP: Zone Location



Zone I

Most posterior
Most severe

Zone II

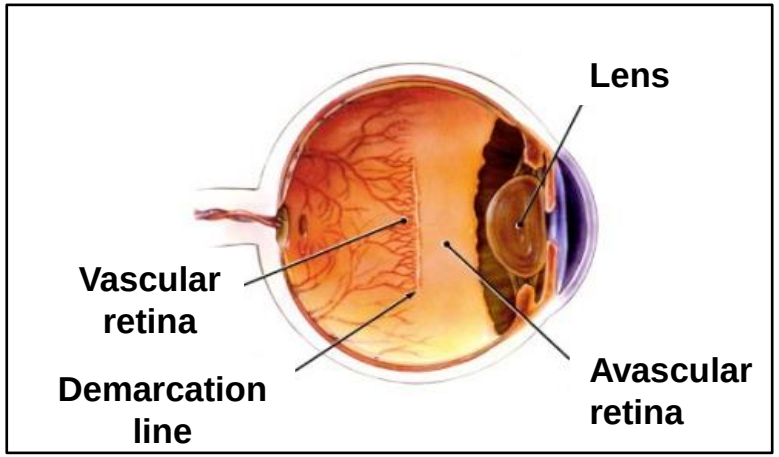
Most common

Zone III

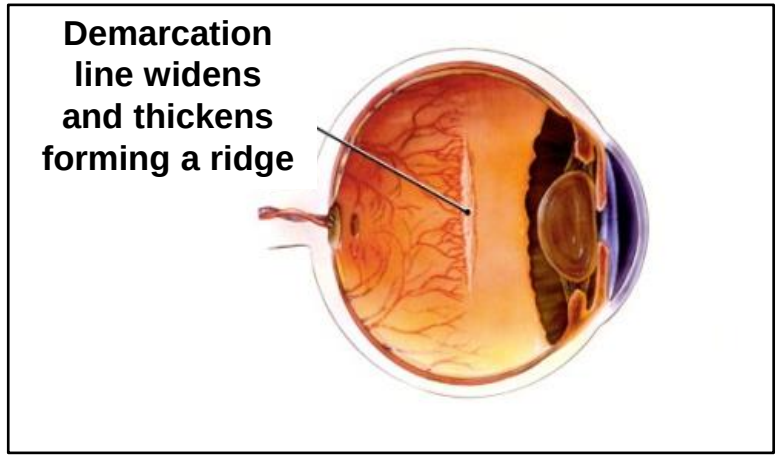
Most peripheral
Least severe

Classification of ROP: Stages of Severity

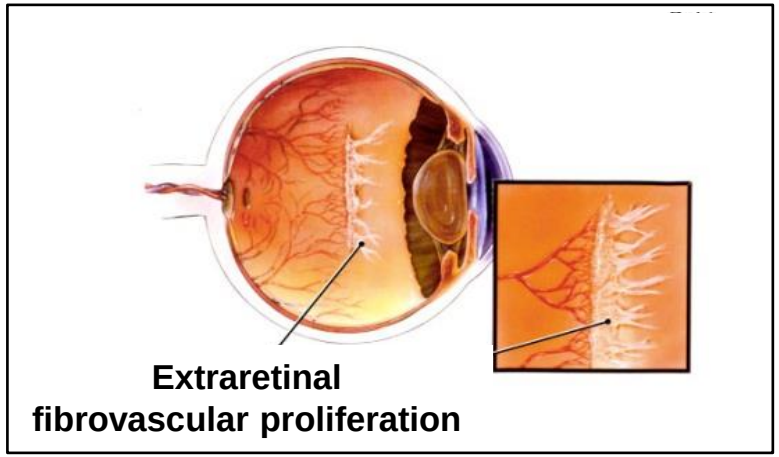
Stage 1: Thin Demarcation Line



Stage 2: Thicker Ridge



Stage 3: Extraretinal Fibrovascular Proliferation



Stage 4: Partial Retinal Detachment

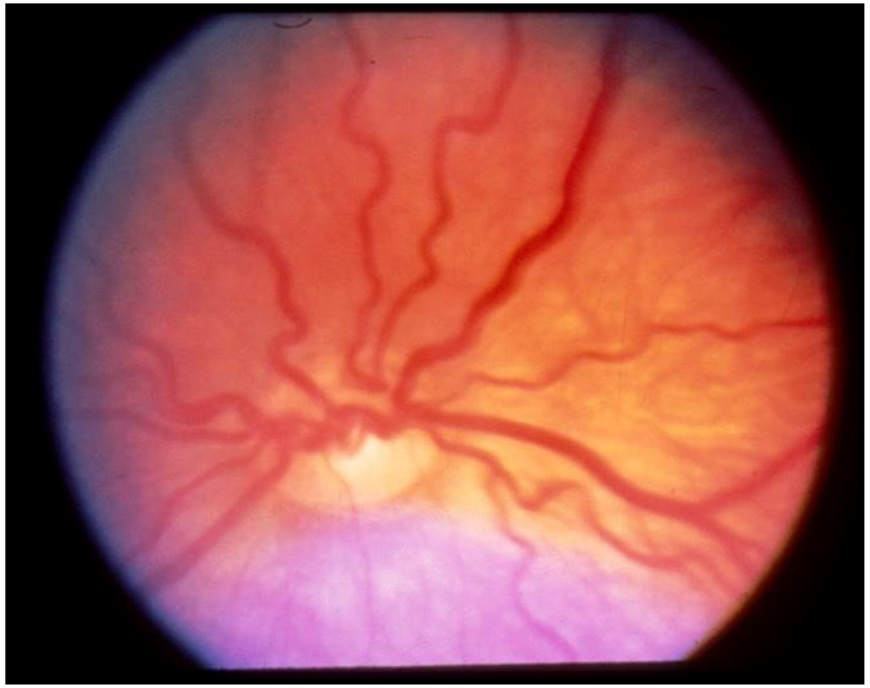
Stage 5: Total Retinal Detachment

→ **Extensive surgery often required**

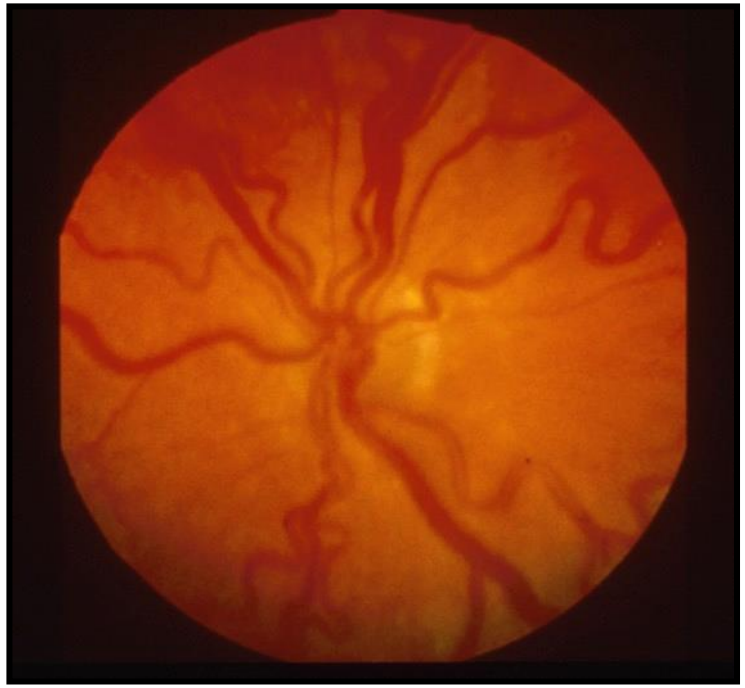
International Committee for the Classification of Retinopathy of Prematurity, 2005

ROP Classification: Plus Disease

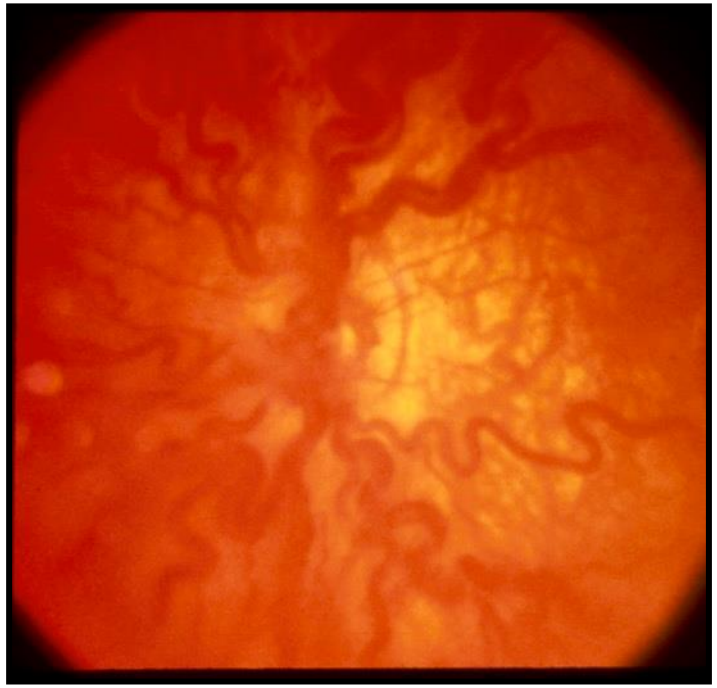
Mild Plus Disease (+)



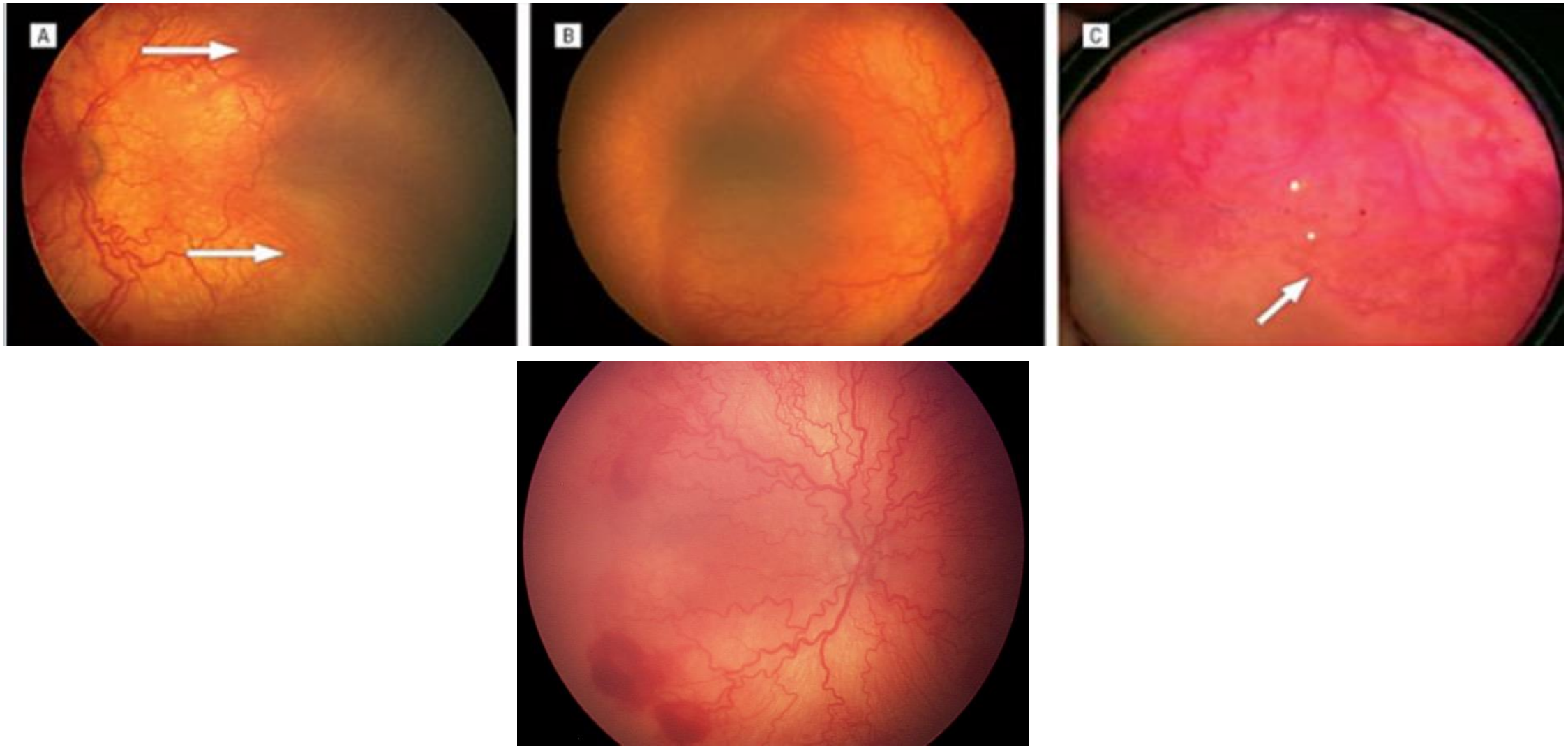
Moderate Plus Disease (+)



Severe Plus Disease (+)



ROP Classification: AP-ROP



AP-ROP = Aggressive posterior retinopathy of prematurity

Treatment-Requiring ROP (Type 1)

Zone I

Stage 1+, 2+, 3, or 3+

or **AP-ROP**

Zone II

Stage 2+ or 3+

or **AP-ROP**

Prompt treatment required to avoid

- Retinal detachment
- Extensive surgery
- Complications
- Blindness

+ = plus disease

Limited Current Options for Patients with ROP

- Standard of care recognized[1]
  - Laser photocoagulation therapy
  - Off-label use of anti-VEGF
- National organizations acknowledge off-label use, potential benefits of anti-VEGF, recommendations for follow-up
- No pharmacologic agents currently approved in US

