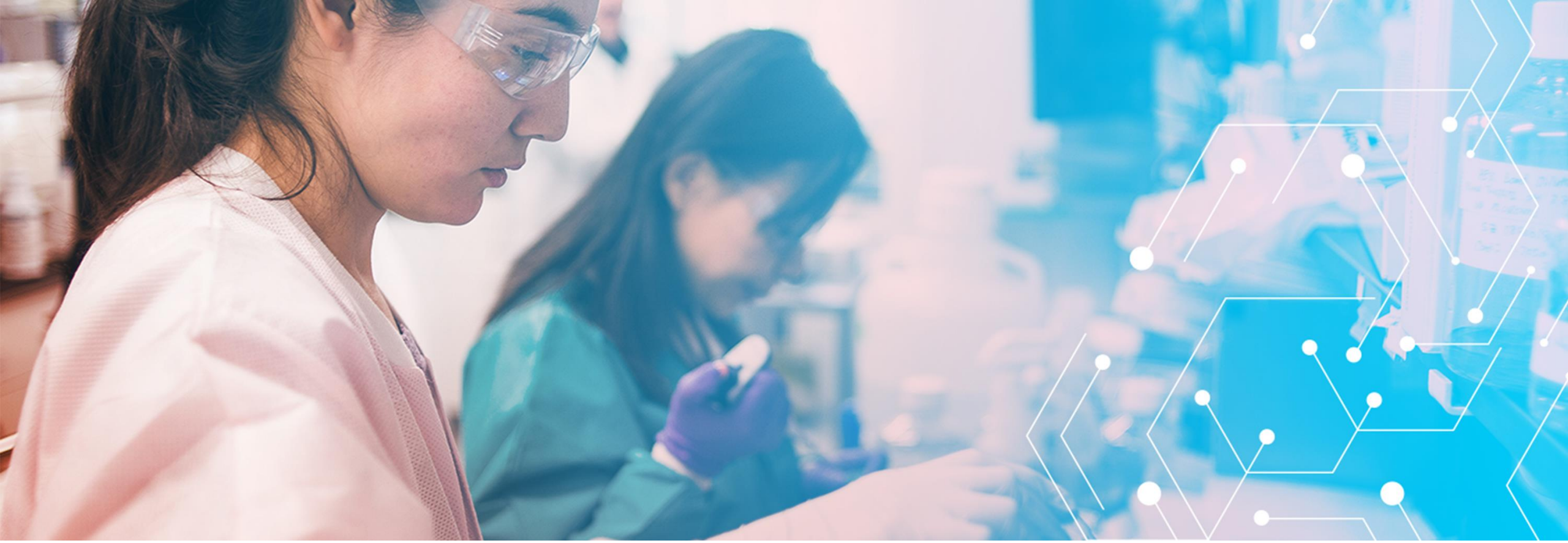


RGX-314 Analyst and Investor Day

Leading Retinal Specialists' Perspectives

February 21, 2019

Ken Mills

CEO

REGENXBIO®

Forward-looking statements

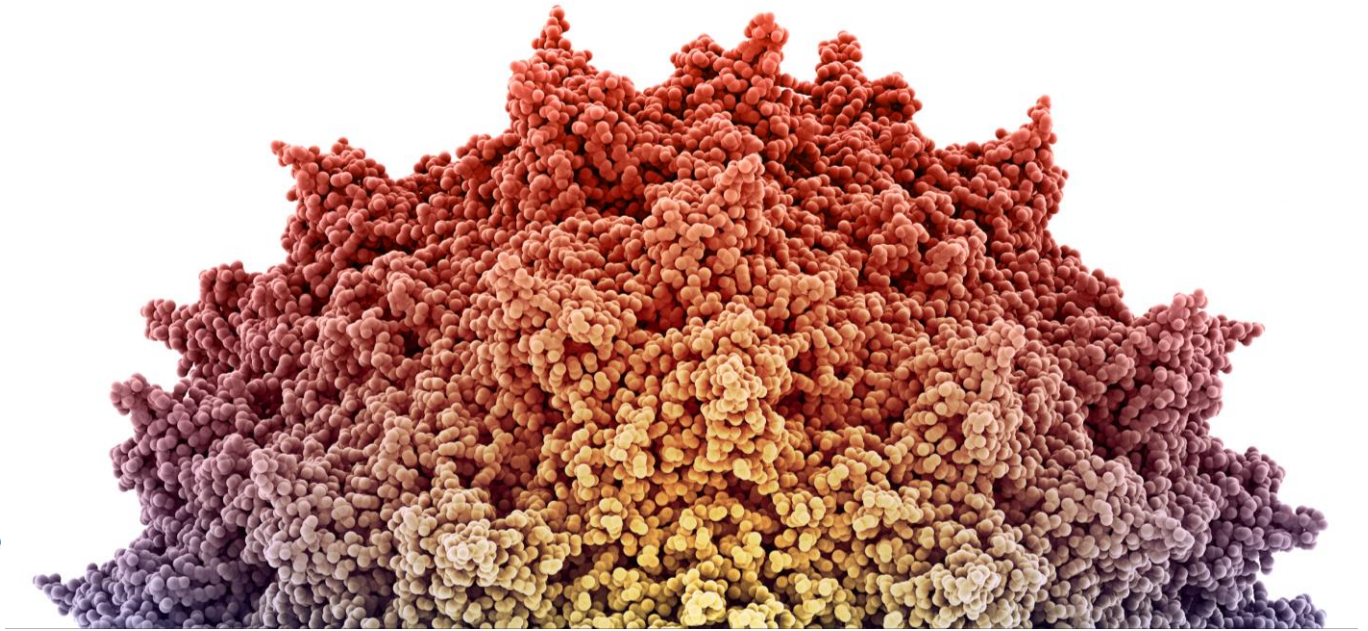
This presentation includes “forward-looking statements,” within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. These statements express a belief, expectation or intention and are generally accompanied by words that convey projected future events or outcomes such as “believe,” “may,” “will,” “estimate,” “continue,” “anticipate,” “design,” “intend,” “expect,” “could,” “plan,” “potential,” “predict,” “seek,” “should,” “would” or by variations of such words or by similar expressions. The forward-looking statements include statements relating to, among other things, REGENXBIO’s future operations, clinical trials, costs and cash flow. REGENXBIO has based these forward-looking statements on its current expectations and assumptions and analyses made by REGENXBIO in light of its experience and its perception of historical trends, current conditions and expected future developments, as well as other factors REGENXBIO believes are appropriate under the circumstances. However, whether actual results and developments will conform with REGENXBIO’s expectations and predictions is subject to a number of risks and uncertainties, including the timing of enrollment, commencement and completion and the success of clinical trials conducted by REGENXBIO, its licensees and its partners, the timing of commencement and completion and the success of preclinical studies conducted by REGENXBIO and its development partners, the timely development and launch of new products, the ability to obtain and maintain regulatory approval of product candidates, the ability to obtain and maintain intellectual property protection for product candidates and technology, trends and challenges in the business and markets in which REGENXBIO operates, the size and growth of potential markets for product candidates and the ability to serve those markets, the rate and degree of acceptance of product candidates, and other factors, many of which are beyond the control of REGENXBIO. Refer to the “Risk Factors” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations” sections of REGENXBIO’s Annual Report on Form 10-K for the year ended December 31, 2017 and comparable “risk factors” sections of REGENXBIO’s Quarterly Reports on Form 10-Q and other filings, which have been filed with the U.S. Securities and Exchange Commission (SEC) and are available on the SEC’s website at www.sec.gov. All of the forward-looking statements made in this presentation are expressly qualified by the cautionary statements contained or referred to herein. The actual results or developments anticipated may not be realized or, even if substantially realized, they may not have the expected consequences to or effects on REGENXBIO or its businesses or operations. Such statements are not guarantees of future performance and actual results or developments may differ materially from those projected in the forward-looking statements. Readers are cautioned not to rely too heavily on the forward-looking statements contained in this presentation. These forward-looking statements speak only as of the date of this presentation. REGENXBIO does not undertake any obligation, and specifically declines any obligation, to update or revise any forward-looking statements, whether as a result of new information, future events or otherwise.

REGENXBIO: seeking to improve lives through the curative potential of gene therapy

4 clinical stage programs
with next data readout for RGX–314 expected in late 2019

13 clinical stage product candidates
being developed by third-party licensees; ***over 20 partnered programs in total***

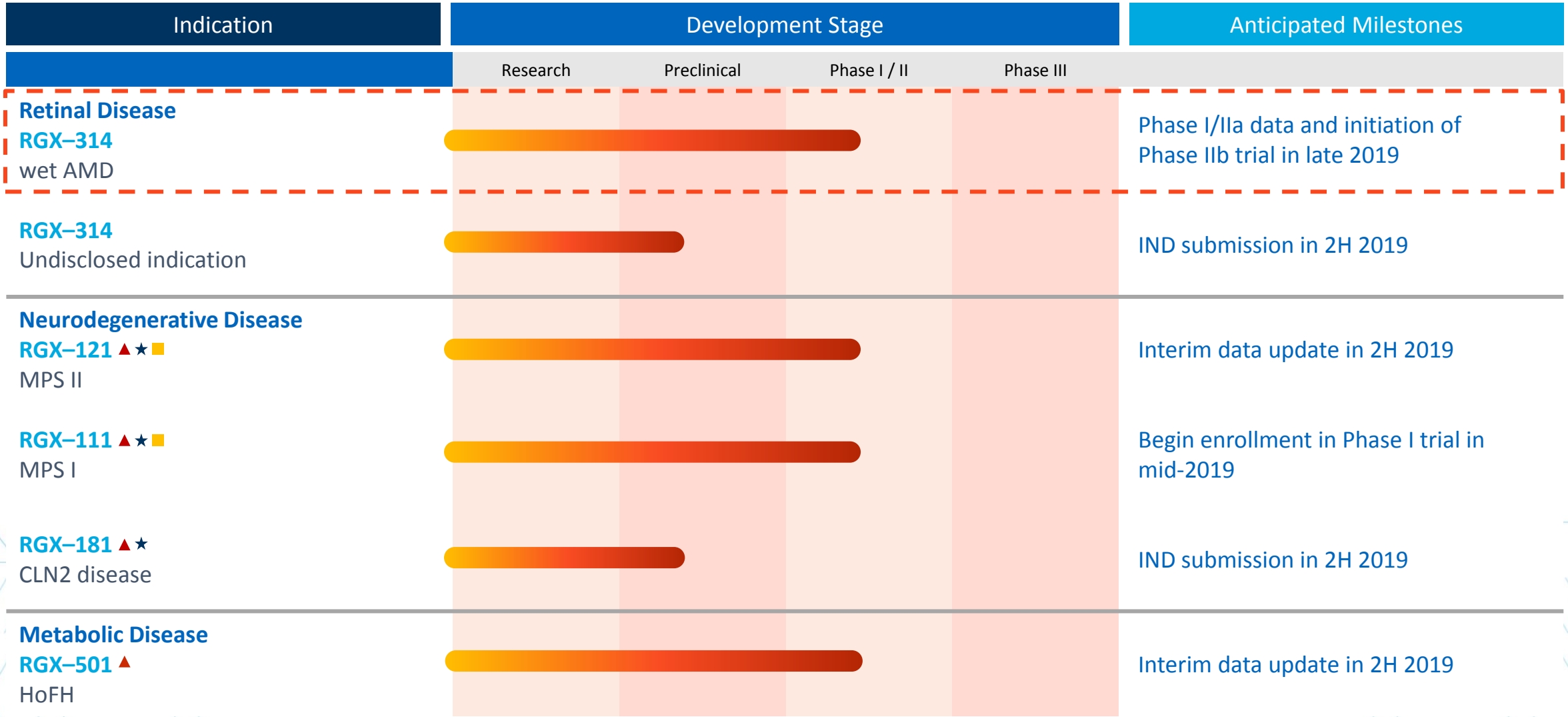
Proprietary **NAV® Technology Platform**
includes exclusive ***worldwide rights to over 100 AAV vectors***, including **AAV7, AAV8, AAV9** and **AAVrh10**