1. Fierson, 2018

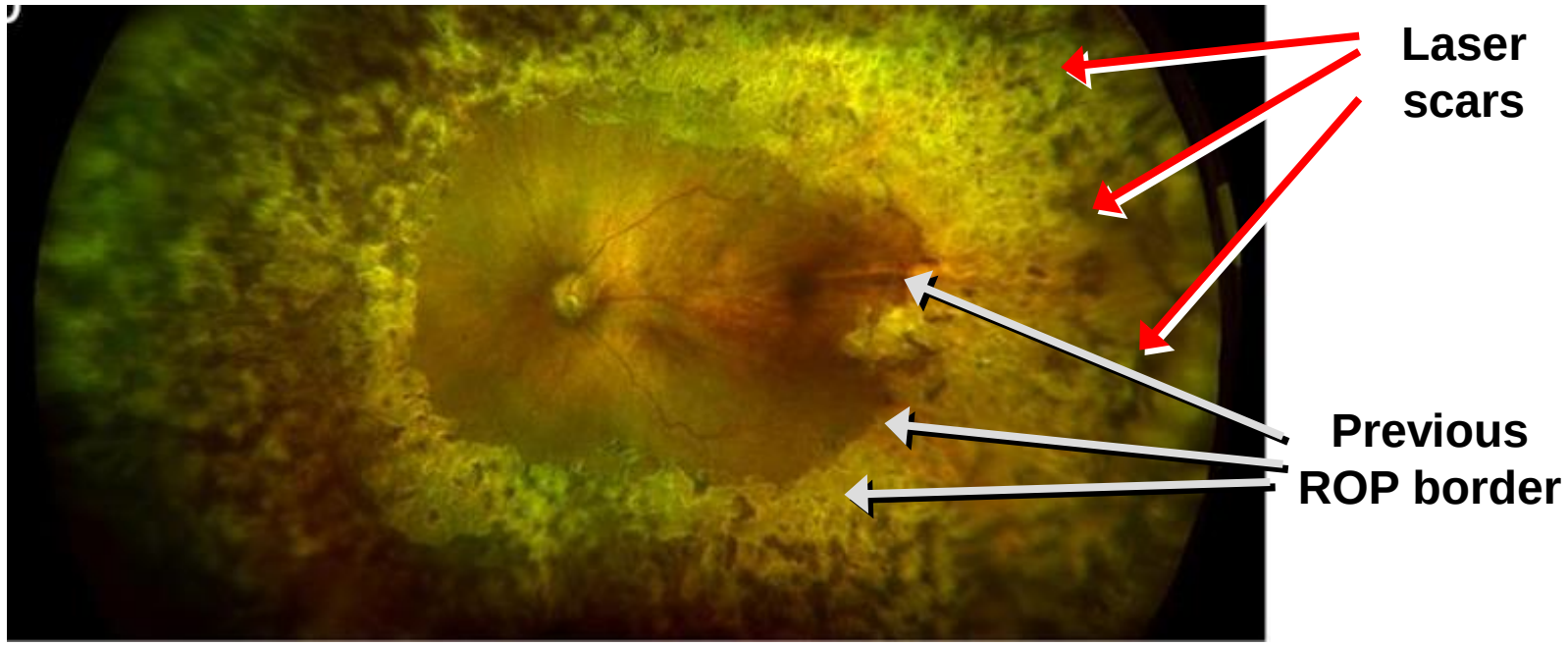
Laser Photocoagulation

Laser Photocoagulation is Effective but Comes with Challenges

- Typically requires prolonged sedation/general anesthesia and location designated for use
- Can limit access to care and require babies to be moved to specialized setting
- Extensive learning curve – improper administration leads to variable outcomes

Laser Therapy Inherently Destructive

- Results in loss of peripheral vision
- ~50% of patients develop high myopia[1]

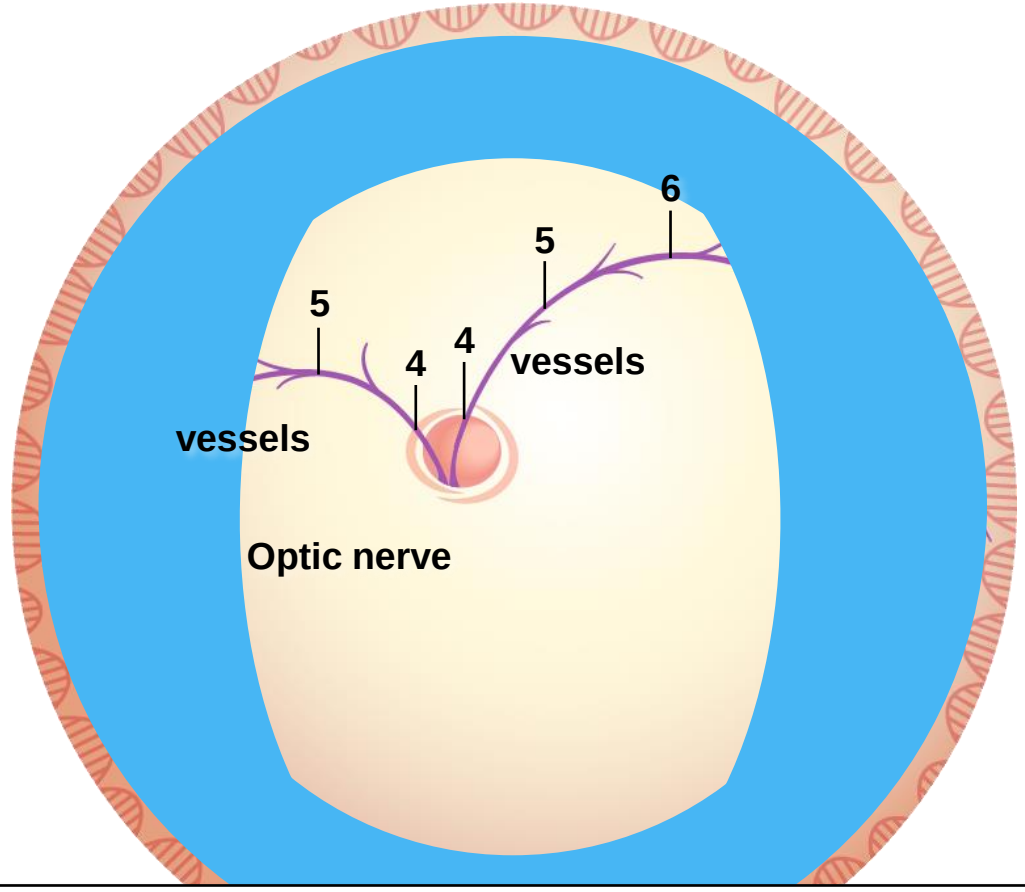


1. Geloneck, 2014

Larger Portion of Retina Destroyed When Normal Vessels are Not Fully Developed

Nasal retina

Vessels complete
in 32 – 34 weeks



Temporal retina

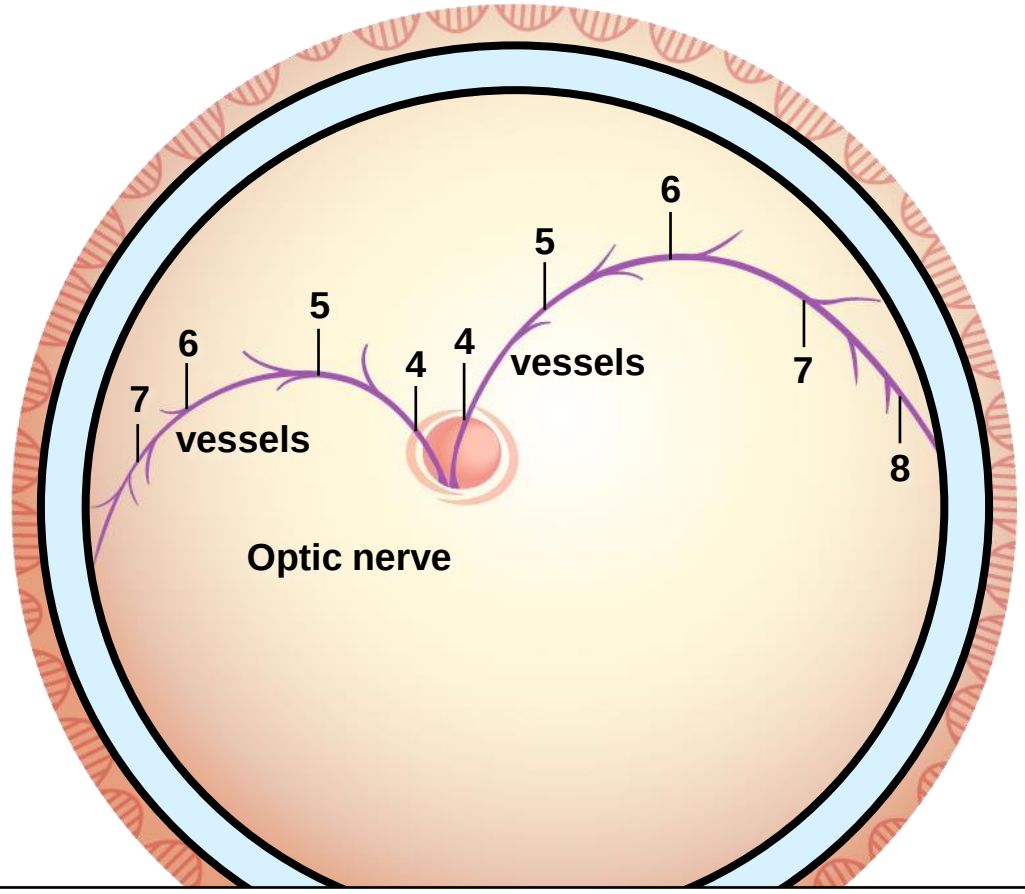
Vessels complete
in ~38 weeks

Blood vessel growth by month from optic nerve toward periphery

Later Use of Laser Therapy, When Normal Vessels Fully Develop, Reduces Retinal Destruction

Nasal retina

Vessels complete in 32 – 34 weeks



Temporal retina

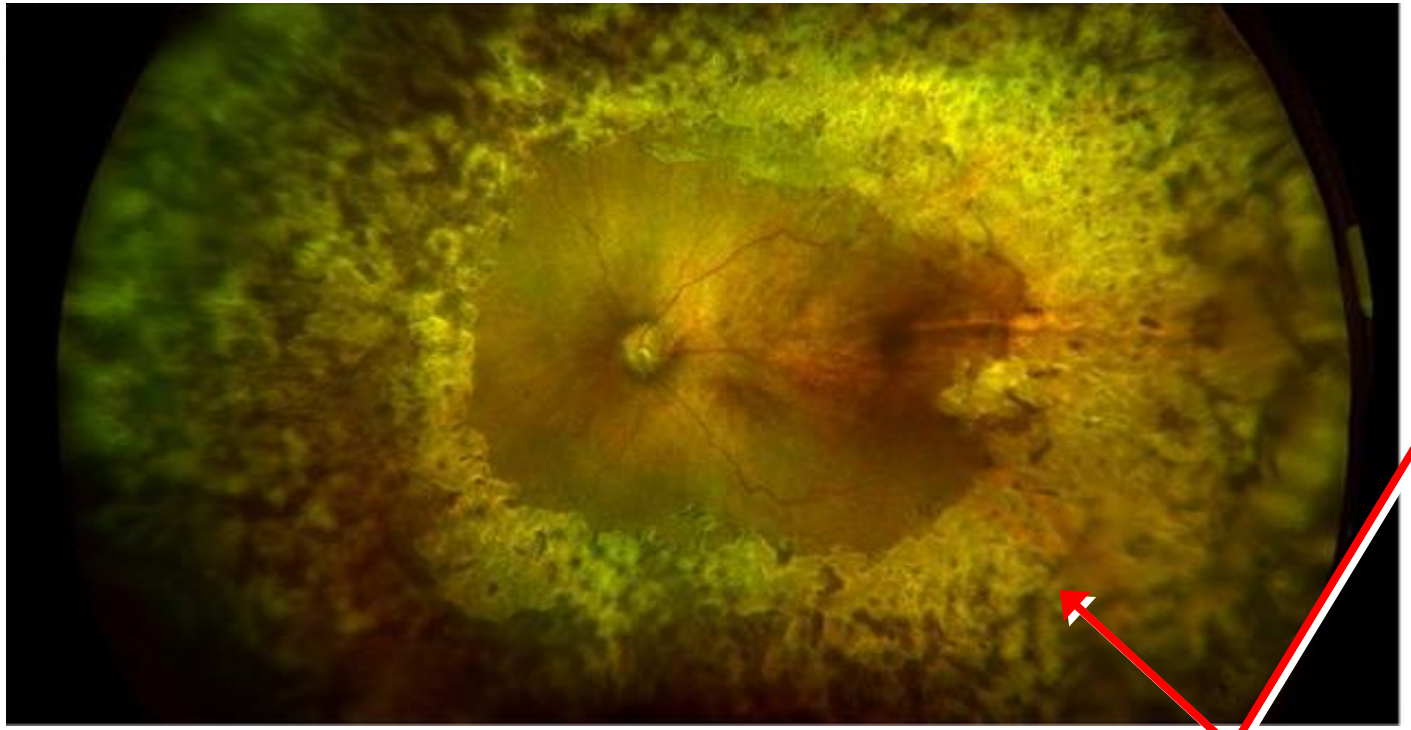
Vessels complete in ~38 weeks

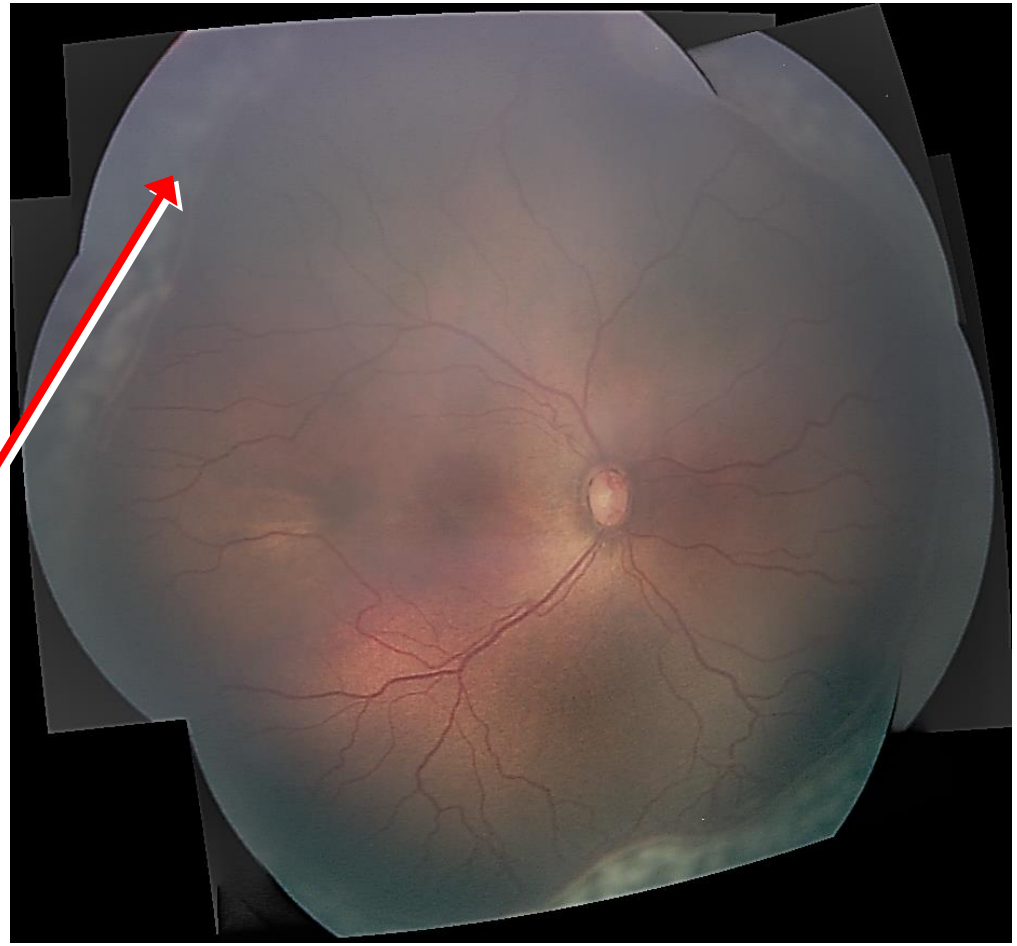
Blood vessel growth by month from optic nerve toward periphery

Retinal Images After Laser Therapy: Less Post-Laser Scaring Achieved in Older Babies

Laser Treatment at 30 weeks

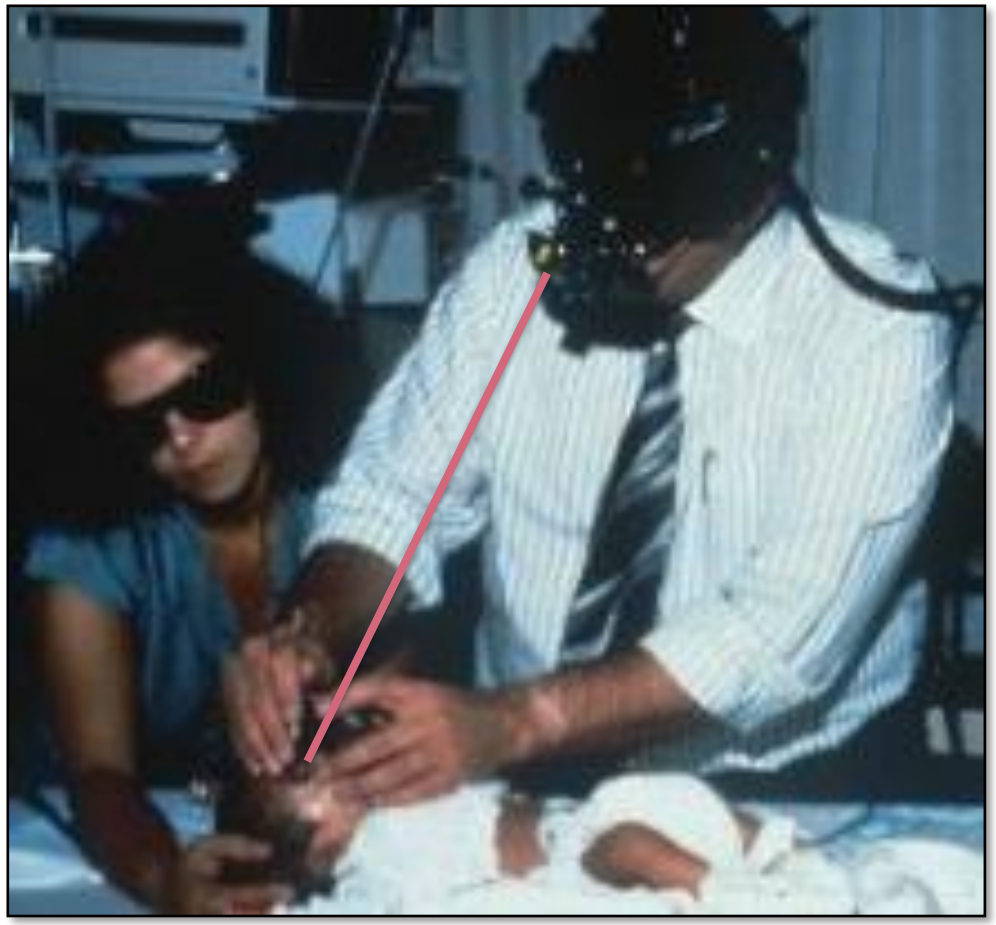
Laser Treatment at 38 weeks





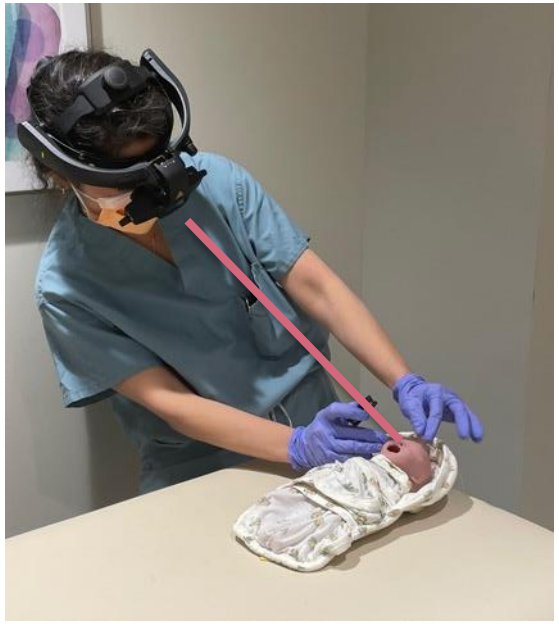
Laser scars

Laser Therapy Procedure is Extremely Challenging and Not Always Possible for Fragile Babies

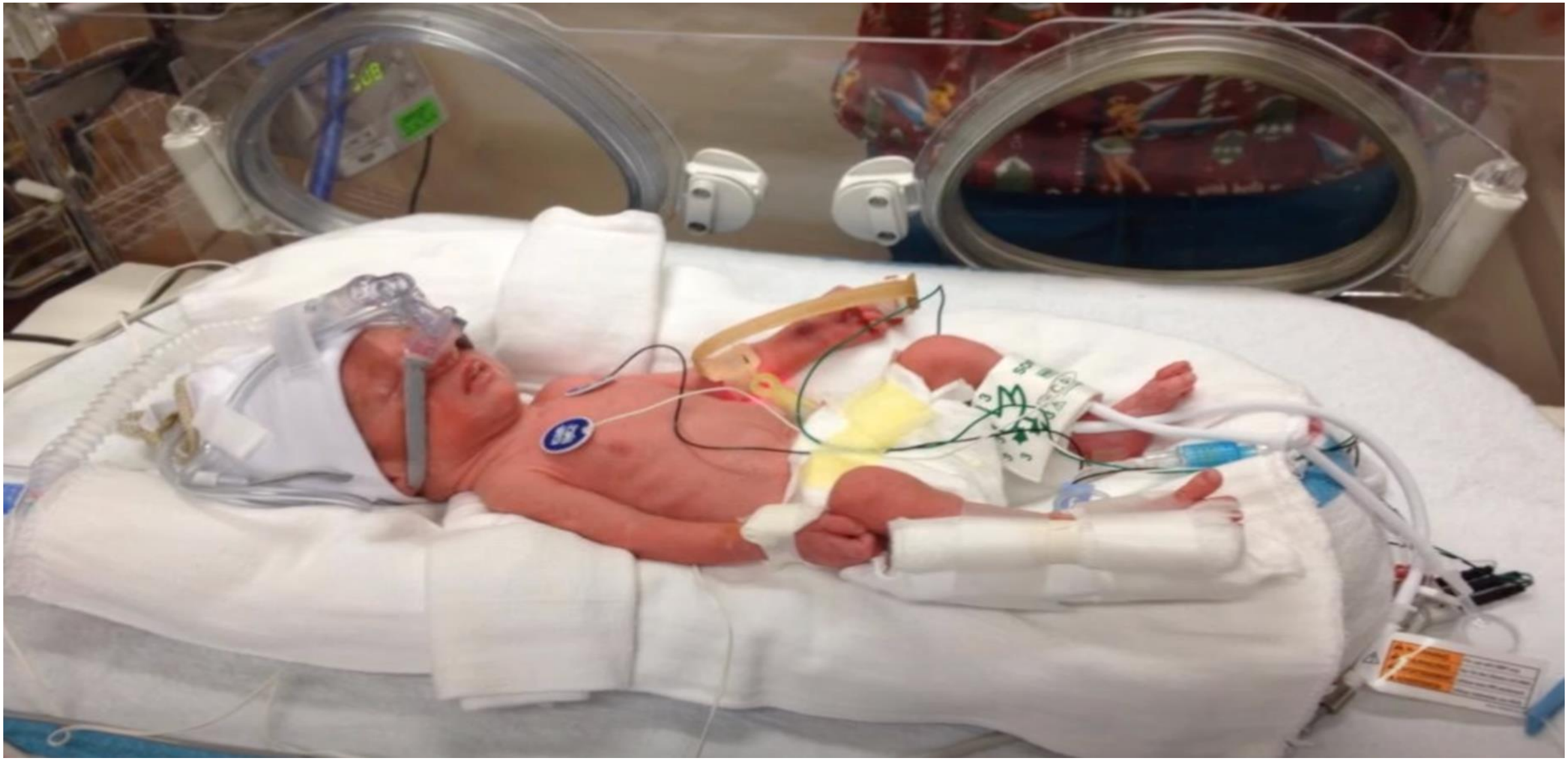


- Surgeon focuses laser on retina
- Small head movements to direct laser
- Maintain stability of lens
- Foot pedal fires laser
- Repeat process 1500 – 2000 times

Laser Therapy Procedure is Extremely Challenging and Not Always Possible for Fragile Babies



Laser Therapy Procedure is Extremely Challenging and Not Always Possible for Fragile Babies



Off-Label Use of Anti-VEGF

Promising Early Data Prompting Off-Label Anti-VEGF Use

- BEAT-ROP: bevacizumab (0.625 mg) vs laser therapy[1]
  - n=75 patients in both groups
  - Patients stratified by Zone I or II
  - Duration: ~20 weeks of follow-up
  - Significant treatment difference in Zone I, comparable in Zone II

- RAINBOW: ranibizumab vs laser therapy[2]
  - 0.1 mg (n=77), 0.2 mg (n=74), laser (n=74)
  - Duration: 24 weeks of follow-up
  - Ranibizumab (0.2 mg): 80% success rate

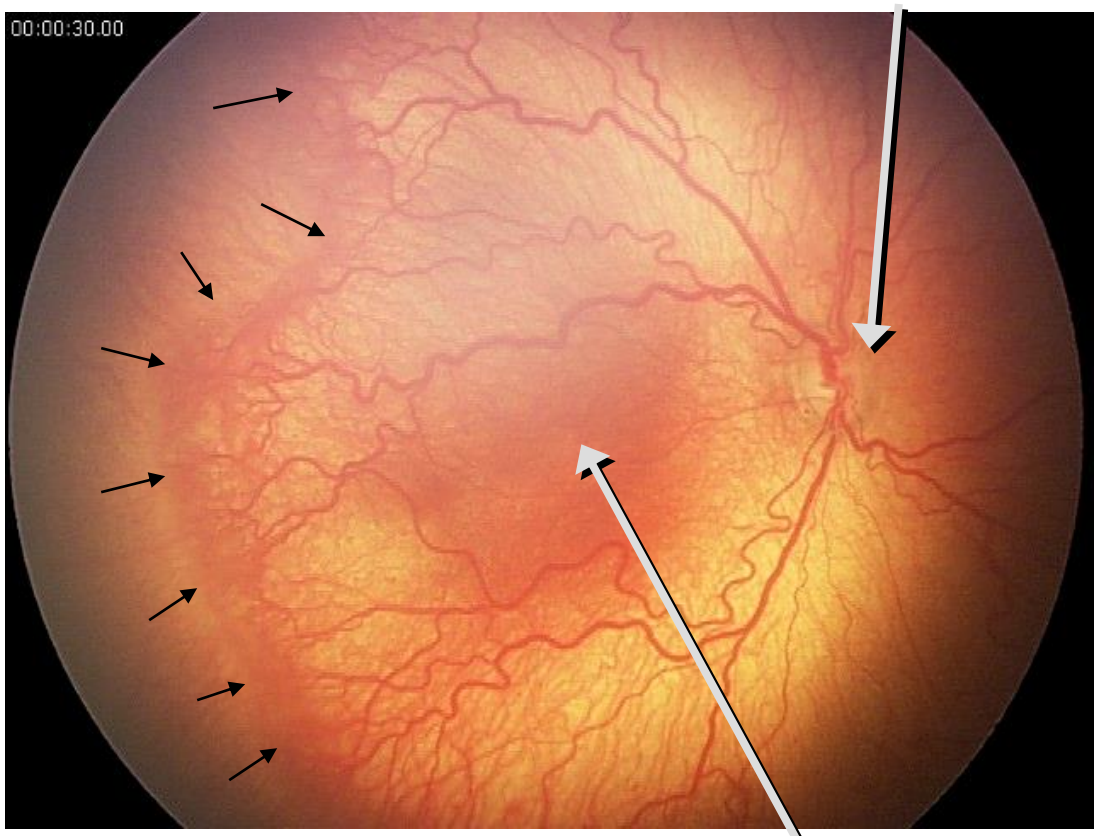
1. Mintz-Hittner, 2011; 2. Stahl, 2019

Advantages of Anti-VEGF for ROP

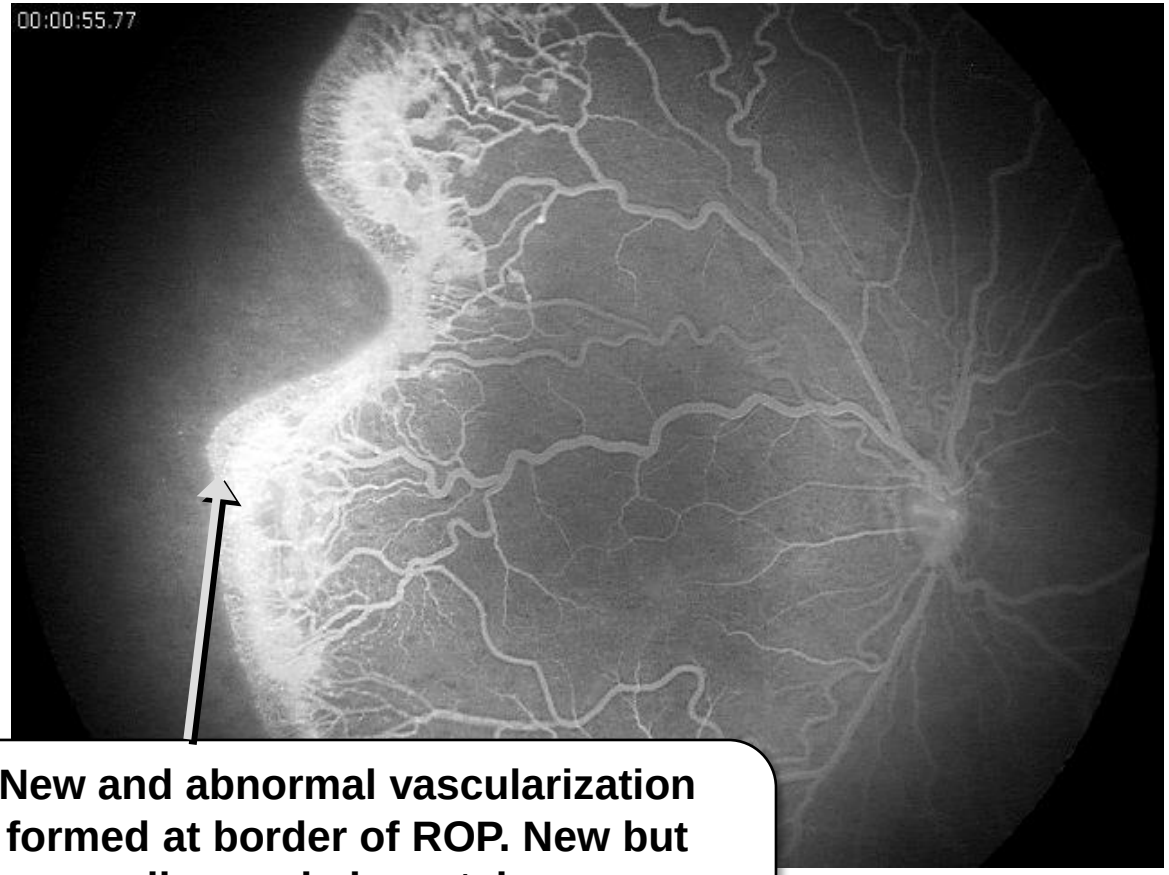
- Rapid neutralization of VEGF
- Rapid effect needed in AP-ROP
- Quick procedure, typically with only topical anesthesia
- Administered at bedside
- Administered even with poor pupil dilation
- Preservation of visual field
- Less high myopia
- Promotes growth of normal vasculature while shrinking growth of abnormal vessels