REGENXBIO®

REGENXBIO's lead programs

Internally developed product candidates



▲ Orphan Drug Designation
★ Rare Pediatric Disease Designation
■ Fast Track Designation

REGENXBIO®

REGENXBIO's **NAV Technology Platform** has been widely adopted

Over 20 partnered product candidates being developed by NAV Technology Licensees

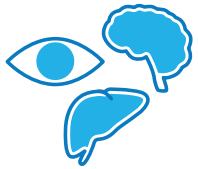
	Research		Preclinical		Phase I / II		Phase III	
	Indication	Licensee	Indication	Licensee	Indication	Licensee	Indication	Licensee
Liver / hematologic	Citrullinemia Type I	ultragenyx			Hemophilia A	Shire		
	PKU	ultragenyx			Hemophilia A	ultragenyx / BAYER		
	Wilson Disease	ultragenyx			OTC Deficiency	ultragenyx		
					GSDIa	ultragenyx		
					Crigler-Najjar	AUDENTES		
Retina	Achromatopsia	Biogen						
	Choroideremia	Biogen						
Central nervous system	Parkinson's w/ GBA	Prevail THERAPEUTICS	Rett Syndrome	NOVARTIS	SMA Type II / III	NOVARTIS	SMA Type I	NOVARTIS
	Undisclosed	Voyager / genzyme	ALS SOD1	NOVARTIS	MPS IIIA	Abeona THERAPEUTICS		
	CDKL5 Deficiency	ultragenyx	ALS SOD1	Voyager THERAPEUTICS	MPS IIIA	LYSOGENE / SAREPTA THERAPEUTICS		
			CLN1	Abeona THERAPEUTICS	MPS IIIA	ESTEVE		
			CLN3	Abeona THERAPEUTICS	MPS IIIB	Abeona THERAPEUTICS		
Cardiac / skeletal muscle	Friedreich's Ataxia	Voyager / genzyme	Danon Disease	rocket pharma	XLMTM	AUDENTES		
			Pompe Disease	AUDENTES	CPVT	AUDENTES		

Simultaneous global regulatory submissions filed in U.S., Europe and Japan

Key features of **REGENXBIO's NAV Technology Platform**

Higher gene expression

Longer-term gene expression



Broad and novel tissue selectivity

Lower immune response

Improved manufacturability

The NEW ENGLAND JOURNAL of MEDICINE

Long-Term Safety and Efficacy of Factor IX Gene Therapy in Hemophilia B

nature biotechnology

Intravascular AAV9 Preferentially Targets Neonatal Neurons and Adult Astrocytes

REGENXBIO | cGMP Manufacturing

Strength in AAV production and deep experience in biologics scale up and commercialization

Mammalian cell-based production

- Natural host for AAV
- Robust process utilizing mammalian cell lines with known regulatory history
- Core in-house capability in adapting adherent cell lines to suspension cell culture-based systems
  - Suspension cell culture process developed and transferred to CMO

Focus on process, quality and analytics

- Deep in-house knowledge of AAV characterization and production
- Focused efforts on integrated upstream and downstream process optimization and scale-up
- Significant expertise and investment in quality systems and downstream analytics

Large-scale cGMP capacity at CMOs

- Agreements with multiple leading biologics CMOs for production of materials under cGMP, including secured large-scale (up to 2,000L) capacity and commercial production at FUJIFILM
- REGENXBIO platform processes transferred to all CMO partners with robust performance and yields
- FUJIFILM relationship supports clinical development and potential future commercial needs
- Leveraging flexibility and scale at CMOs to ensure supply while managing capital investment

Clinical manufacturing status

- Completed production of investigational product for four lead product candidates in an amount which is expected to supply on-going clinical trials; GMP campaign in progress for RGX–181
- In-house GMP testing established to accelerate release of clinical supplies
- Capability to progress from candidate selection to clinical material in 12 months

The REGENXBIO team

Name	Position	Prior Affiliations
Ken Mills	President, CEO & Co-Founder; Director	FOXKISER, MSD
Olivier Danos, Ph.D.	SVP and Chief Scientific Officer	Biogen, cnrs
Vit Vasista	SVP and Chief Financial Officer	PRTM, MSD
Curran Simpson	SVP, Product Development and Chief Technology Officer	gsk, Human Genome Sciences
Ram Palanki, Pharm.D.	SVP, Commercial Strategy and Operations	Santen, Genentech A Member of the Roche Group
Patrick Christmas, J.D.	SVP and General Counsel	Lumara Health, Wellstat Therapeutics
Laura Coruzzi, Ph.D., J.D.	SVP, Intellectual Property	Jones Day
Shiva Fritsch	SVP, Human Resources	NOVAVAX, Human Genome Sciences

RGX–314 for treatment of wet age-related macular degeneration **(wet AMD)**

THE DISEASE

- Blurring of central vision and progressive vision loss due to formation of leaky blood vessels in the eye
- VEGF inhibitors are standard of care to treat fluid and associated vision loss
- Frequency / uncomfortable administration of current anti-VEGF therapies affects compliance and ultimately efficacy
- >2 million patients estimated in U.S., Europe and Japan

RGX–314 PRODUCT CANDIDATE

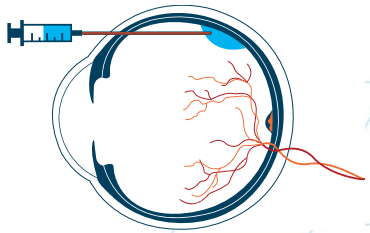
Vector: AAV8 | **Gene:** anti-VEGF fab

Mechanism of action

Reducing leaky blood vessel formation by giving ocular cells the ability to produce an anti-VEGF fab

Route of administration

Subretinal



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RGX-314 clinical trial summary through six months

	Aqueous RGX–314 protein one month post–treatment	Mean # of anti–VEGF injections through six months	Mean change in CRT through six months (range)	Mean change in BCVA through six months
Cohort 1 $3x10^9$ GC/eye (N=6)	2.4 ng/ml	4.7 inj*	-14 µm** (-181µm to +92 µm)	-2 letters** (-8 to +10 letters)
Cohort 2 $1x10^{10}$ GC/eye (N=6)	12.8 ng/ml	3.8 inj	+26 µm (-7µm to +62 µm)	+7 letters (-4 to +15 letters)
Cohort 3 $6x10^{10}$ GC/eye (N=6)	**160.2 ng/ml**	**1.3 inj**	**-14 µm (-27µm to +7 µm)**	**+8 letters (0 to +21 letters)**

* One subject in Cohort 1 discontinued from the study at four months with four injections and was imputed as requiring six injections through six months

** N=5; one subject in Cohort 1 discontinued from the study at four months

Cohort 3: Three subjects with no additional anti–VEGF injections through nine months

Previous therapy	▪ Study subjects received on average **>35 injections since wet AMD diagnosis**
Post-RGX–314 anti–VEGF injections	▪ **0 injections** through nine months post-RGX–314
BCVA	▪ Mean change in BCVA of **+13 ETDRS** letters from baseline through nine months
SD–OCT	▪ Maintained with a **mean change in CRT of -37 µm** from baseline through nine months

Featured Retina Specialist Guest Speakers

John Pollack, M.D.

- Partner at Illinois Retina Associates
- Assistant Professor of Ophthalmology at Rush University Medical Center
- President of the American Society of Retina Specialists (ASRS)

Pravin U. Dugel, M.D.

- Managing Partner at Retinal Consultants of Arizona, Phoenix
- Clinical Professor at Roski Eye Institute and University of Southern California Keck School of Medicine
- Subspecialty Day Board Chairman Emeritus for the American Academy of Ophthalmology (AAO) Board of Directors and Executive Committee of ASRS
- Board of Trustees of EURETINA

Allen C. Ho, M.D.

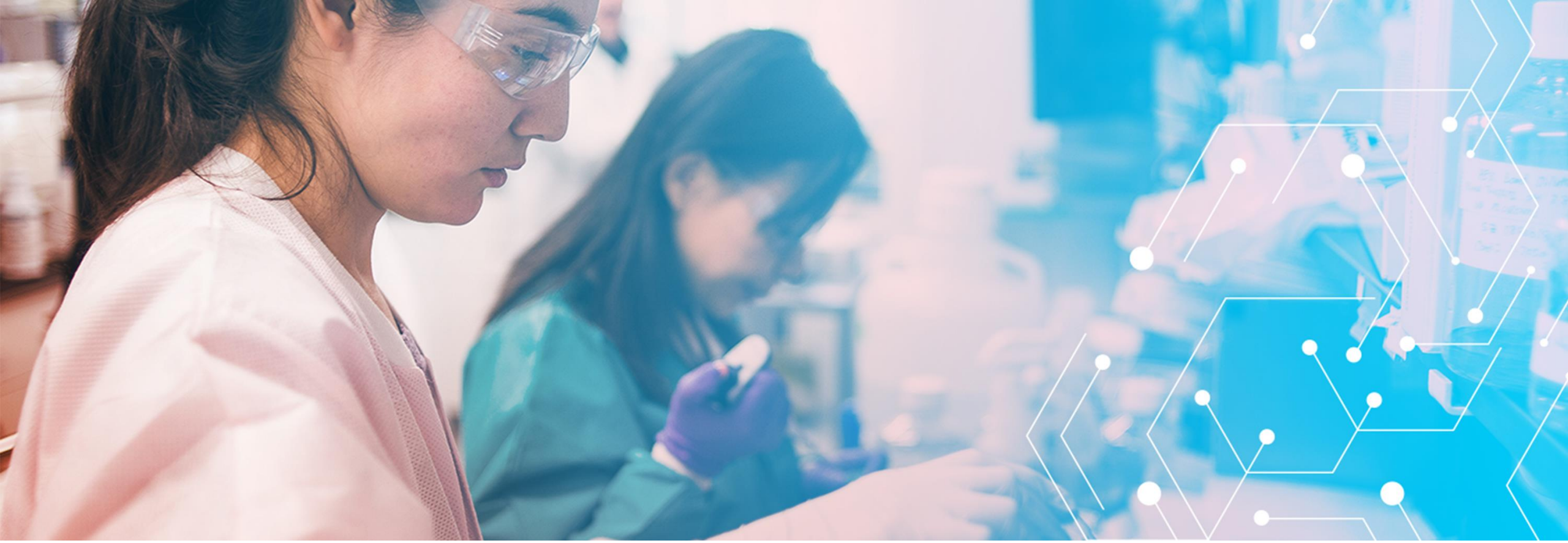
- Professor of Ophthalmology at Sidney Kimmel Medical College at Thomas Jefferson University
- Director of Retina Research at Wills Eye Hospital
- Executive Committee of the Retina Society
- Investigator in the RGX-314 Phase I/IIa clinical trial

Jeffrey Heier, M.D.