Patient with Significant ROP Requiring Treatment: Zone 1 Stage 3 ROP with Plus Disease

Optic nerve: retinal vessels grow from nerve head into retina



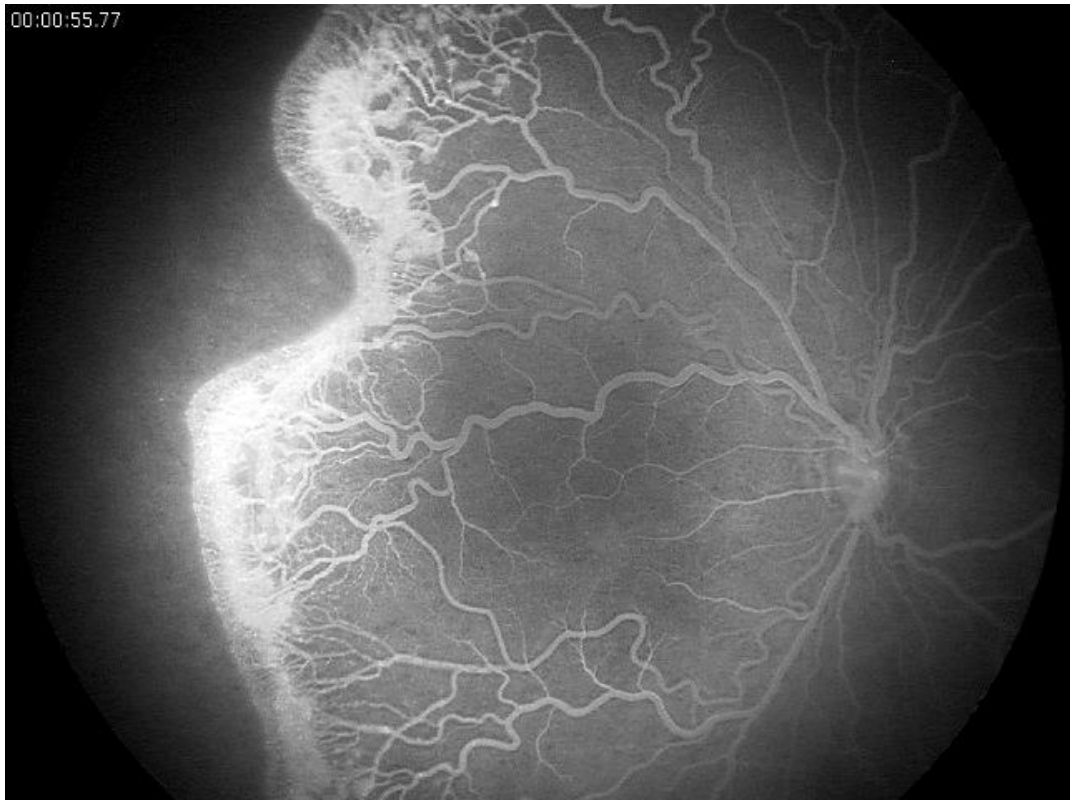
Fovea: Central vision corresponds to this anatomical structure



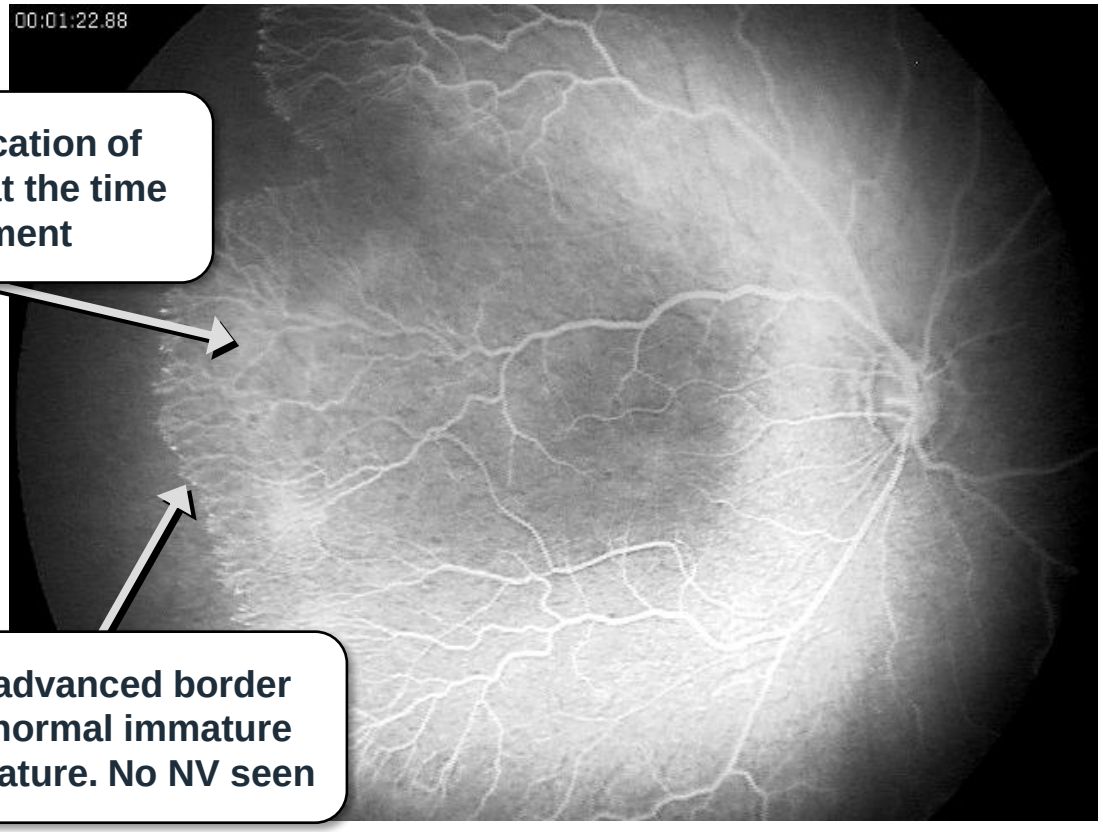
New and abnormal vascularization formed at border of ROP. New but small vessels have taken up fluoresceine dye as they light up as white, under dark background

Zone 1 Stage 3 ROP with Plus Disease Fluorescein Angiography

Before Treatment

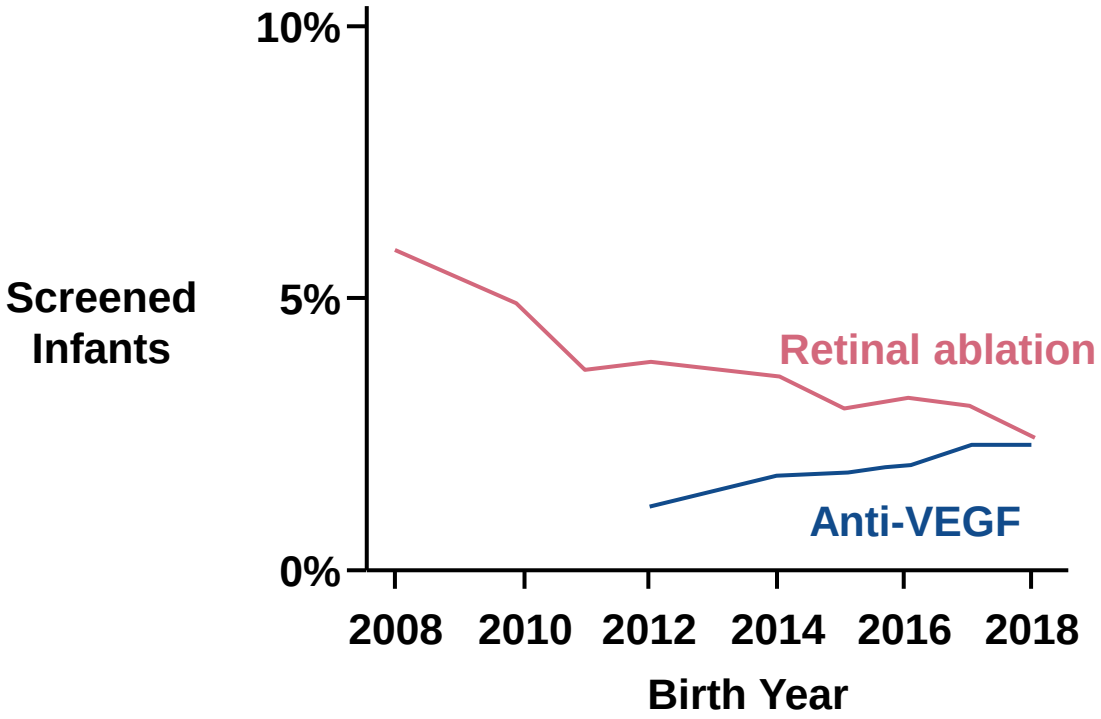


1 Month after Anti-VEGF Treatment



Off-Label Use of Anti-VEGF Therapy Increasing Due to Promising Efficacy and Safety Findings

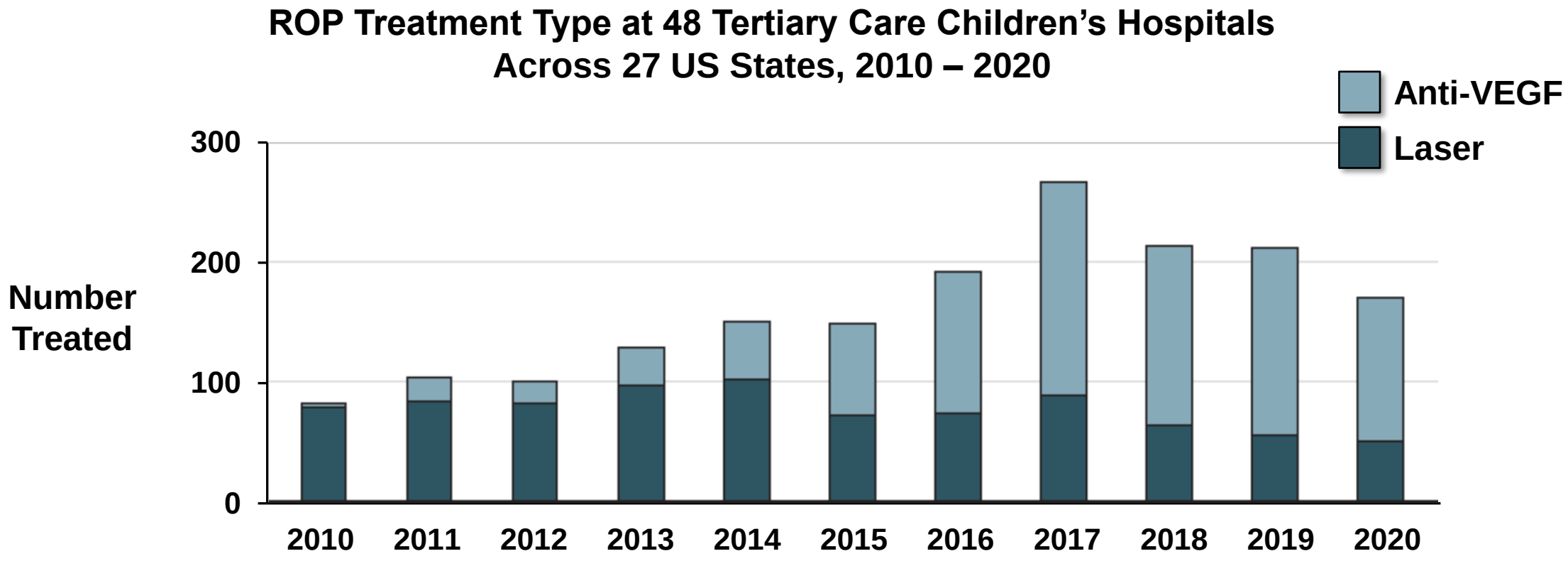
Trends in Retinopathy of Prematurity Screening and Treatment: 2008 – 2018



381,065 very low birth weight infants at 819 US NICU participating in Vermont Oxford Network

Prakalapakorn, 2019

Use of Anti-VEGF Treatment has Increased Among ROP-Treated Patients in United States



N at risk	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Anti-VEGF	3	20	19	31	49	77	118	178	149	158	121
Laser	81	85	83	99	103	74	76	90	66	56	51

Nitkin, *JAMA Ophthalmol.*, 2022 *infants receiving both laser and anti-VEGF excluded from study

Follow-up After Anti-VEGF Treatment

- Growth of normal vessels could be at a different pace after anti-VEGF treatment
- Baby needs to be followed to rule out reactivation or until their retinal vasculature is matured
- Subset of babies whose vessels do not mature will end up needing laser
- Appropriate follow-up should be performed after any ROP treatment, including anti-VEGFs
- Follow-up recommended in current treatment guidelines and in common practice of ROP community

Summary of Unmet Need

Pharmaceutical option comparable to laser needed

- Without associated safety and practice challenges

Approved labeling of an anti-VEGF treatment

- Provide consistent information for use
- Appropriate monitoring
- Improve access for patients

Advances needed for treatment of ROP

Efficacy

Robert Vitti, MD, MBA

VP, Clinical Sciences Ophthalmology
Regeneron Pharmaceuticals, Inc.