- Co-President, Medical Director and Retina Service Director of Retina Research Ophthalmic Consultants of Boston
- Principal Investigator of the RGX-314 Phase I/IIa clinical trial

Agenda

Olivier Danos, PhD SVP and Chief Scientific Officer	Optimizing the gene therapy construct for wet AMD
John Pollack, MD	Overview of retinal diseases, standard of care and unmet need in wet AMD
Pravin U. Dugel, MD	Changing retinal landscape and implications for future therapies
Allen C. Ho, MD	Facts about vitrectomies and subretinal procedures
Jeff Heier, MD	RGX-314 Phase I/IIa clinical data
Ram Palanki SVP, Commercial Strategy & Operations	RGX-314 market opportunity
Q&A Moderator: Ram Palanki	



RGX-314 Analyst and Investor Day

Optimizing the gene therapy construct

February 21, 2019

Olivier Danos, Ph.D.
SVP and Chief Scientific Officer

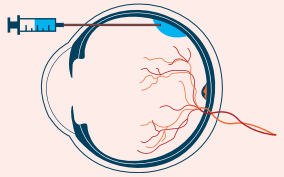
REGENXBIO®

RGX–314 for treatment of wet age-related macular degeneration (wet AMD)

RGX–314 PRODUCT CANDIDATE

Vector: AAV8 | **Gene:** anti-VEGF fab

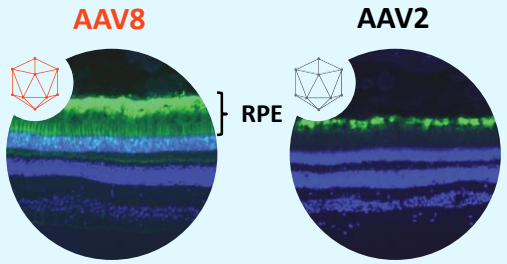
Route of administration: Subretinal



Mechanism of action:

Reducing leaky blood vessel formation by giving ocular cells the ability to produce an anti-VEGF fab

Improved AAV vector technology



More efficient gene delivery to the RPE[1]

+

Leveraging current standard of care in transgene

- Current standard of care includes FDA-approved mAbs and mAb fragments that inhibit VEGF
- **RGX–314 gene encodes an anti-VEGF mAb fragment (fab)**

=

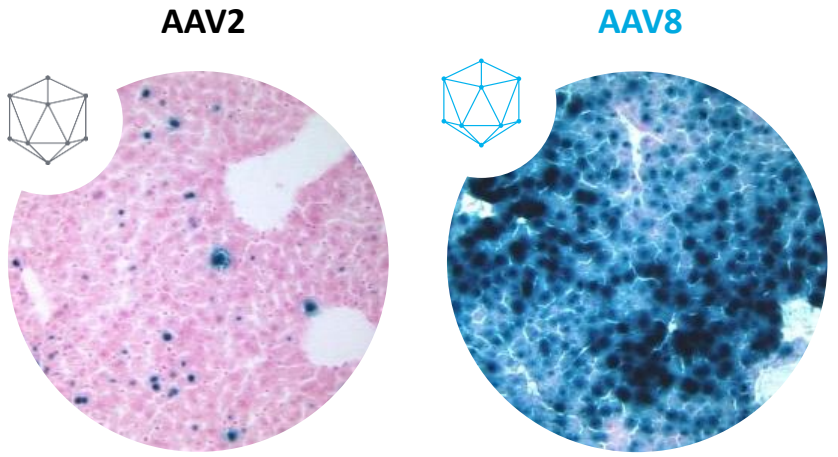
RGX–314: AAV8 encoding anti–VEGF fab

Potential for long-term therapeutic anti-VEGF expression

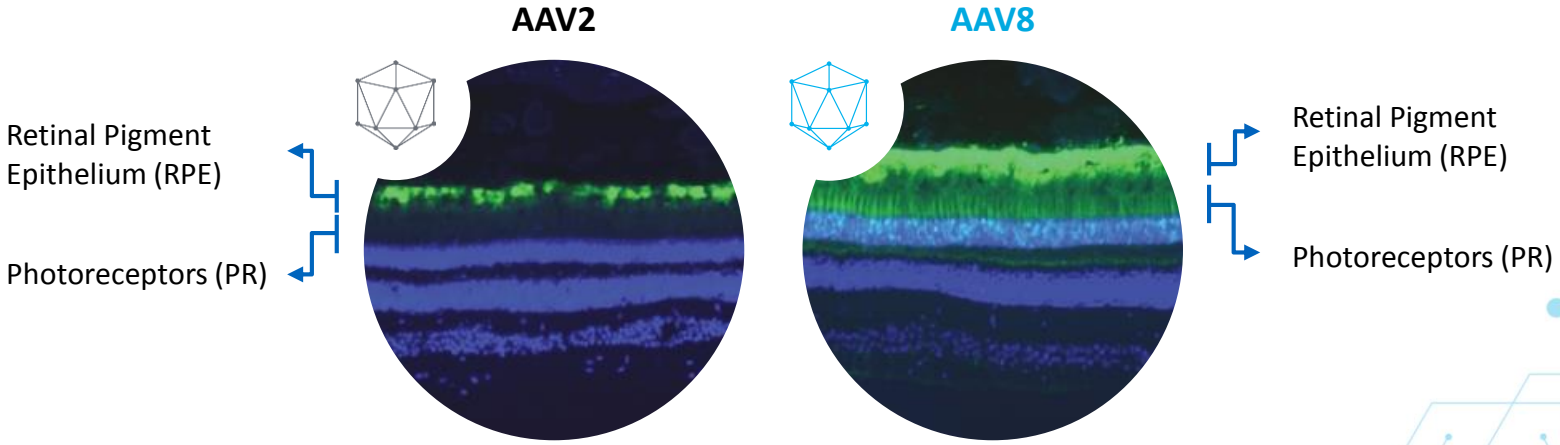
1 Vandenberghe et al. 2011 Science Translational Medicine

NAV Vectors: higher gene expression than early generation AAV vectors

NAV Vector AAV8**: 10x–100x greater gene expression**



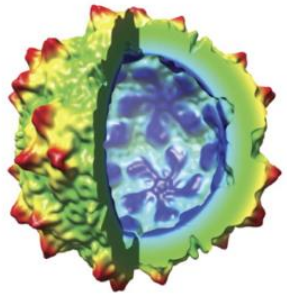
NAV Vector AAV8: **More efficient gene delivery** to sites of most retinal dystrophies[1]



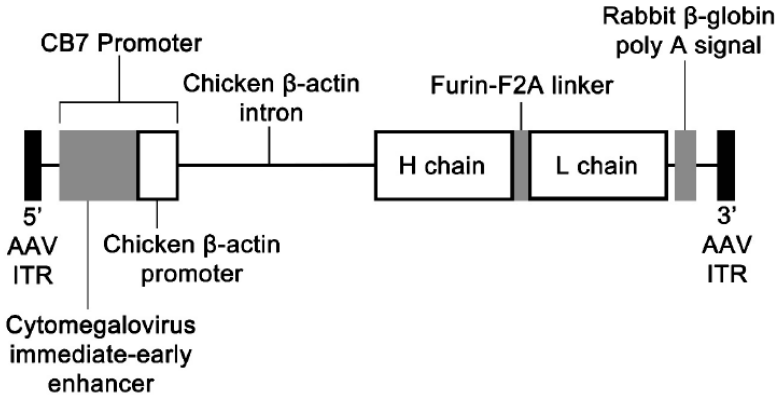
[1] Vandenberghe et al. 2011 *Science Translational Medicine*

AAV8 anti-VEGF fab (RGX-314)

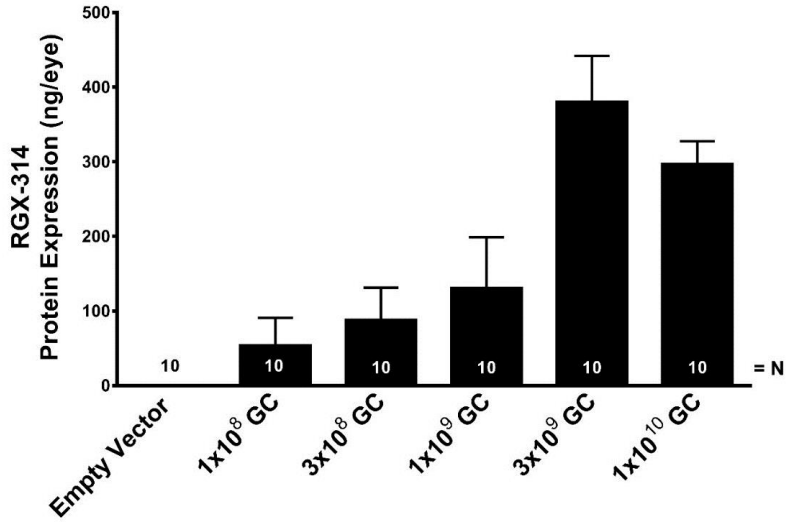
RGX-314 (AAV2/8.CB7.CI.amd42.rBG) is a non-replicating, recombinant adeno-associated virus (AAV), serotype 8 (AAV8) vector containing an amd42 expression cassette encoding for a soluble anti-VEGF Fab protein



AAV8 Capsid:
An icosahedron formed by three viral proteins, VP1, VP2 and VP3



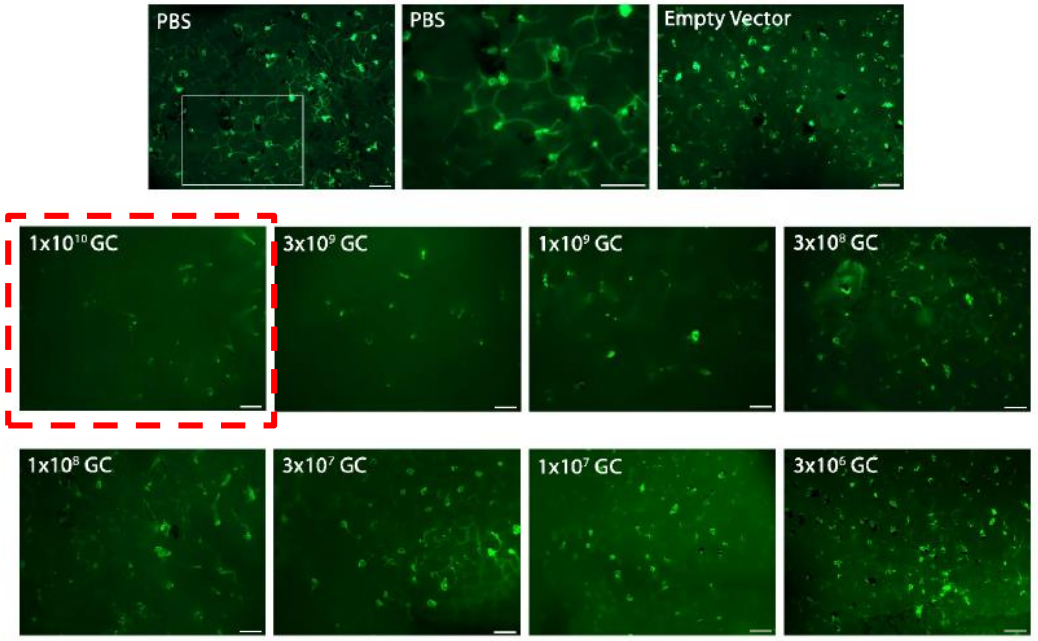
RGX-314 protein expression



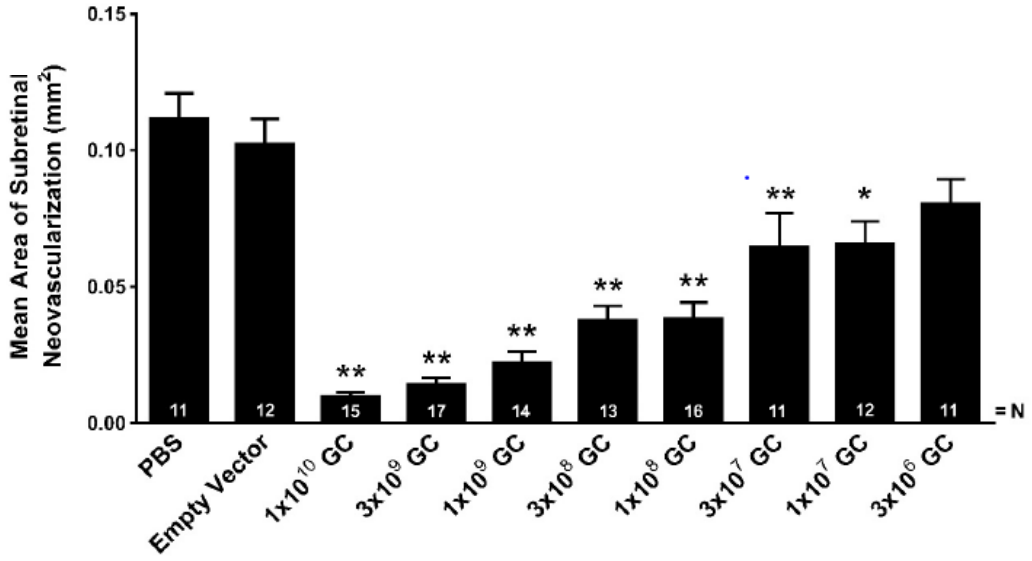
Source: Liu et al. AAV*-antiVEGFfab ocular gene transfer for neovascular age-related macular degeneration. Mol Ther. 2018.

Subretinal injection of RGX-314 suppresses choroidal neovascularization in mice

Rho/VEGF neovascularization in mice in response to RGX-314



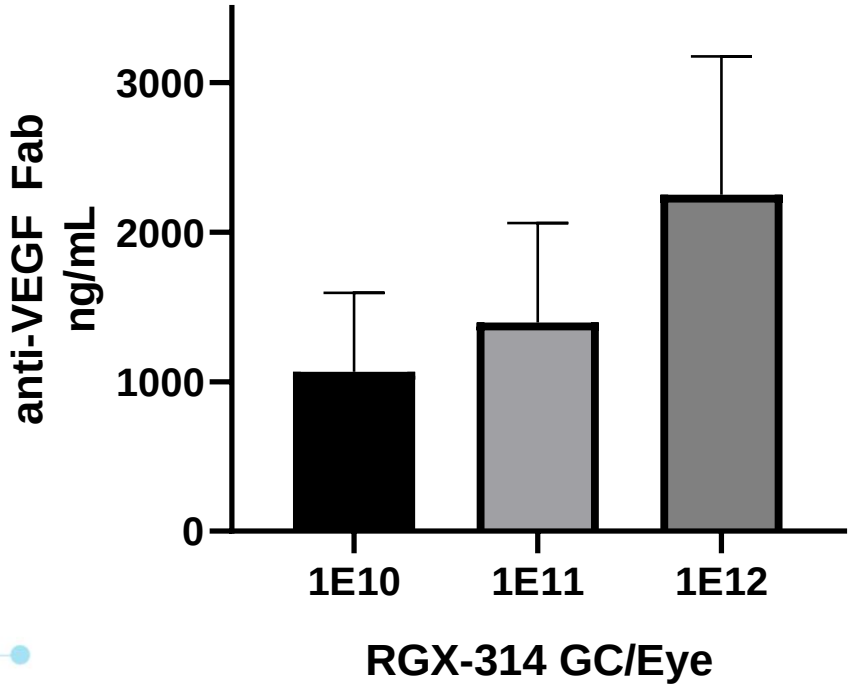
Dose response: area of neovascularization



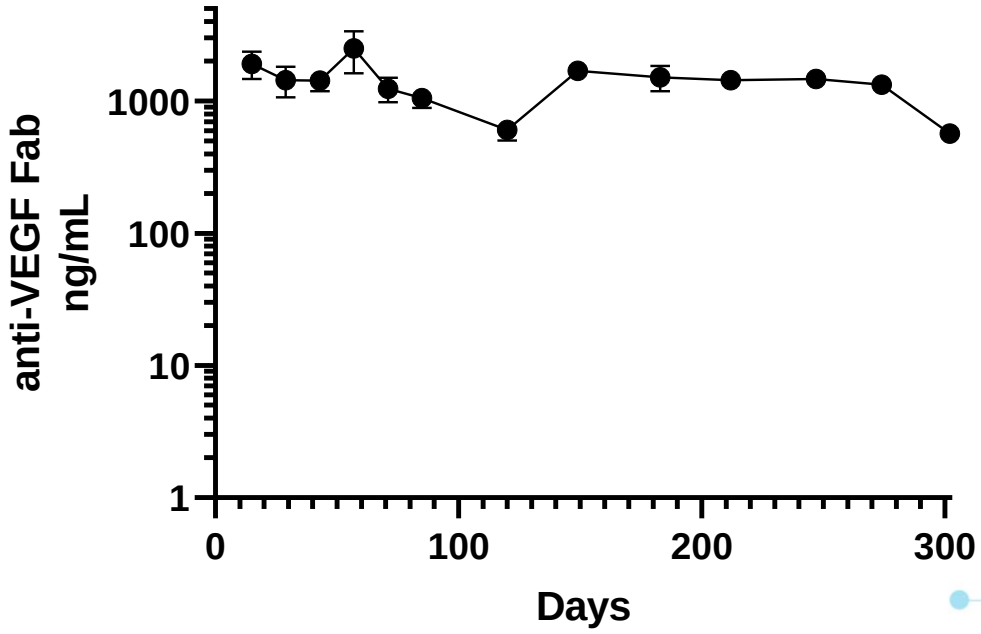
Source: Liu et al. AAV*-antiVEGFfab ocular gene transfer for neovascular age-related macular degeneration. Mol Ther. 2018.

Long-term anti-VEGF protein expression is measured in non-human primates

4 week protein expression[1]



Protein expression up to 300 days[2]



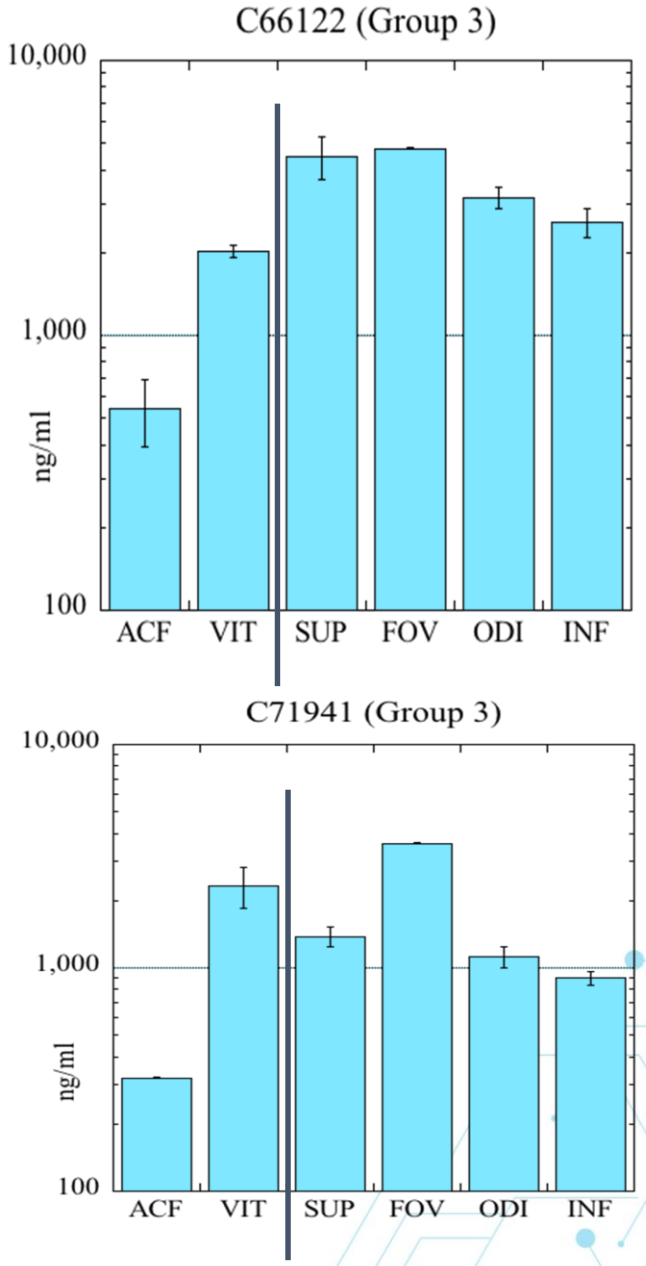
1. NHP Study #8 & #12
2. RGX-314 1E11, group 6

Data on file at REGENXBIO

RGX–314 anti-VEGF fab distributes throughout the retina

- Cynomolgus monkeys administered 1×10^{11} GC/eye of AAV8 vector subretinally

- Concentrations of anti-VEGF Fab were determined in:
  - ACF = anterior chamber fluid
  - VIT = vitreous
  - Retina:
    - SUP = superior retinal section
    - FOV = fovea
    - ODI = middle section w optic disk
    - INF = inferior retinal section



Transgene product distributes beyond peripheral injection site

Source: NHP Study #14
Data on file at REGENXBIO

RGX–314 transgene product binding and affinity for VEGF

- Compared binding of in vitro synthesized RGX–314 transgene product with synthesized ranibizumab on human tissue samples
  - No difference in tissue binding profile vs. ranibizumab
- Determined binding affinity of RGX–314 transgene product for human VEGF[1]
  - RGX–314 transgene product affinity as high or higher than published range for ranibizumab
  - Measured by Biacore (surface plasmon resonance)

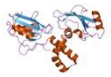
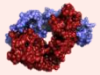
Ligand	Analyte	ka (1/Ms)	kd (1/s)	R_{max}	K_D (M)	Concentration (nM)	χ^2
VEGF (97 RU)	RGX-314 transgene product	2.42×10^{5}	8.06×10^{-5}	21.8	3.33×10^{-10}	0 to 100	0.0653

Abbreviations: ka = association rate constant; kd = dissociation rate constant; K_D equilibrium binding affinity constant; R_{max} = maximum binding capacity (in RU) of ligand captured/immobilized on the surface; RU = response unit.