Clinical Development Program

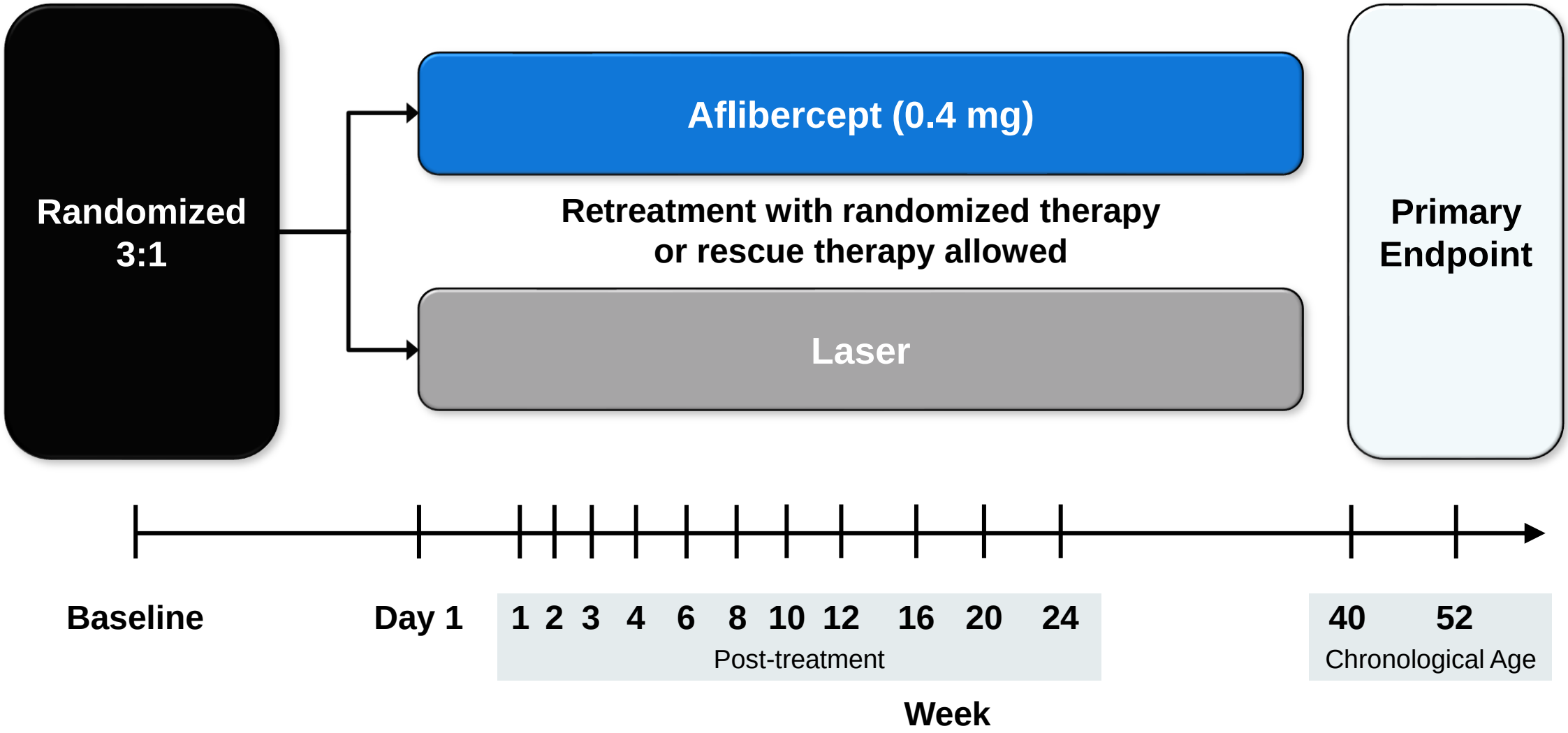
BUTTERFLEYE / BUTTERFLEYE NEXT
(Study 1920 / 2036)

- **Aflibercept vs laser therapy**
- **39 global sites: US, Europe, Asia, South America**
- **1° at 52 weeks chronological age**
- **Observational follow-up through 5 years of age**

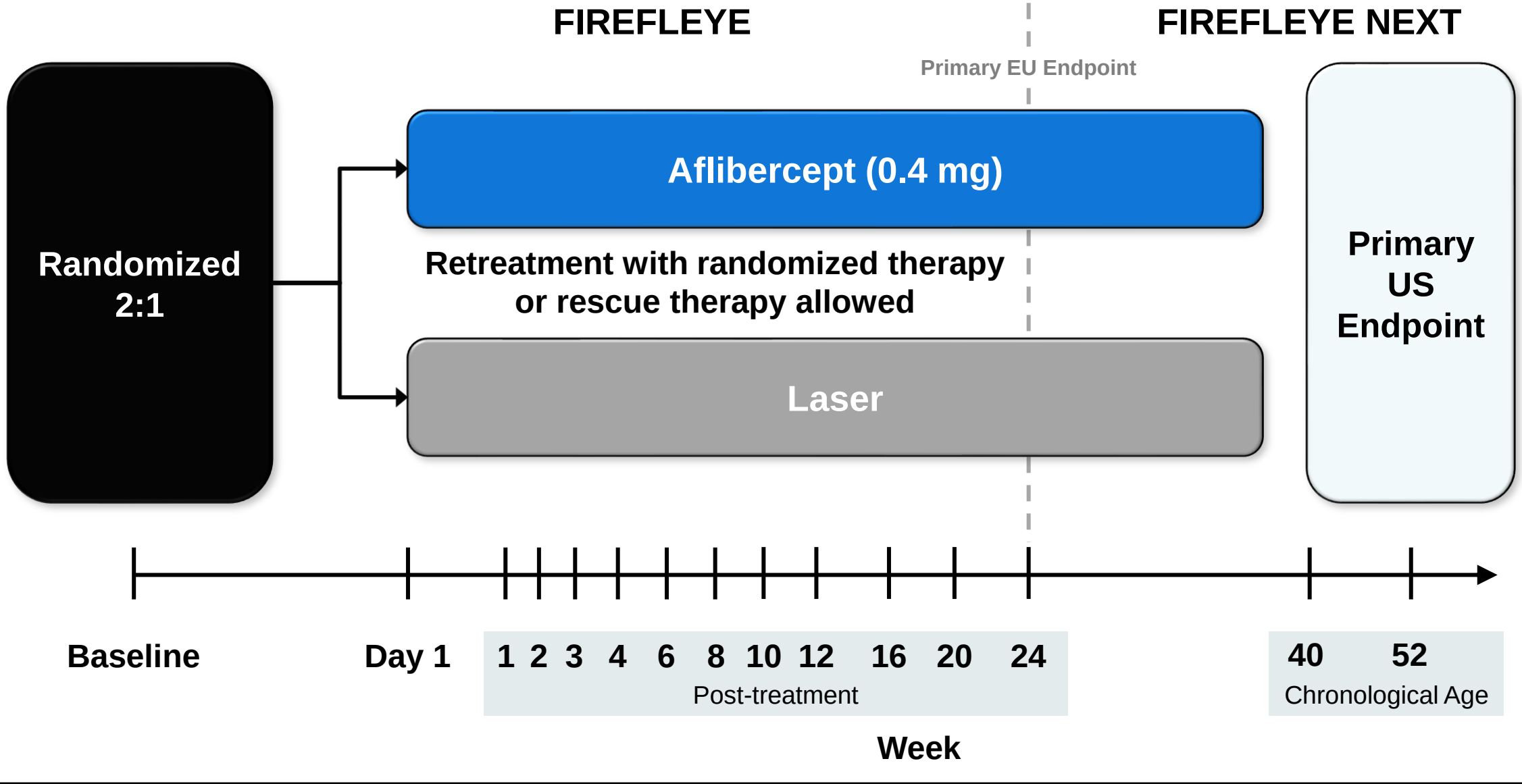
FIREFLEYE / FIREFLEYE NEXT
(Study 20090 / 20275)

- **Aflibercept vs laser therapy**
- **63 global sites: Europe, Asia, South America**
- **1° at 52 weeks chronological age**
- **Observational follow-up through 5 years of age**

Study Design – BUTTERFLEYE



Study Design – FIREFLEYE / FIREFLEYE NEXT



Similar Patient Population in Both Phase 3 Studies

- Gestational age at birth ≤ 32 weeks or birth weight ≤ 1500 g
- Weight at baseline (day of treatment) ≥ 800 g
- Treatment-naïve ROP classified according to ICROP* in at least one eye
  - Zone I Stage 1 plus, or 2 plus, or 3 non-plus or 3 plus, or
  - Zone II Stage 2 plus or 3 plus, or
  - Aggressive posterior-ROP (AP-ROP)
- If only one eye treated, second eye monitored for Type I ROP development, received same randomized treatment if needed

*ICROP = International Classification of ROP

Same Endpoints in Both Phase 3 Studies

- Primary endpoint
  - Proportion of patients with absence of both active ROP and unfavorable structural outcomes at 52 weeks CA
- Secondary endpoints
  - Proportion of patients requiring intervention with a second treatment modality to 52 weeks CA
  - Proportion of patients with recurrence of ROP to 52 weeks CA
- Relevant exploratory endpoints
  - Requirement for sedation or general anesthesia
  - Time required to perform treatment

CA = Chronological age

Basis of Non-Inferiority Design and Margin

- Orphan population strong consideration for sample size
  - N = 150 infants treated with aflibercept across two studies
  - FDA agreed adequate to assess safety and tolerability
- NI design pragmatic way to establish efficacy
  - Appropriate to compare two treatments with evidence of effectiveness
  - Anti-VEGF offers additional benefits
- RAINBOW informed NI margin of 5%
  - RAINBOW[1] (ranibizumab vs laser) showed laser success rate of 66% and anti-VEGF success rate of 80%
- 2-sided significance level of 0.049 (adjusted for IDMC assessments)

1. Stahl, 2019; NI = non-inferiority

Demographics Similar Across Studies

	BUTTERFLEYE		FIREFLEYE	
	Aflibercept N = 93	Laser N = 27	Aflibercept N = 75	Laser N = 38
Male	**44%**	**63%**	**55%**	**50%**
Race				
White	**28%**	**41%**	**73%**	**74%**
Asian	**47%**	**48%**	**23%**	**24%**
Black or African American	**7%**	**7%**	**3%**	**0%**
Other/Not reported*	**18%**	**4%**	**1%**	**3%**
Gestational age at birth (weeks), mean (SD)	**27.3** (2.8)	**27.1** (2.7)	**26.5** (2.1)	**26.0** (1.6)
Chronological age at baseline (weeks), mean (SD)	**9.8** (3.1)	**11.1** (4.3)	**10.4** (2.8)	**10.2** (2.3)
Birth weight (g), mean (SD)	**991.2** (407.0)	**934.1** (406.6)	**881.1** (305.6)	**824.6** (230.8)
Baseline weight (g), mean (SD)	**2058.3** (548.3)	**2248.1** (725.0)	**2026.7** (678.9)	**1850.9** (546.1)

***Includes self-reported multiracial in BUTTERFLEYE**

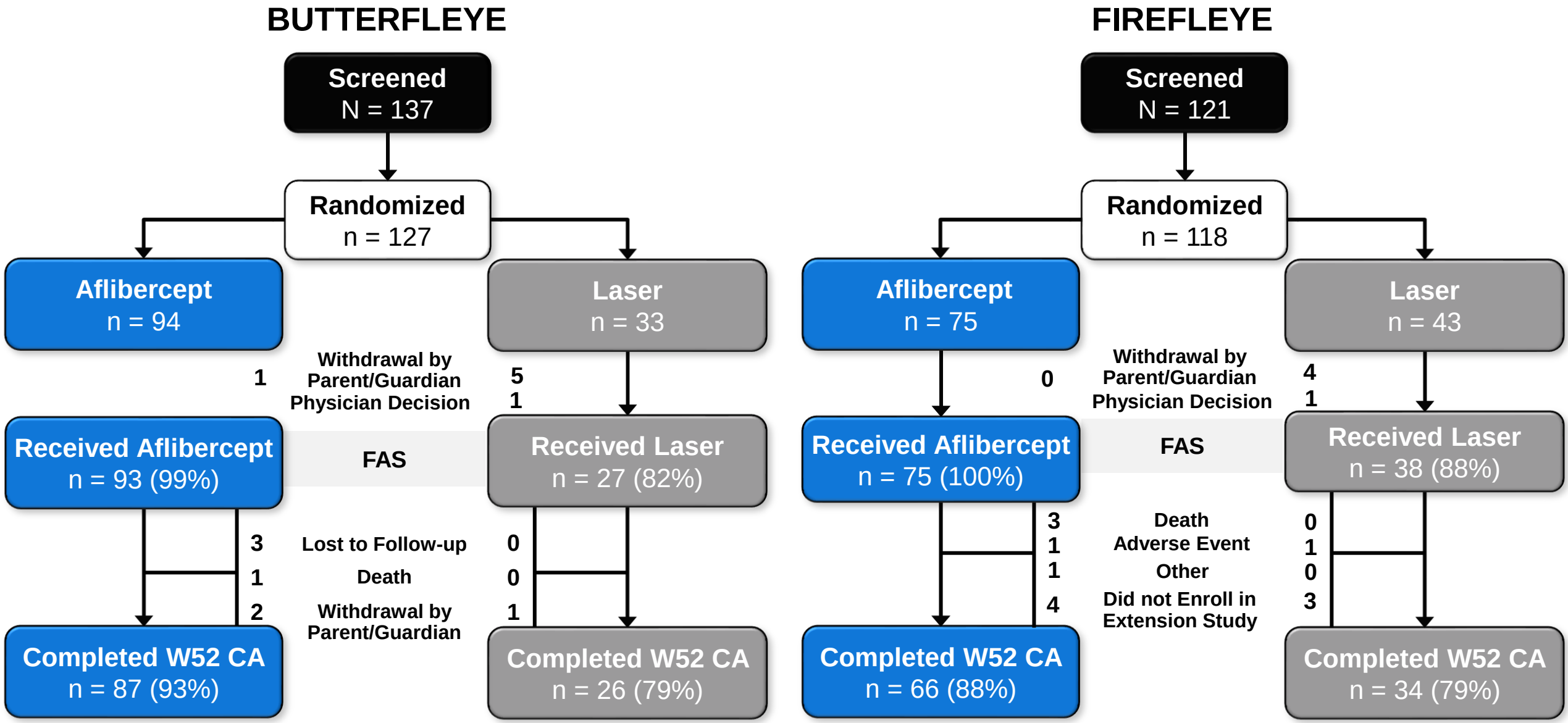
Disease Characteristics Similar Across Studies

	BUTTERFLEYE		FIREFLEYE	
	Aflibercept N = 93	Laser N = 27	Aflibercept N = 75	Laser N = 38
Laterality of eyes treated				
Unilateral	**8%**	**15%**	**5%**	**11%**
Bilateral	**92%**	**85%**	**95%**	**89%**
Number of eyes treated	**179**	**50**	**146**	**72**
ROP Zone, by eye				
Zone I	**26%**	**26%**	**35%**	**29%**
AP-ROP	**11%**	**6%**	**16%**	**11%**
Zone II	**74%**	**74%**	**65%**	**71%**
AP-ROP	**4%**	**6%**	**3%**	**3%**

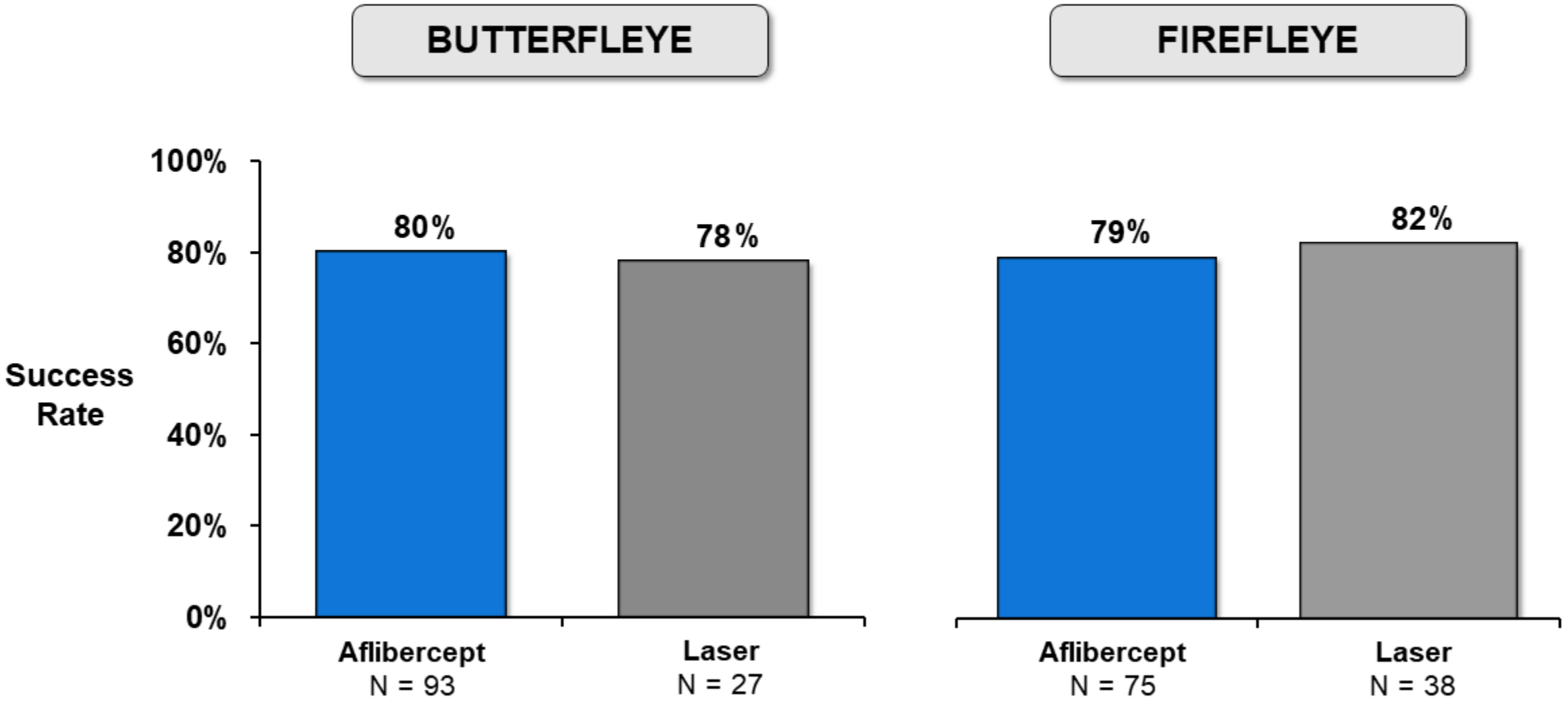
Significant Medical History at Baseline Associated with Prematurity