RGX–314 transgene product binding and affinity for VEGF consistent with ranibizumab data

1. Binding data from Study Report 14. Data on file.

RGX–314 has potential advantages over earlier generation candidates for wet AMD gene therapy

Sponsor	genzyme[1]	AVALANCHE BIOTECH[2]	REGENXBIO
Vector	 AAV2	 AAV2	 **AAV8**
ROA	Intravitreal	Subretinal	**Subretinal**
Transgene	 sFLT01	 sFlt	 **anti-VEGF fab**
Dose (GC/eye)	2.4e10	8.0e11	**1.0e11**
Max. expression (ng/ml)[3]	528	0.217	**4,992**

[1] MacLachlan et al. 2011 Molecular Therapy
[2] Lai et al. 2012 Gene Therapy
[3] Maximum expression in the anterior chamber of non-human primate eyes

Overview of retinal diseases, standard of care and unmet need in wet AMD

John Pollack, MD

FINANCIAL DISCLOSURES

Allegro - Consultant

Covalent Medical – Stock

Dutch Ophthalmic Research Company – Consultant

Genentech – Grant Support, Consultant

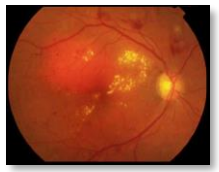
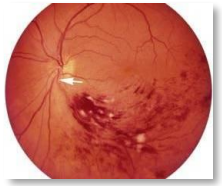
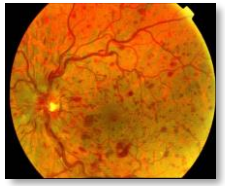
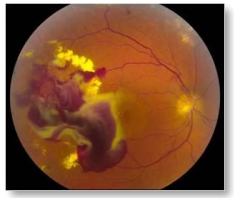
Notal Vision - BOD, Stock, Consultant

Novartis - Consultant

REGENXBIO - Consultant

Vestrum Health - Stock

MAJOR RETINAL DISEASES OVERVIEW

	Avg age of onset	Prevalence* (MM)	Disease overview	Treatments	
Wet AMD	**70 yrs**	**1.9**	• **A leading cause of blindness** in the elderly	• **PDT & chronic anti-VEGF therapy**	 *wAMD*
Diabetic Macular Edema	**60 yrs**	**1.9**	• **Most frequent cause of blindness** in middle aged adults	• **Anti-VEGF, steroids, laser & surgeries**	 *DME*
Retinal Vein Occlusion	**55 yrs**	**2.5**	• **Second most common cause of vision loss** due to vascular disease	• **Anti-VEGF, steroids & laser**	 *BRVO*  *CRVO*
Diabetic Retinopathy w/o DME	**45-50 yrs**	**5.1**	• **Common cause of vision loss** among diabetics • Classified as non-proliferative (NPDR) and proliferative (PDR)	• **PRP, anti-VEGF & surgeries**	 *NPDR*  *PDR*

wAMD = wet AMD; DME = Diabetic Macular Edema; BRVO = Branch Retinal Vein Occlusion; CRVO = Central Retinal Vein Occlusion; NPDR = Non-Proliferative Diabetic Retinopathy; PDR = Proliferative Diabetic Retinopathy

Note: Numbers may be rounded; Source: epidemiology data based on multiple literature sources, diagnosis rates based on Datamonitor Report, DRG Market Forecast Assumptions; other sources: Regeneron USA: 230k anti-VEGF treated patients, Roche USA: 200k patients under ophtha care https://www.gene.com/stories/retinal-diseases-fact-sheet and DRG Market Forecast Assumptions
*US, EU5, Japan

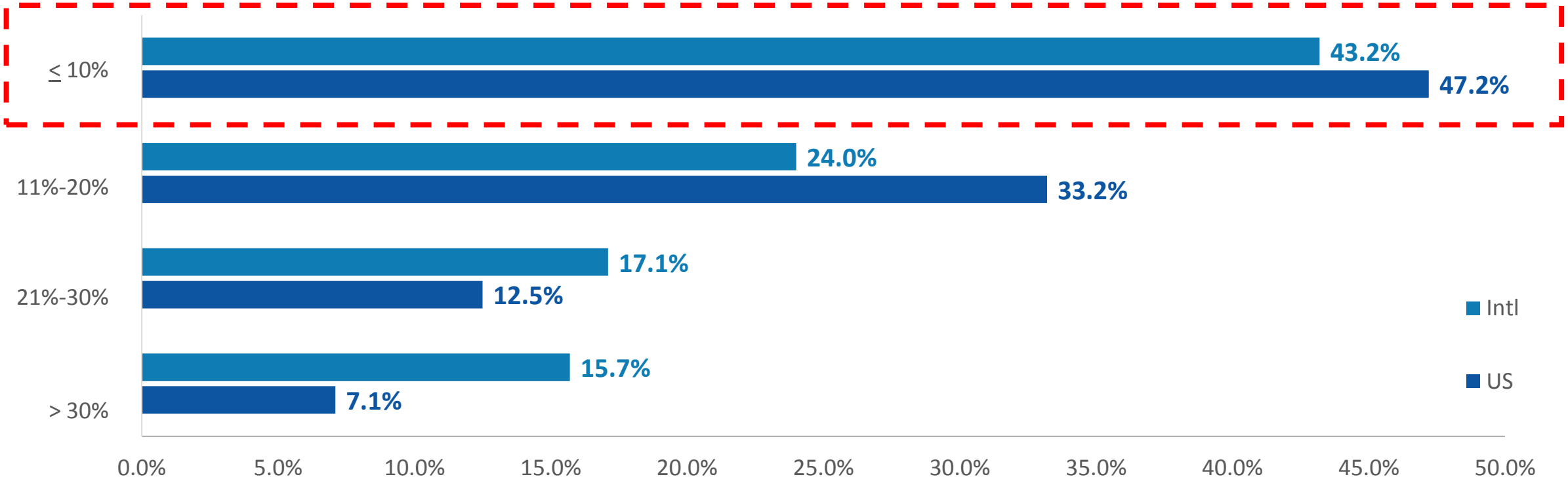
ANTI-VEGF TREATMENT EFFICACY IN PHASE III TRIALS

Study Name	Drug Name	Dose Frequency	Mean age (years) Baseline	Mean ETDRS letters Baseline	Mean Gain in ETDRS letters at 24 months
[1]ANCHOR	Ranibizumab	0.5mg every 4 wks	76	47.1	+10.7
[2]MARINA	Ranibizumab	0.5mg every 4 wks	77	53.7	+6.6
[3]CATT	Ranibizumab	0.5mg every 4 wks	79	60.1	+8.8
[3]CATT	Bevacizumab	1.25mg every 4 wks	80	60.2	+7.8
[4]VIEW 1 & 2	Aflibercept	2mg every 8 wks	76	55.7	+7.6
[4]VIEW 1 & 2	Ranibizumab	0.5mg every 4 wks	76	54.0	+7.9
[5]HARBOR	Ranibizumab	0.5mg every 4 wks	79	54.2	+9.4
[5]HARBOR	Ranibizumab	0.5mg PRN	79	54.5	+7.9
				Mean	8.3

1 Brown DM, Kaiser PK, Michels M, et al., ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age related macular degeneration. Ophthalmology 2009;116:57-65.
2 Rosenfeld PJ, Brown DM, Heier JS, et al., MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419 –31.
3 CATT Research Group, Martin DF, Maguire MG, et al., Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011;364:1897–908.
4 Heier JS et al., Ophthalmology. 2012 Dec;119(12):2537-48.
5 Ho AC et al., HARBOR Study 2-Year Results. Ophthalmology 2014.

THE MAJORITY OF WET AMD PATIENTS DO NOT RECEIVE RECOMMENDED TREATMENT REGIMEN

What percentage of your wet-AMD patients do you continue treating with q4w anti-VEGF injections?



ASRS American Society of Retina Specialists

Stone TW, ed. *ASRS 2018 Preferences and Trends Membership Survey*. Chicago, IL. American Society of Retina Specialists; 2018.

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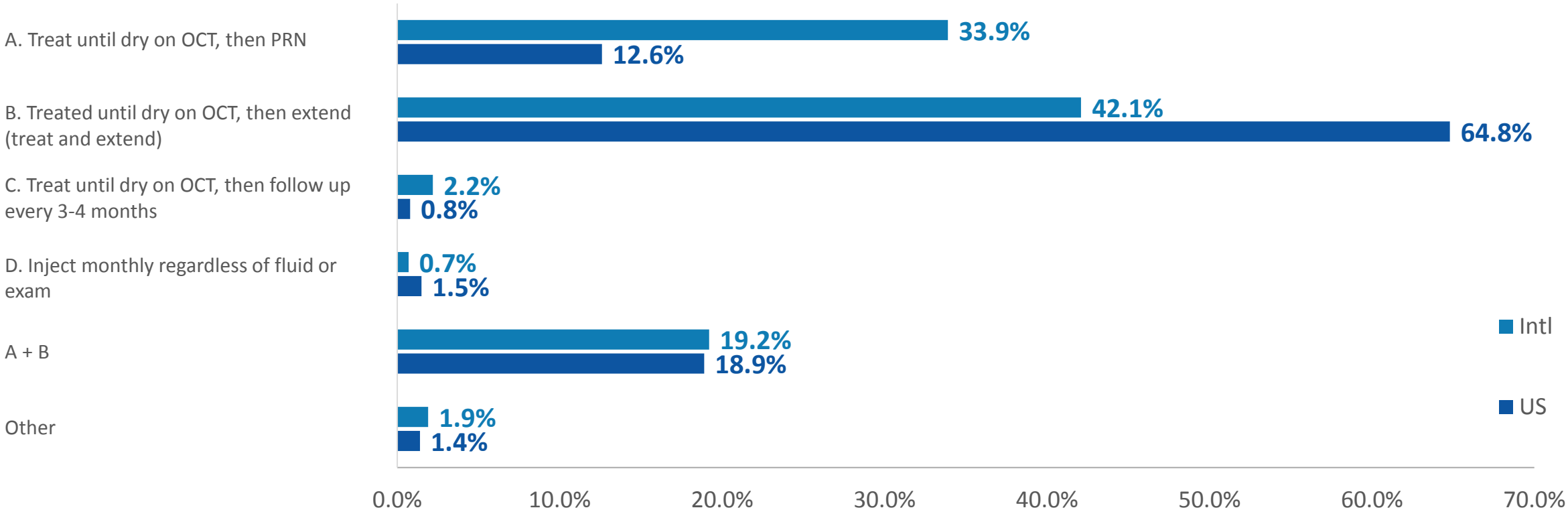
MULTIPLE TREATMENT REGIMENS ARE USED IN THE ”REAL WORLD”

In general, how do you treat wet-AMD patients with active CNV?



ASRS American Society of Retina Specialists

ASRS 2015 Preferences and Trends Membership Survey. Vienna, Austria. American Society of Retina Specialists 2015 © 2015 American Society of Retina Specialists. All rights reserved.

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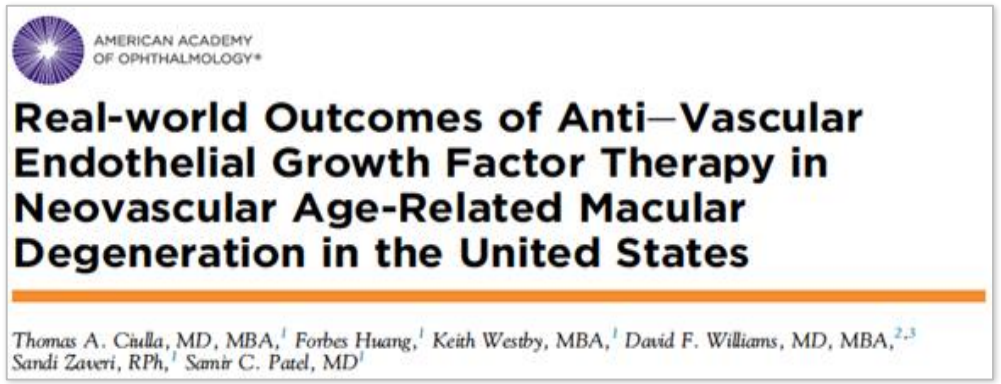
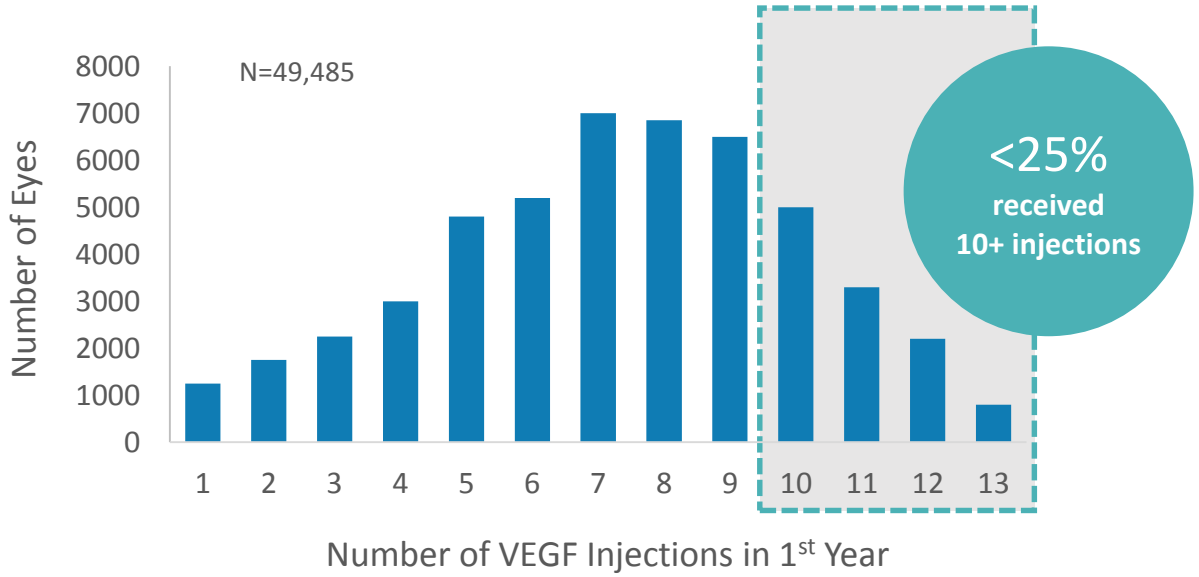
REAL WORLD OUTCOMES HAVE SIGNIFICANT ROOM FOR IMPROVEMENT


AMERICAN ACADEMY OF OPHTHALMOLOGY®

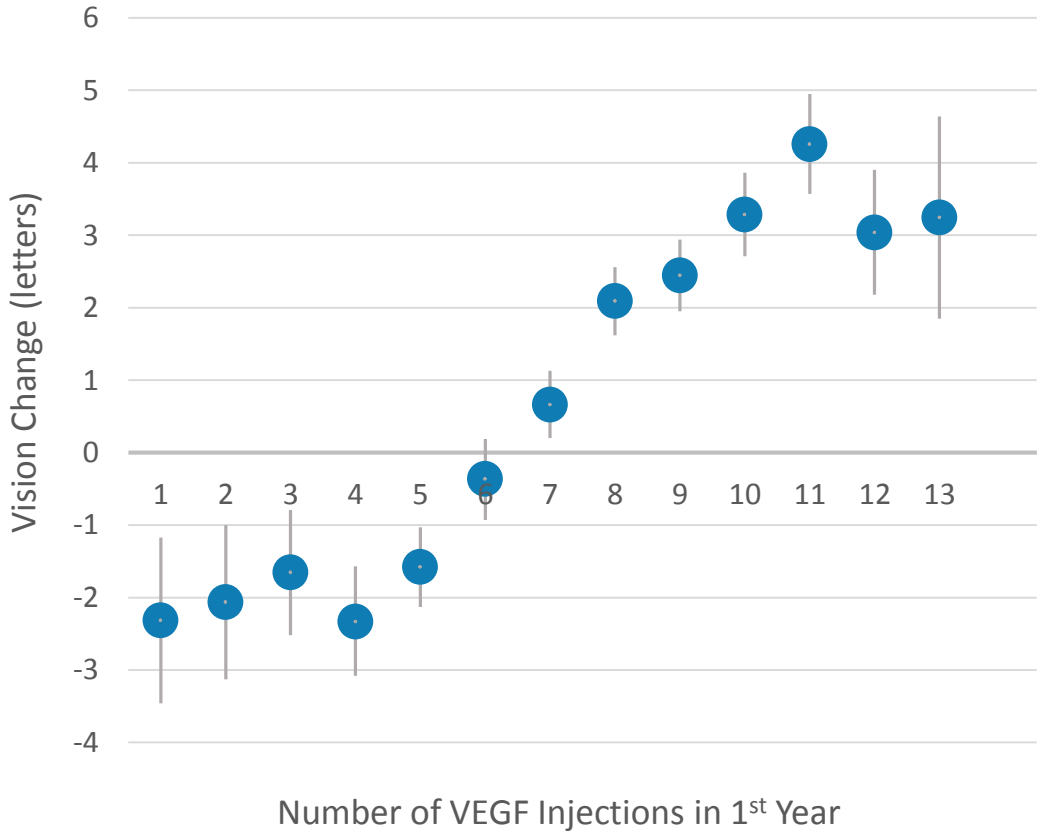
Real-world Outcomes of Anti–Vascular Endothelial Growth Factor Therapy in Neovascular Age-Related Macular Degeneration in the United States

Thomas A. Ciulla, MD, MBA,[1] Forbes Huang,[1] Keith Westby, MBA,[1] David F. Williams, MD, MBA,[2,3] Sandi Zaveri, RPh,[1] Samir C. Patel, MD[1]

wAMD treatment frequency in real world



Number of anti-VEGF injections correlates with vision improvement



Source: Ciulla et al., Real-world outcomes of anti-vascular endothelial growth factor therapy in neovascular age-related macular degeneration in the United States. Ophthalmology Retina. 2018.

UNDERTREATMENT LEADS TO SIGNIFICANT VISION LOSS OVER TIME

CATT 5-YEAR OUTCOMES

AMERICAN ACADEMY™ OF OPHTHALMOLOGY

CrossMark

Five-Year Outcomes with Anti–Vascular Endothelial Growth Factor Treatment of Neovascular Age-Related Macular Degeneration

The Comparison of Age-Related Macular Degeneration Treatments Trials

*Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group**
Writing Committee: Maureen G. Maguire, PhD,[1] Daniel F. Martin, MD,[2] Gui-shuang Ying, PhD,[1] Glenn J. Jaffe, MD,[3] Ebenezer Daniel, MBBS, PhD,[1] Juan E. Grunwald, MD,[1] Cynthia A. Toth, MD,[3] Frederick L. Ferris III, MD,[4] Stuart L. Fine, MD[5]

Purpose: To describe outcomes 5 years after initiating treatment with bevacizumab or ranibizumab for neovascular age-related macular degeneration (AMD).
Design: Cohort study.
Participants: Patients enrolled in the Comparison of AMD Treatments Trials.
Methods: Patients were assigned randomly to ranibizumab or bevacizumab and to 1 of 3 dosing regimens. After 2 years, patients were released from the clinical trial protocol. At 5 years, patients were recalled for examination.
Main Outcome Measures: Visual acuity (VA) and morphologic retinal features.
Results: Visual acuity was obtained for 647 of 914 (71%) living patients with average follow-up of 5.5 years. The mean number of examinations for AMD care after the clinical trial ended was 25.3, and the mean number of treatments was 15.4. Most patients (60%) were treated 1 time or more with a drug other than their assigned drug. At the 5-year visit, 50% of eyes had VA of 20/40 or better and 20% had VA of 20/200 or worse. Mean change in VA was −3 letters from baseline and −11 letters from 2 years. Among 467 eyes with fluorescein angiography, mean total lesion area was 12.9 mm^2, a mean of 4.8 mm^2 larger than at 2 years. Geographic atrophy was present in 213 of 515 (41%) gradable eyes and was subfoveal in 85 eyes (17%). Among 555 eyes with spectral-domain optical coherence tomography, 83% had fluid (61% intraretinal, 38% subretinal, and 36% sub–retinal pigment epithelium). Mean foveal total thickness was 278 μm, a decrease of 182 μm from baseline and 20 μm from 2 years. The retina was abnormally thin (<120 μm) in 36% of eyes. Between 2 and 5 years, the group originally assigned to ranibizumab for 2 years lost more VA than the bevacizumab group (−4 letters; $P = 0.008$). Otherwise, there were no statistically significant differences in VA or morphologic outcomes between drug or regimen groups.
Conclusions: Vision gains during the first 2 years were not maintained at 5 years. However, 50% of eyes had VA of 20/40 or better, confirming anti–vascular endothelial growth factor therapy as a major long-term therapeutic advance for neovascular AMD. *Ophthalmology 2016;123:1751-1761 © 2016 by the American Academy of Ophthalmology.*

*Supplemental material is available at www.aaojournal.org.

Patients who switched from monthly to prn (year 2) lost **-2 to -3 letters**

Post-protocol, real-world outcomes show patients lost an additional **-11 letters**

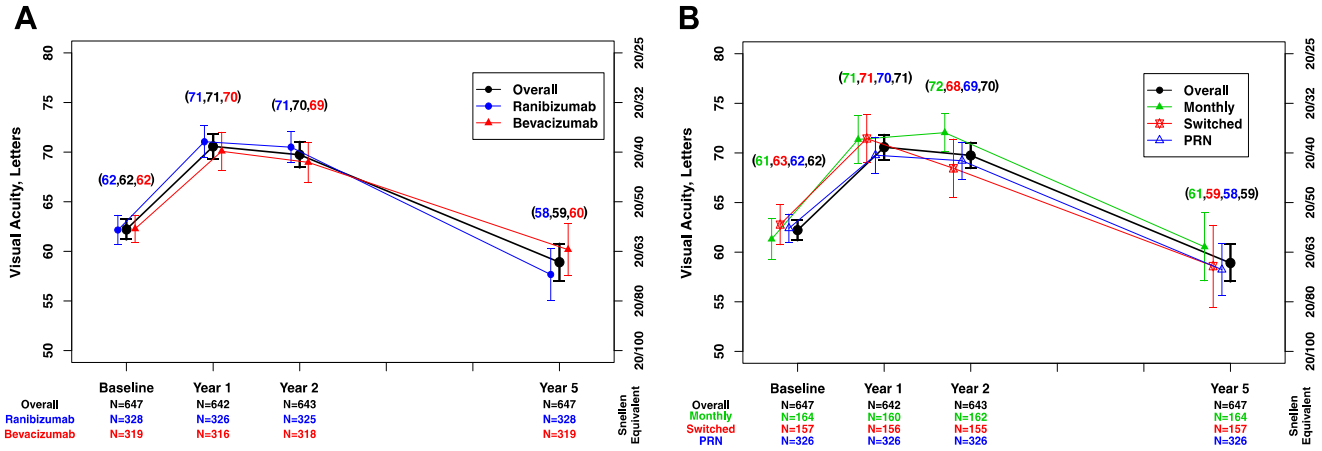


Figure 2. Graphs showing the mean visual acuity and 95% confidence interval for 647 patients in the Comparison of Age-Related Macular Degeneration Treatments Trials Follow-up Study: (**A**) overall and by drug assigned in the clinical trial and (**B**) overall and by dosing regimen assigned in the clinical trial. PRN = pro re nata.