	BUTTERFLEYE		FIREFLEYE	
	Aflibercept N = 93	Laser N = 27	Aflibercept N = 75	Laser N = 38
Sepsis	55%	56%	43%	40%
Bronchopulmonary dysplasia	49%	59%	65%	76%
Respiratory distress / Neonatal respiratory distress syndrome	49%	59%	67%	68%
Infantile apnea	48%	48%	35%	29%
Patent ductus arteriosus	43%	22%	40%	47%
Neonatal anemia	37%	41%	60%	74%
Necrotizing enterocolitis	17%	11%	20%	13%

Disposition: More Patients Completed Aflibercept Treatment at 52 Weeks vs Laser Therapy

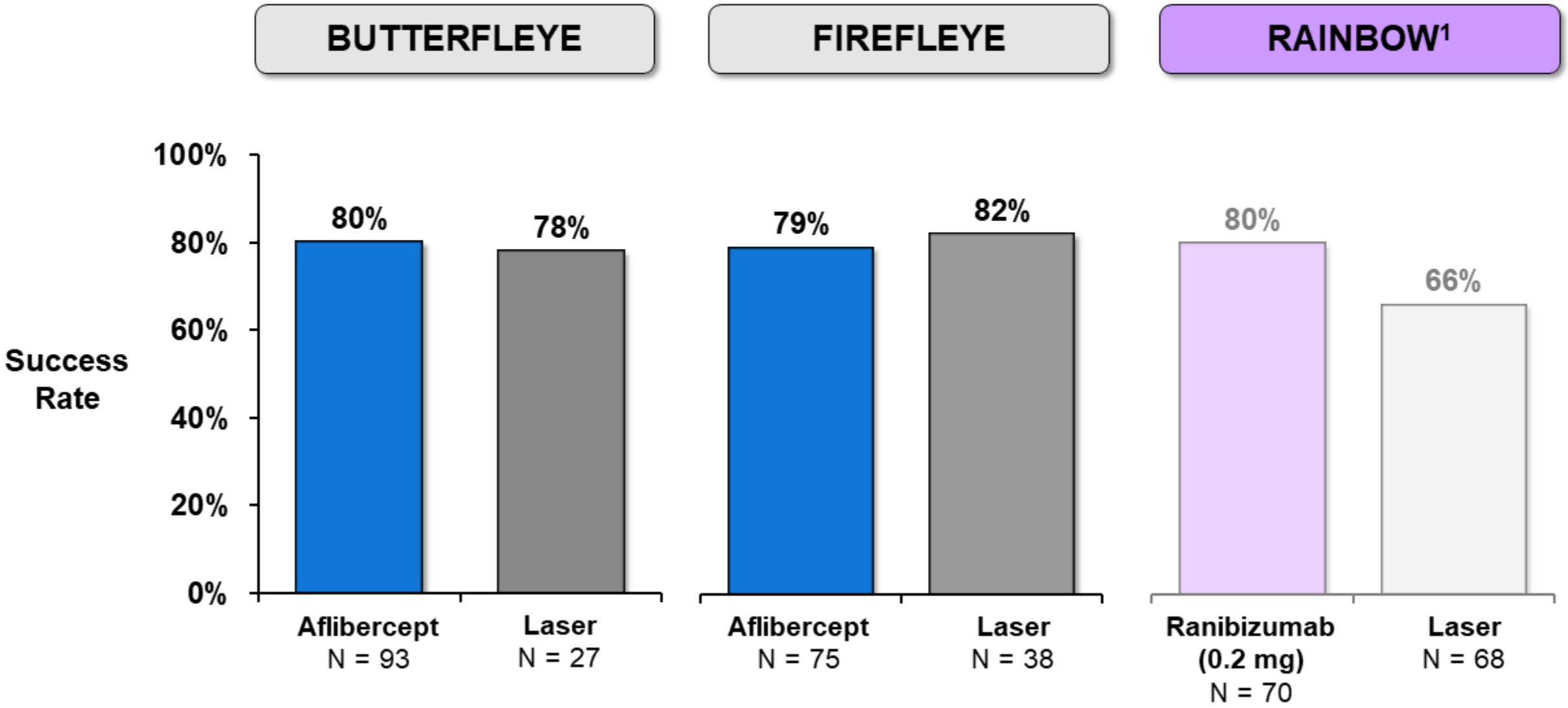


High Success Rate Across Studies and Treatments (FAS)



Primary endpoint: proportion of patients with absence of both active ROP and unfavorable structural outcomes at 52 weeks CA

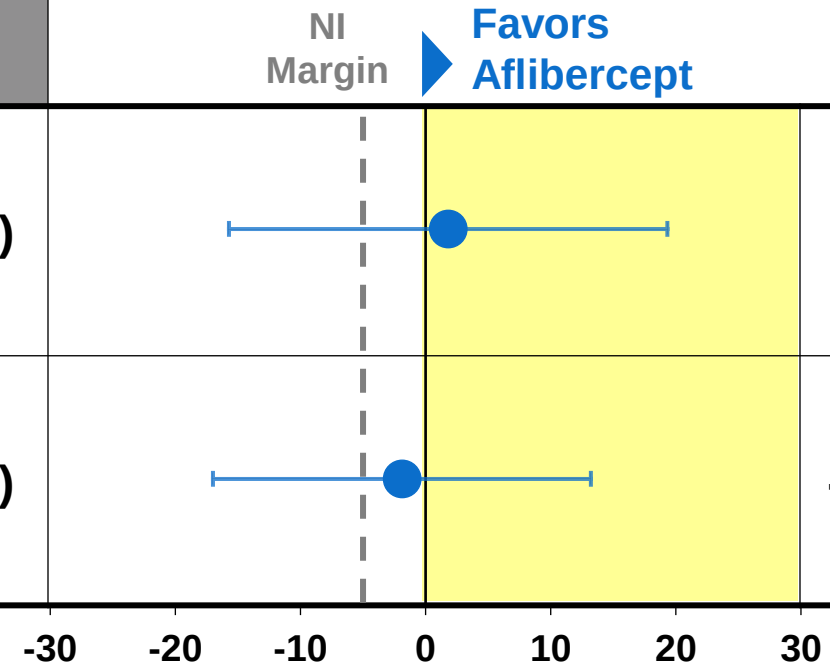
Anti-VEGFs Performed Similarly Across Studies, Laser Therapy Point Estimates Differed from RAINBOW



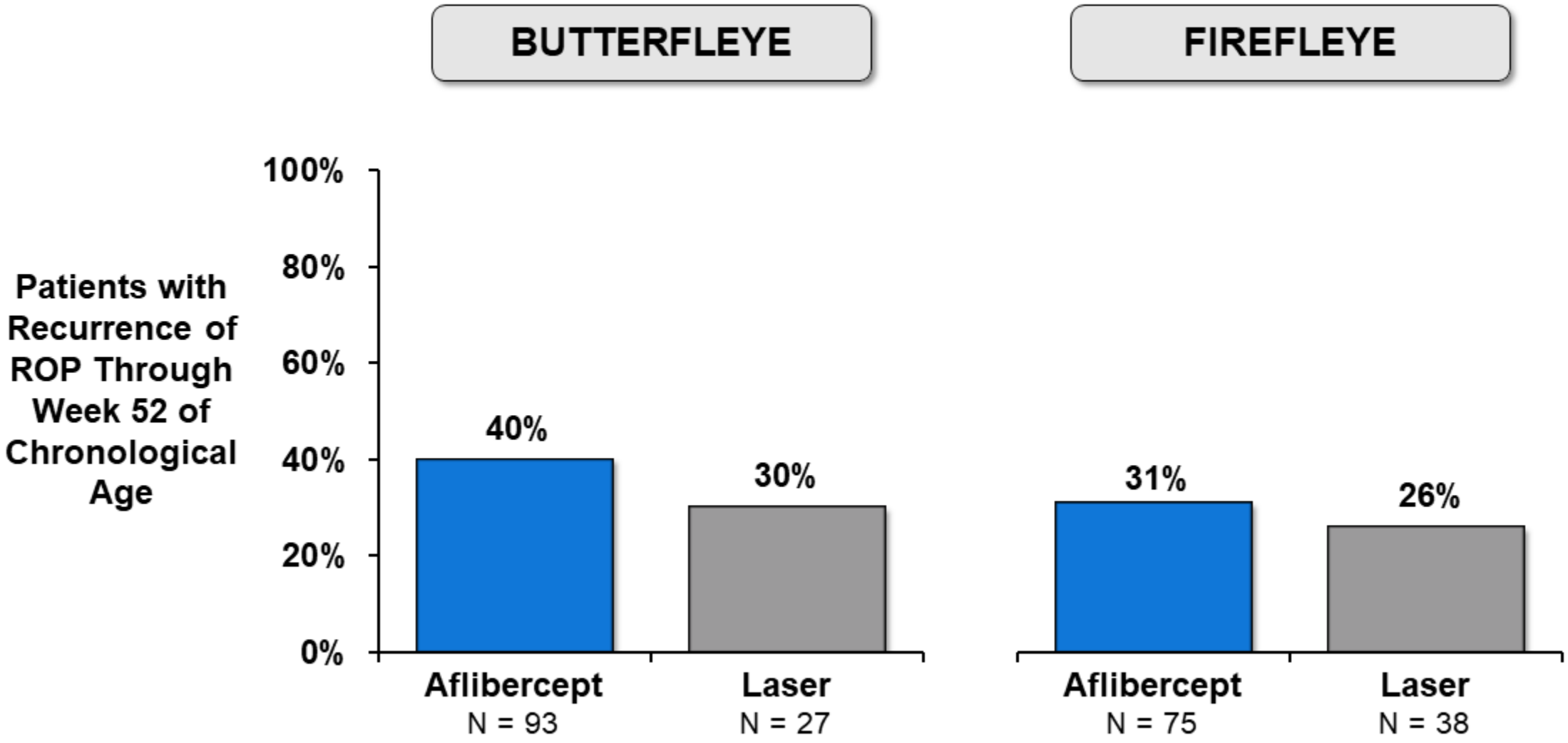
1. Stahl, 2019

Primary Efficacy Results Clinically Important Across Studies

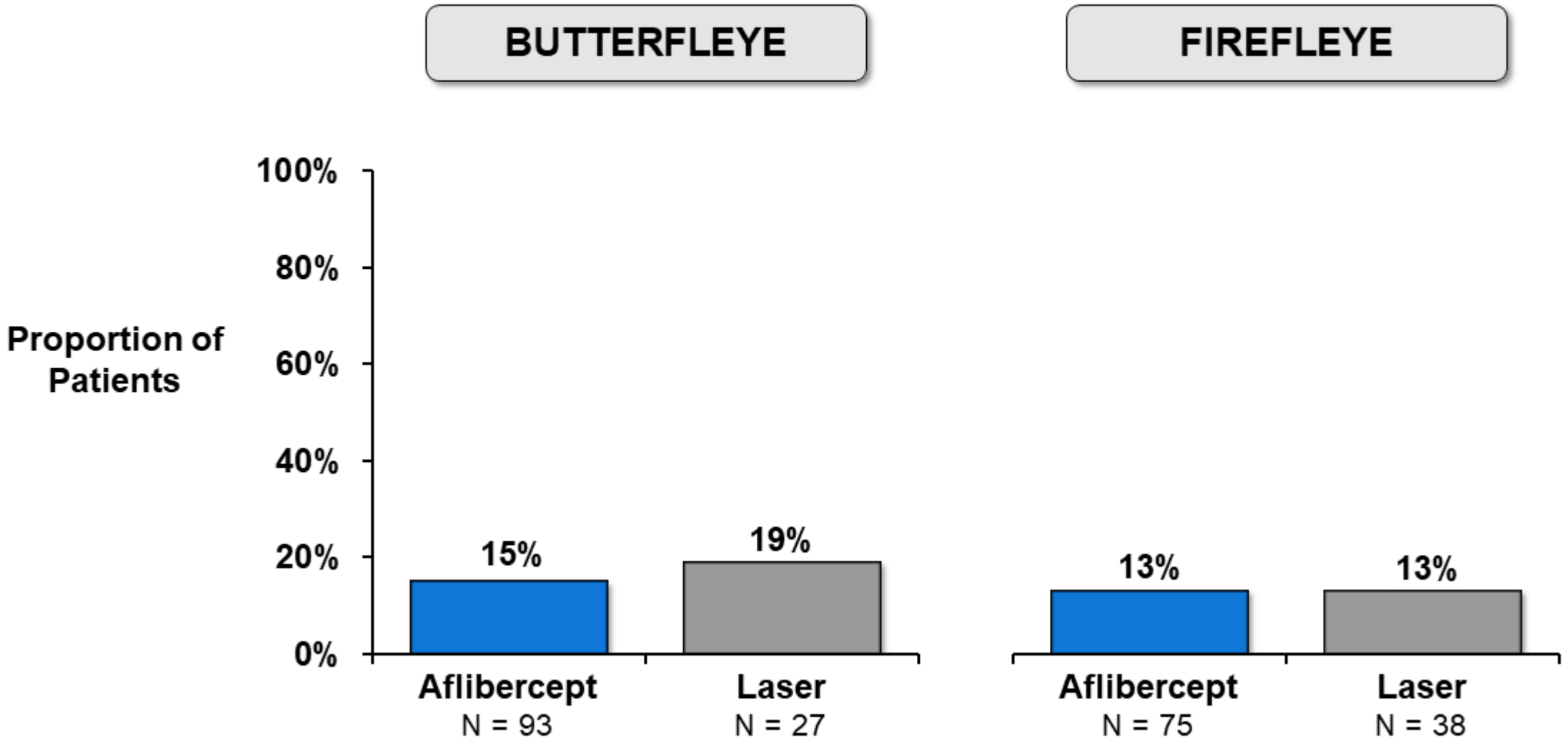
	Aflibercept	Laser	Adjusted Difference % (95.1% CI)
BUTTERFLEYE (FAS)	74/93 **(80%)**	21/27 **(78%)**	**1.81%** (-15.71, 19.33)
FIREFLEYE (FAS)	59/75 **(79%)**	31/38 **(82%)**	**-1.88%** (-16.99, 13.23)



Secondary Endpoint – Recurrence of ROP Within 52 Weeks (FAS)



Secondary Endpoint – Requirement of Second Treatment Modality* Within 52 Weeks (FAS)

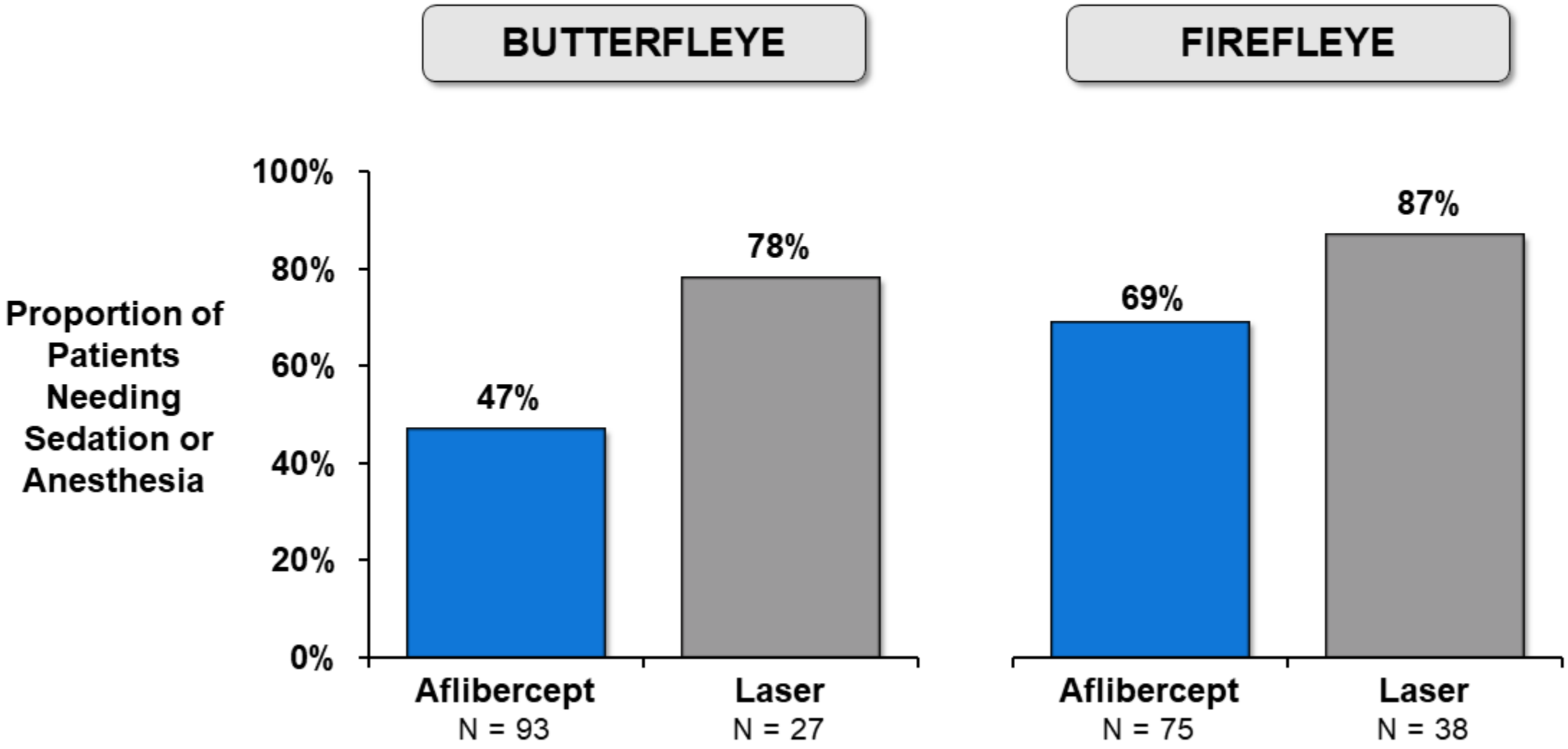


*Any treatment other than randomized assignment

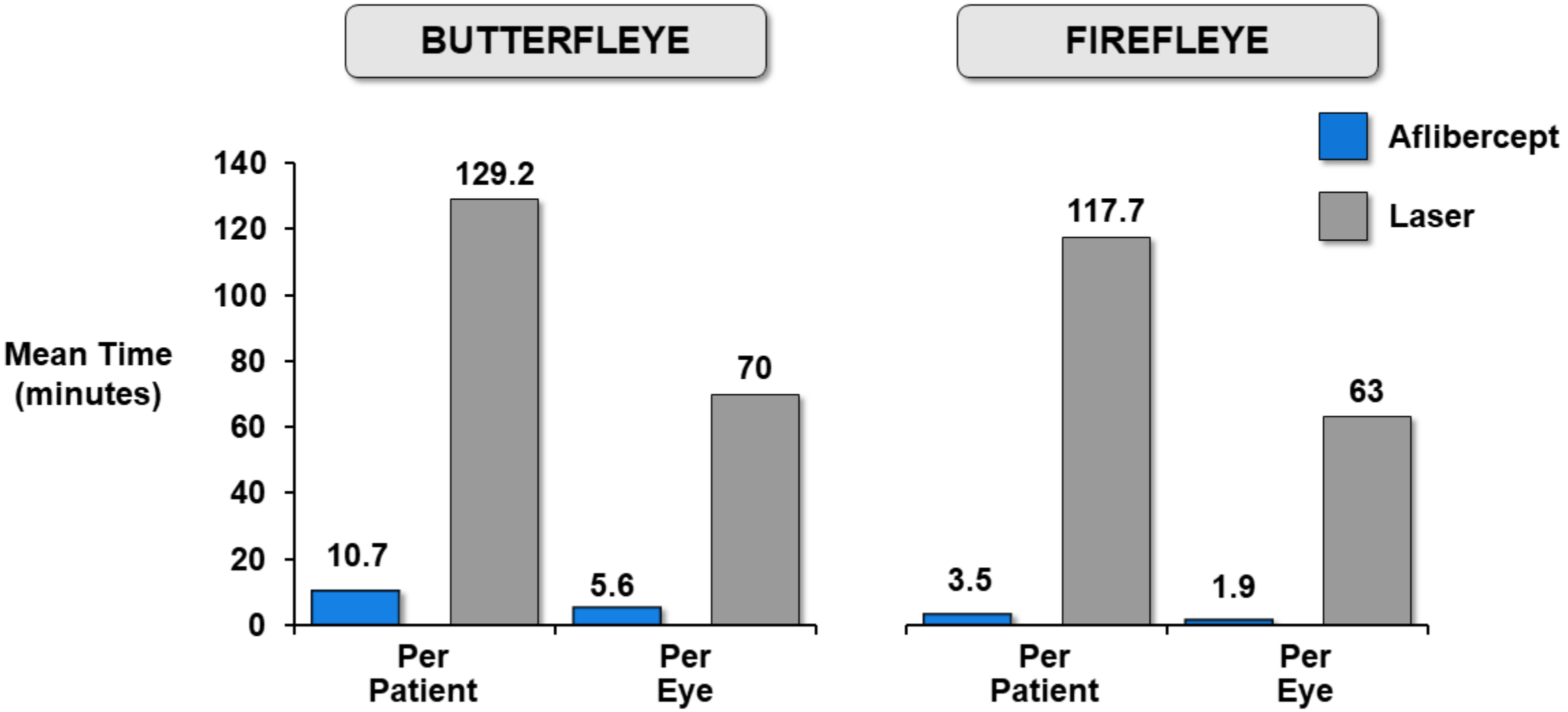
Few Aflibercept Patients Needed Laser Rescue Treatment – Most had Favorable Outcome

	BUTTERFLEYE	FIREFLEYE
	Aflibercept N = 93	Aflibercept N = 75
Patients not requiring laser rescue	**80 (86%)**	**70 (93%)**
Patients needing laser rescue	**13 (14%)**	**5 (7%)**
Met primary endpoint criteria at week 52 CA	**8**	**3**
Retinal detachment	**5**	**1**
Patients without data at week 52 CA	**0**	**1**

Exploratory Endpoints – Requirement for Sedation and General Anesthesia



Exploratory Endpoints – Time Required to Perform Treatment



Summary of Efficacy

- BUTTERFLEYE and FIREFLEYE studies demonstrate benefit of aflibercept 0.4 mg
- ~80% of infants in aflibercept groups met primary endpoint
  - Numerically similar to laser therapy
  - Point estimate demonstrated meaningful efficacy
- Secondary and exploratory endpoints important efficacy considerations
  - Aflibercept requires less time under sedation / anesthesia and easier to administer than laser therapy

Safety

Suzanne Green, MBChB

Therapeutic Area Head, Global Patient Safety

Regeneron Pharmaceuticals, Inc.

Summary of Exposure
Aflibercept Injections and Laser Administrations

	BUTTERFLEYE		FIREFLEYE	
	Aflibercept N = 93	**Laser** N = 27	**Aflibercept** N = 75	**Laser** N = 38
Injections/Administrations Per Patient				
1	**7.5%**	**0**	**5.3%**	**0**
2	**72.0%**	**14.8%**	**73.3%**	**7.9%**
3	**8.6%**	**0**	**8.0%**	**2.6%**
4+	**11.8%**	**0**	**13.3%**	**0**
Injections/Administrations Per Eye				
1	**83.2%**	**16.0%**	**82.2%**	**9.7%**
2	**14.0%**	**0**	**17.8%**	**1.4%**
3	**2.8%**	**0**	**0**	**0**

Comparable Safety Profile Across Studies

	BUTTERFLEYE		FIREFLEYE	
	Aflibercept N = 93	**Laser** N = 27	**Aflibercept** N = 75	**Laser** N = 38
Any AE	**74%**	**85%**	**95%**	**92%**
Any TEAE	**56%**	**59%**	**76%**	**76%**
Ocular	18%	26%	39%	37%
Non-Ocular	47%	52%	53%	66%
TEAE Leading to Discontinuation	**0**	**0**	**4%**	**3%**
SAE	**34%**	**44%**	**33%**	**45%**
TE SAE	**19%**	**19%**	**12%**	**26%**
Ocular	7%	11%	8%	8%
Non-Ocular	13%	7%	7%	18%
Death*	**1 (1%)**	**0**	**3 (4%)***	**0**

TEAE = treatment-emergent adverse events occurring in 30 days of last treatment; *2 deaths within 30 days of last treatment

Ocular TEAEs in Study Eye Balanced (≥ 5% of Patients in Either Study)

Preferred term	BUTTERFLEYE		FIREFLEYE	
	Aflibercept N = 93	Laser N = 27	Aflibercept N = 75	Laser N = 38
Any Ocular TEAE	**18%**	**26%**	**39%**	**37%**
Retinal detachment	6%	7%	5%	5%
Conjunctival hemorrhage	5%	0	5%	0
Retinal hemorrhage	3%	4%	7%	13%
Conjunctivitis	0	0	4%	11%
Eyelid edema	0	4%	3%	8%

Ocular Treatment Emergent SAEs (≥ 2 Patients in Either Study)

Preferred term, n (%)	BUTTERFLEYE		FIREFLEYE	
	Aflibercept N = 93	Laser N = 27	Aflibercept N = 75	Laser N = 38
Any Ocular TE SAE	**6 (6%)**	**3 (11%)**	**6 (8%)**	**3 (8%)**
Retinal detachment	**6 (6%)**	**2 (7%)**	**3 (4%)**	**2 (5%)**
Vitreous hemorrhage	**2 (2%)**	**0**	**1 (1%)**	**0**
Retinal hemorrhage	**0**	**0**	**2 (3%)**	**0**

Non-Ocular TEAEs By Preferred Term in ≥ 5% of Patients

Preferred term	BUTTERFLEYE		FIREFLEYE	
	Aflibercept N = 93	Laser N = 27	Aflibercept N = 75	Laser N = 38
Any Non-Ocular TEAE	**47%**	**52%**	**53%**	**66%**
Bronchopulmonary dysplasia	7%	0	3%	0
Inguinal hernia	7%	7%	3%	3%
Umbilical hernia	5%	0	3%	8%
Anemia / anemia neonatal	7%	0	1%	11%
Gastroesophageal reflux disease	3%	7%	1%	3%
Apnea / infantile apnea	2%	15%	3%	13%
Bacterial disease carrier	1%	4%	0	5%
Constipation	1%	11%	0	0
Oxygen saturation decreased	1%	7%	4%	0
Hemorrhage subcutaneous	0	0	0	8%

Non-Ocular TE SAEs in ≥ 2 Patients By Preferred Term

Preferred term	BUTTERFLEYE		FIREFLEYE	
	Aflibercept N = 93	**Laser** N = 27	**Aflibercept** N = 75	**Laser** N = 38
Any Non-Ocular TE SAE	**13%**	**7%**	**7%**	**18%**
Apnea / infantile apnea	2%	7%	0	8%
Inguinal hernia	2%	0	0	0
Pneumonia	1%	0	1%	0
Bronchiolitis	0	0	3%	3%

Deaths Not Considered to be Related to Treatment

Study	Sex / Gest. Age (weeks)	Birth Weight (grams)	Key Medical History / *AE Leading to Death*	AE Onset (Study day)	Death (Study day)
BUTTERFLEYE	Female 24w 5d	620	Necrotizing enterocolitis, bowel obstruction, chronic lung disease, post-surgery for division of ductus arteriosus, adrenal cortical insufficiency / *Multiple organ dysfunction syndrome*	29	59
FIREFLEYE	Female 23w 6d	445	Bronchopulmonary dysplasia (ongoing at study entry), anemia of prematurity, hypoglycemia and osteoporosis / *Bronchopulmonary dysplasia and pneumothorax*	142	144
	Female 24w 1d	640	Neonatal sepsis bronchopulmonary dysplasia interstitial pulmonary emphysema, anemia / *Bronchiolitis*	53	57
	Male 26w	790	Bronchopulmonary dysplasia, respiratory failure, apnea, brain damage, atrial septal defect, severe anemia / *Bronchopulmonary dysplasia*	61	61

Note: Mean birth weight BUTTERFLEYE 990 grams, FIREFLEYE 880 grams
Mean gestational age BUTTERFLEYE 27.3 weeks, FIREFLEYE 26.5 weeks

Aflibercept: Favorable Safety Profile

- Safety database includes data in 325 eyes / 168 infants
- Majority of observed events mild and comparable to laser
- TE SAEs more common in laser group
  - Related to complications of extreme prematurity and low birth weight
- Deaths occurred in patients with complicated medical histories
- No additional deaths or TE SAEs reported in safety update report

Clinical Perspective

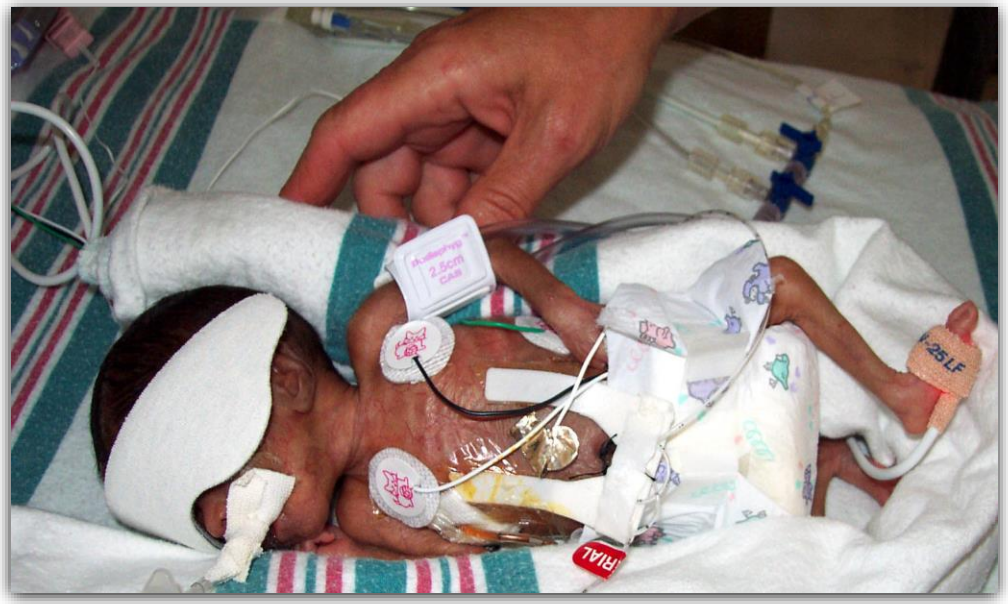
Steven Donn, MD, FAAP, FAARC

Professor Emeritus of Pediatrics
Division of Neonatal-Perinatal Medicine

C.S. Mott Children's Hospital
University of Michigan Medical School

Approved Pharmacologic Agent Needed for Babies with ROP

- Laser therapy effective, but practical and clinical limitations
  - Needs specialized equipment and skill; labor intensive
  - Not accessible to all in need, vulnerable babies sometimes need to move locations for treatment
  - Requires long durations of sedation / anesthesia
  - Sustained side effects



Anti-VEGFs Currently Used Off-label to Treat ROP

- Anti-VEGF off-label use noted in treatment guidelines due to promising efficacy and safety[1]
- Aflibercept data build on already established literature supporting anti-VEGF use in ROP

1. Fierson, 2018

Clinical Considerations Support Proposed Labeling

- Critically ill babies with a rare, serious, vision impairing disease
- Anti-VEGFs already used as primary initial treatment off-label
- Aflibercept benefit
  - Consistently high success rates through 52 weeks
  - Ease of use, reduced time under sedation
  - Earlier treatment of vascular proliferation
  - Administered at bedside
  - Reduces potential for unfavorable side effects (loss of peripheral vision, high myopia)
  - Postponing laser even by one month is a major advantage
- Aflibercept demonstrated expected safety comparable to laser with potential for less long-term complications

Aflibercept: A Promising Treatment for ROP

- Prospective data outcomes align with goal of treatment – to stop ROP and restore the retina
- Acceptable safety profile, aligns with expectations of an anti-VEGF treatment
- Aflibercept labeling for ROP
  - Allows proper communication of use
  - Reduces variability in treatment
- Proactive education for physicians on appropriate patient follow-up
- Important step towards meeting unmet medical need of preterm babies

EYLEA® (aflibercept) for the Treatment of Retinopathy of Prematurity (ROP)

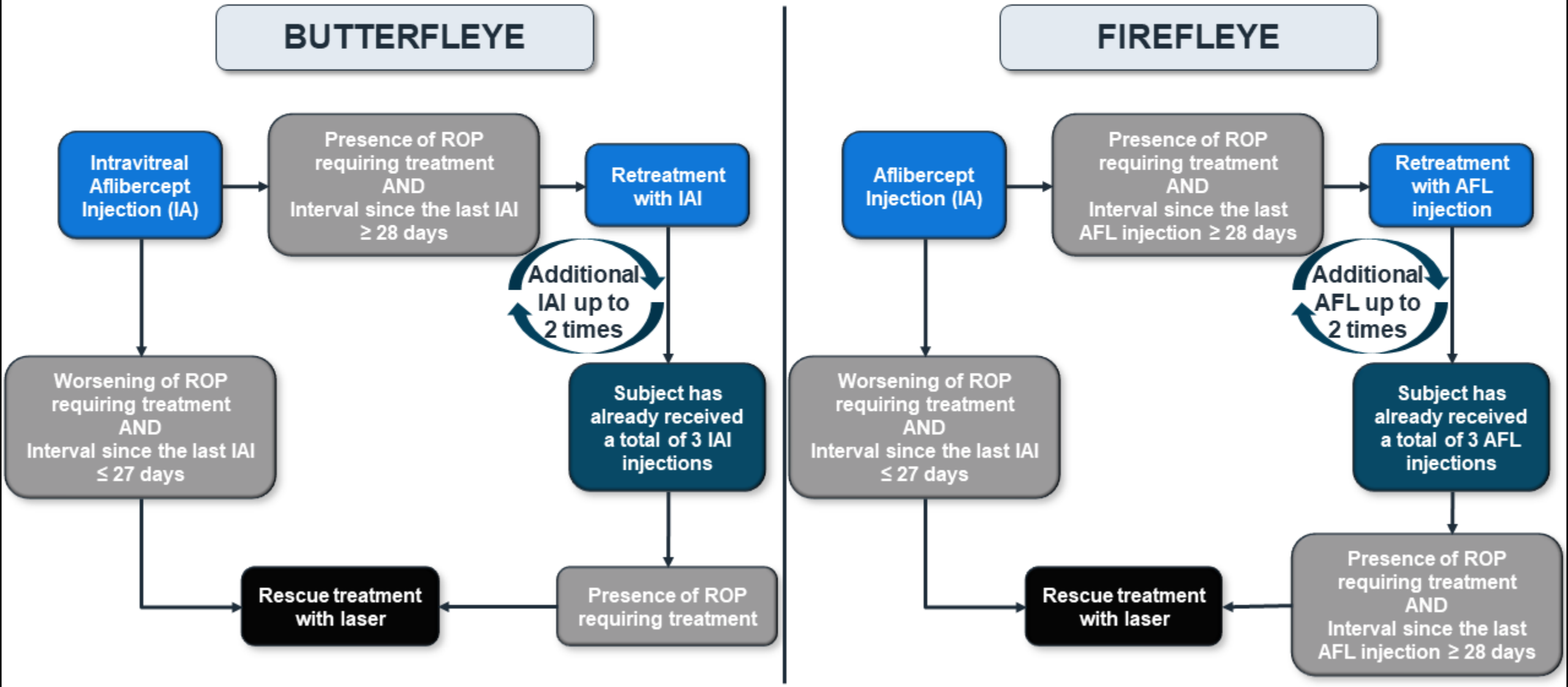
January 09, 2023

Dermatologic and Ophthalmic Drugs Advisory Committee

Regeneron Pharmaceuticals, Inc.

Q&A Backup Slides Shown

Aflibercept Treatment, Retreatment, and Rescue Treatment



Proportion of Patients and Eyes with Complete Vascularization of the Retina at Week 52 CA (without rescue)

By Patient*	BUTTERFLEYE Aflibercept N = 73	FIREFLEYE Aflibercept N = 59
Patients with completion of vascularization of peripheral retina within 1 disc diameter of Ora Serrata	**68%**	**75%**

By Eye*	BUTTERFLEYE Aflibercept N = 141	FIREFLEYE Aflibercept N = 114
Eyes with completion of vascularization of peripheral retina within 1 disc diameter of Ora Serrata	**67%**	**74%**

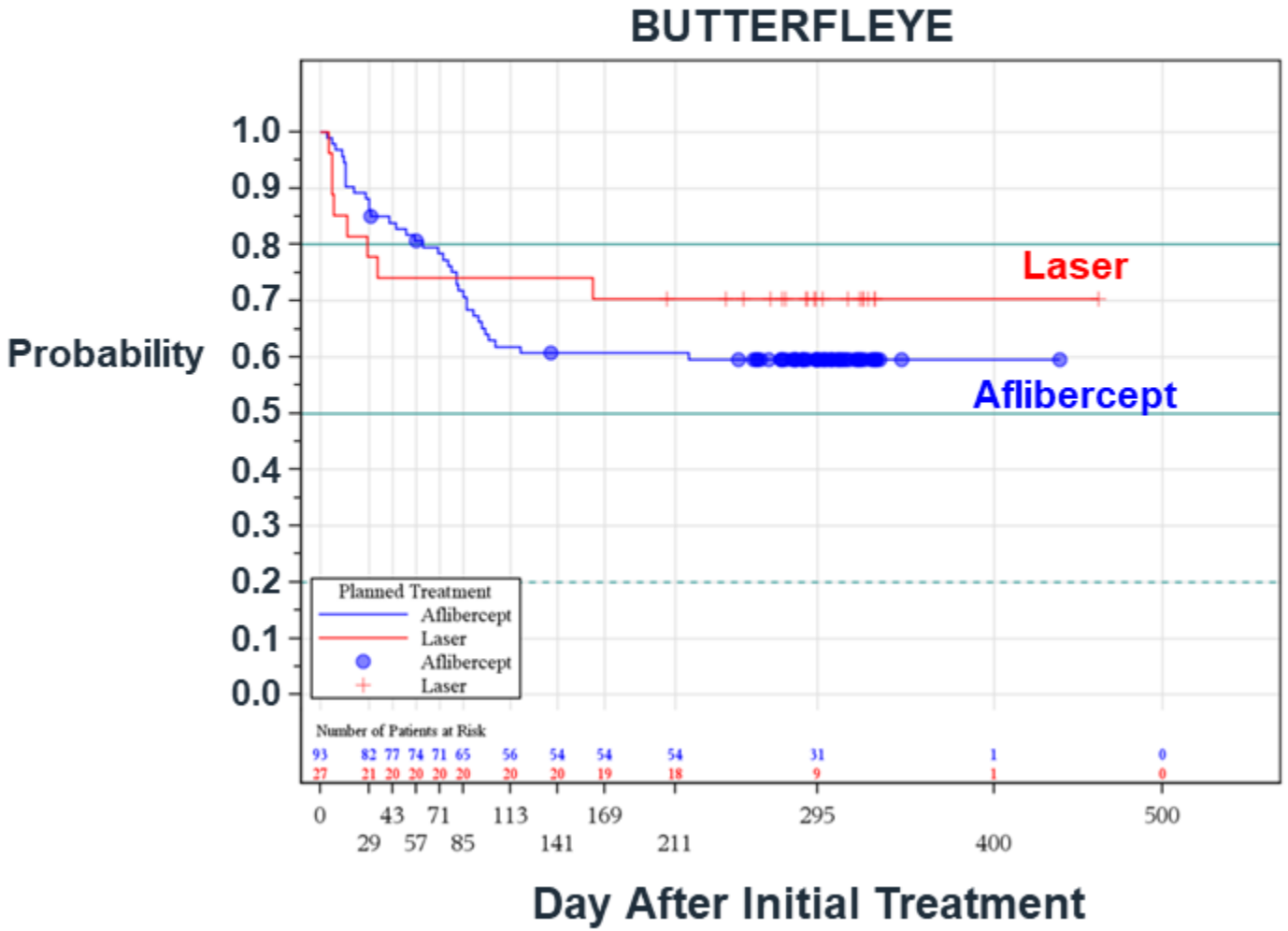
*Patients completing Week 52 CA visit and **not** receiving a second treatment modality

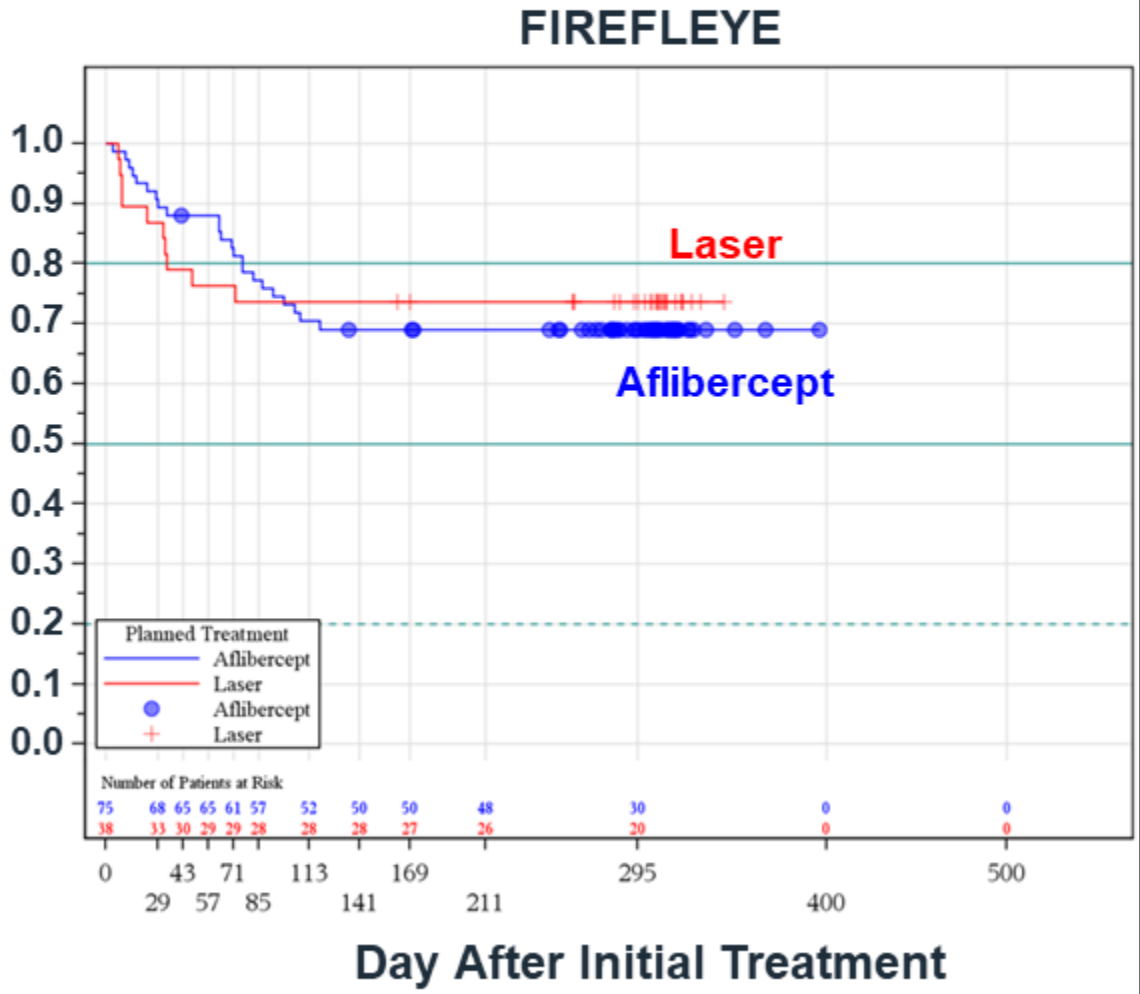
RAINBOW – 2 Year Follow-Up
Rates of Complete Vascularization

- Among the 298 eyes treated with ranibizumab only, full vascularization was recorded in 177 (59%) infants
  - Ranibizumab 0.2 mg 62% (91/146) of eyes
  - Ranibizumab 0.1 mg 57% (86/152) of eyes

Marlowe, 2021.

Time to First Recurrence of ROP
Most Recurrence Occurs Within 16 Weeks of Initial Treatment





Dots (Aflibercept) or vertical lines (Laser) represent day of last follow-up in patients without recurrence

Patients with Recurrence to Type I ROP or Worse Through Week 52 CA