Source: CATT Research Group, Martin DF, Maguire MG, et al., Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011;364:1897–908.

PROJECTED ANNUAL COSTS ASSOCIATED WITH BLINDNESS DUE TO RETINAL DISEASES

In **2020**, the prevalent number of cases of bilateral blindness (VA ≤20/200) due to retinal diseases (wAMD, DME & PDR) is **estimated to be 246,422**

By **2050**, the number of individuals with bilateral blindness is projected to **increase more than two-fold** and the overall cost burden is estimated to **triple to $64 billion**

CAREGIVING COSTS ARE THE LARGEST CONTRIBUTOR

	2020	2030	2040	2050
Number of cases	246,423	346,273	461,722	515,745
Direct cost, $ billions	1.22	1.84	2.71	3.48
Indirect (caregiver) cost, $ billions	13.46	23.18	36.54	47.41
QALYs lost	61,757	86,748	115,621	129,133
Years of life lost	9,741	14,468	20,434	23,170
Intangible cost, $ billions	6.18	8.68	11.56	$12.91
Total cost, $ billions	**20.85**	**33.70**	**50.81**	**63.81**

Source: DME, diabetic macular edema; PDR, proliferative diabetic retinopathy; RVO, retinal vein occlusion; wAMD,wet age-related macular degeneration. Moshfeghi et al, Angiogenesis 2019.

SUMMARY

1

Frequent intravitreal anti-VEGF treatment has been shown to reduce the risk of blindness in RCTs*

Real world evidence shows patients lose vision over time due to a treatment burden of current anti-VEGF injections

2

The societal cost of blindness is significant

Treatment strategies that mitigate the social and economic impact of blindness are urgently needed

3

Sustained treatment strategies that close the gap between RCTs and real world outcomes are needed

Single interventions that can provide long-lasting treatment outcomes would be ideal

**Randomized Controlled Trials*

Changing retinal landscape and implications for future therapies

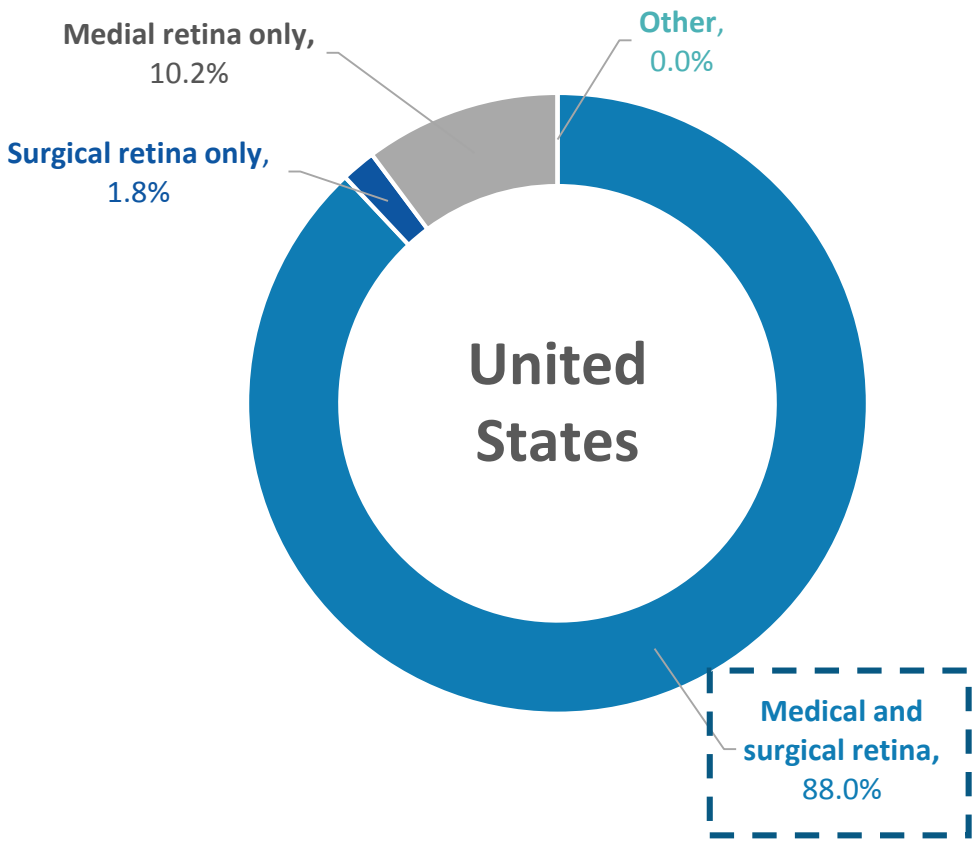
Pravin U. Dugel, MD

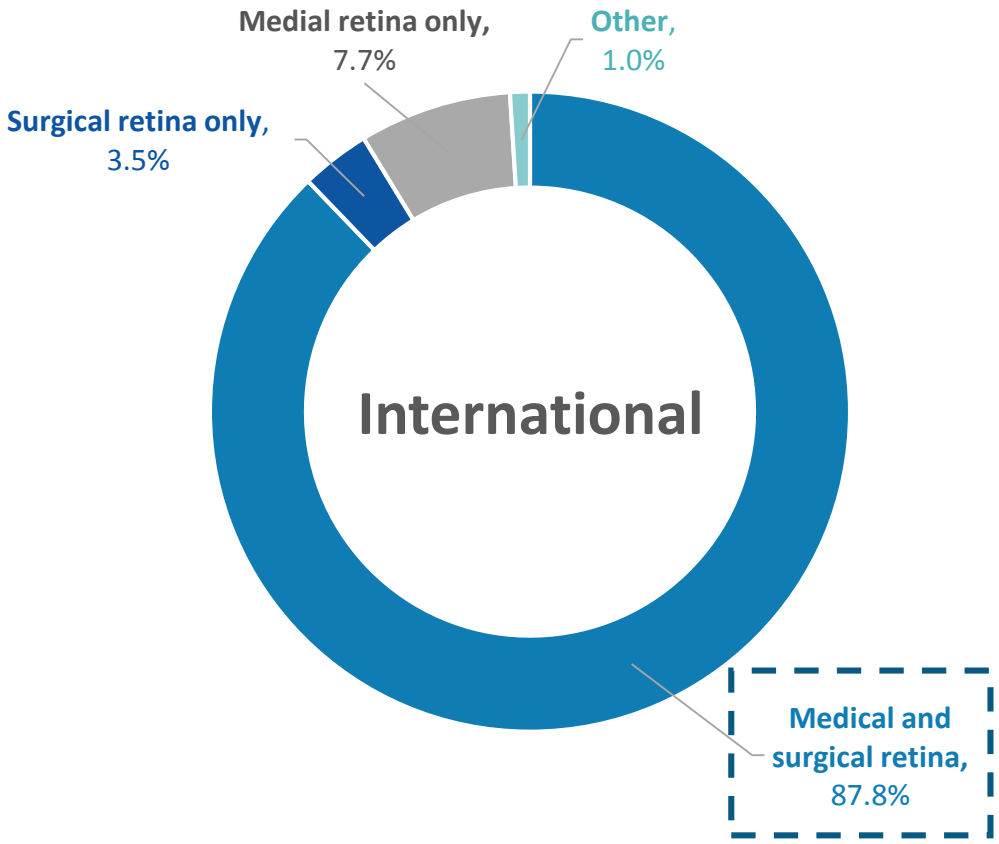
FINANCIAL DISCLOSURES

- Bausch + Lomb Pharma
- ORA
- Omeros
- Alcon Surgical (RACII)
- Santen Inc
- Clearside Biomedical
- Shire Human Genetics
- Genentech
- Allergan
- Avalanche
- Opthea
- Alcon Surgical
- Ophthotech
- TrueVision
- Graybug Vision
- Alcon Pharmaceutical (C)
- Lux BioScience
- Orbis International
- CDR-Life Inc
- NeoVista
- Digisight
- Lutronic
- Irenix
- MacuSight
- Roche
- Alimera Sciences
- ByeOnics
- Novartis (C)
- Acucela
- Neurotech
- PanOptica
- ArcticDX
- TopCon
- Optovue
- Chengdu Kanghong Biotechnology
- AMO
- Stealth Biotherapeutics
- Aerpio
- SciFluor Life Sciences
- Thrombogenics
- Pentavision
- DOSE Medical
- Annidis

THE MAJORITY OF RETINA SPECIALISTS ARE TRAINED TO DO SURGERIES…

Are you a medical retina specialist, a surgical retina specialist, or both?





ASRS American Society of Retina Specialists

Stone TW, ed. *ASRS 2018 Preferences and Trends Membership Survey*. Chicago, IL. American Society of Retina Specialists; 2018.

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… BUT THIS IS THE CURRENT STATUS OF RETINAL PRACTICE

PRINCIPLES OF ACTIVITY BASED COSTING (ABC)

1. Identify main activities
   - Profit/loss centers
2. Assign time and resource values to each activity
3. Determine total $ and per unit costs for each activity

Total Practice Profit/Loss, $

ABC's for two distinct practice types calculated:

Large Single Specialty Retina Practice
- (Retinal Consultants of Arizona)

#1 Ranked University Practice in Ophthalmology
- (Bascom Palmer Eye Institute, Miami)

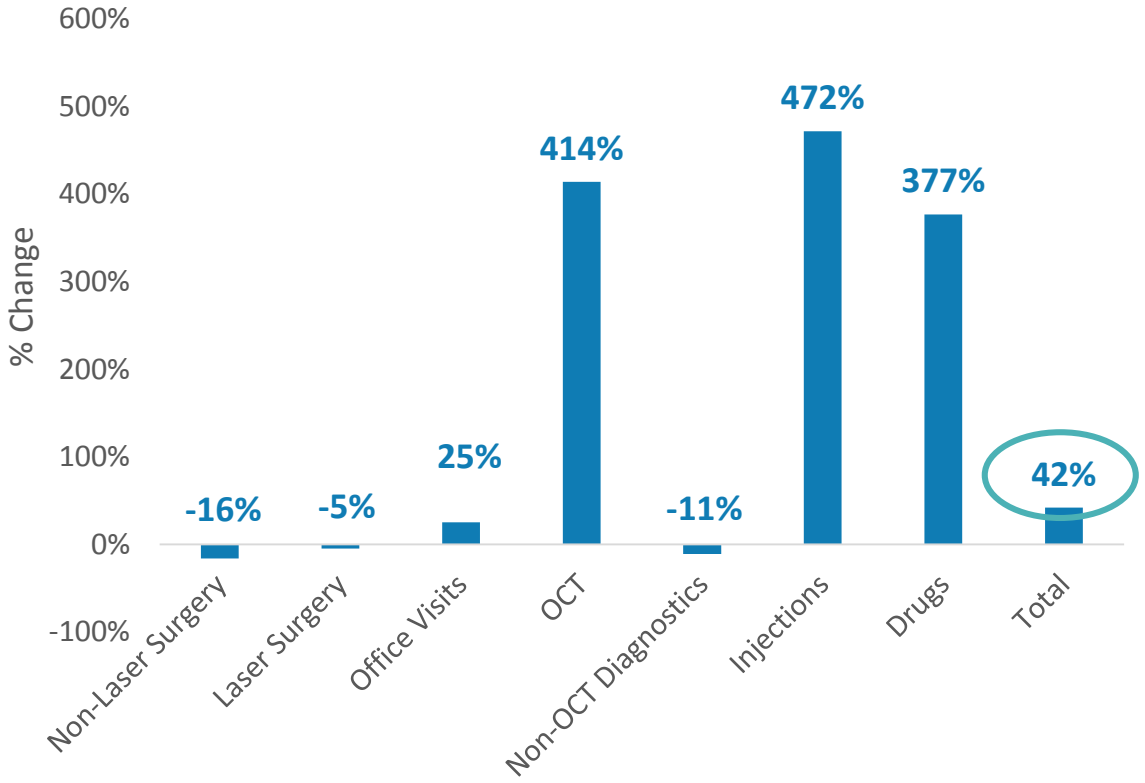
Seven service centers analyzed:

1. Non-laser surgery (SB, PPV, PR)
2. Laser surgery (Thermal, PDT)
3. Office visits
4. OCT
5. Non-OCT diagnostic (FA, ICG, ULS, VF)
6. Injections
7. Drugs

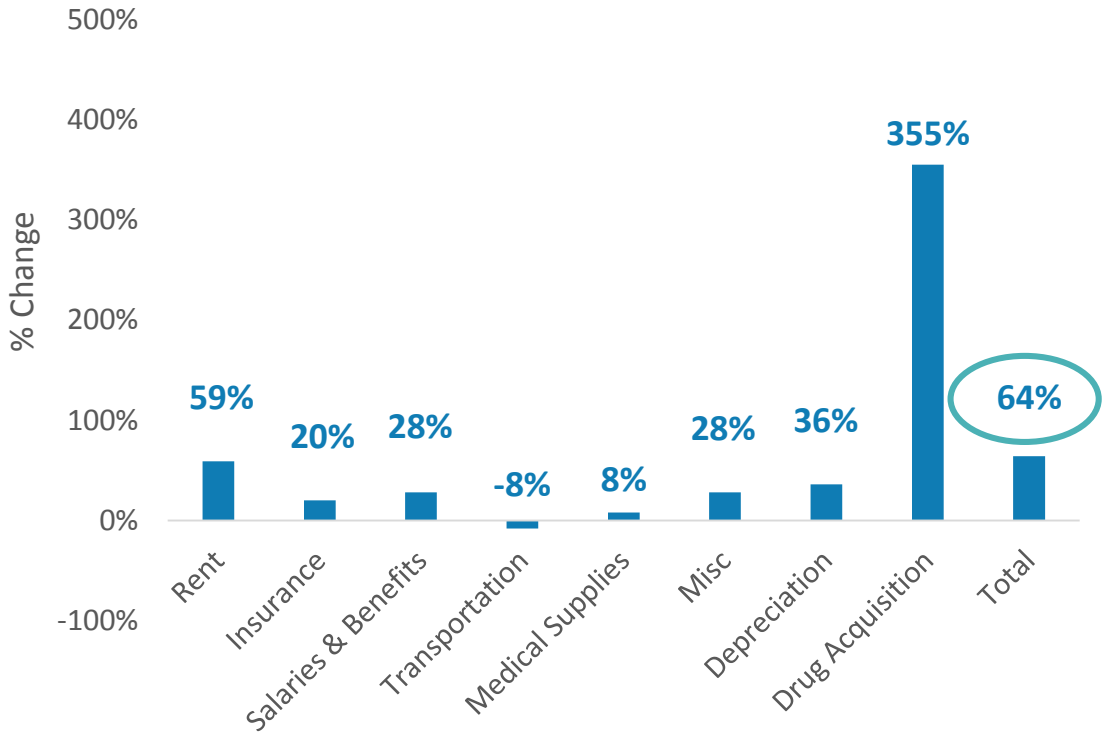
Source: Pravin U. Dugel and Kuo Bianchini Tong. Development of an Activity-based Costing Model to Evaluate Physician office Practice Profitability. Ophthalmology, 2011; Clinical Ophthalmology 2011:5 913–925. © 2011 Murray et al, publisher and licensee Dove Medical Press Ltd

THE RISE OF INTRAVITREAL INJECTIONS INCREASED REVENUE AND OPERATING COSTS

Change in collections by service



Increase in Operating Costs



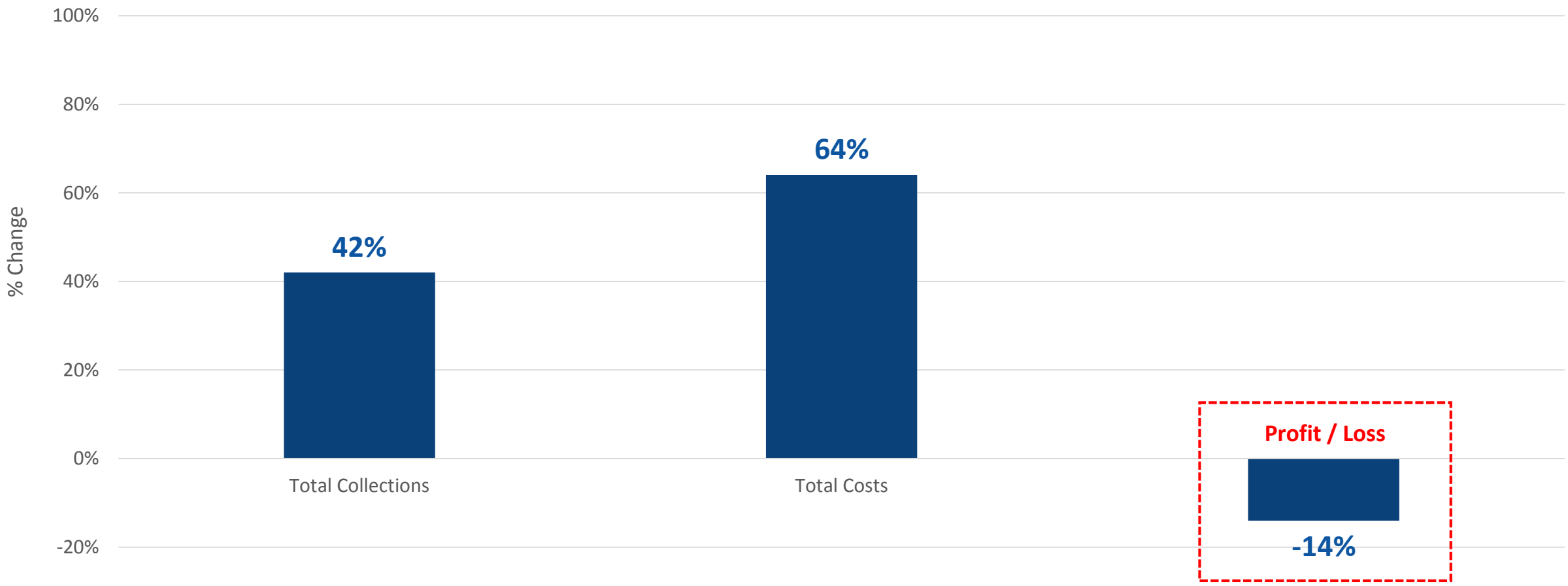
Intravitreal injections to treat wet AMD led to **increases in revenues** from injections, drugs and monitoring

Surgical revenues **decreased** over the same period

Operating costs, related to drugs, **increased more than revenues**

Source: Pravin U. Dugel and Kuo Bianchini Tong. Development of an Activity-based Costing Model to Evaluate Physician office Practice Profitability. Ophthalmology, 2011.

TOTAL PRACTICE PROFIT MARGIN COMPARISON

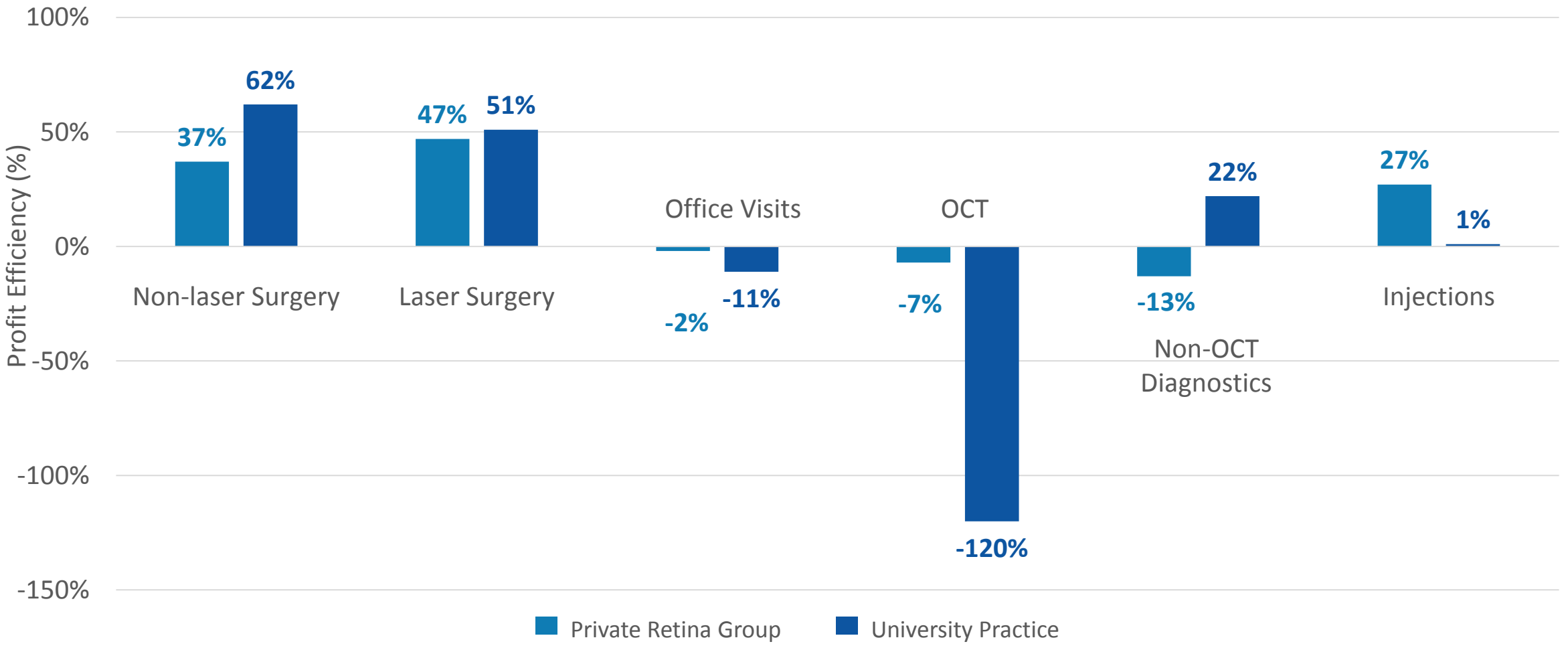


Despite a large increase in revenues, the practice has seen a 14% decline in profit margin

Source: Pravin U. Dugel and Kuo Bianchini Tong. Development of an Activity-based Costing Model to Evaluate Physician office Practice Profitability. Ophthalmology, 2011.

PRACTICE EFFICIENCY STUDY GROUP RESULTS

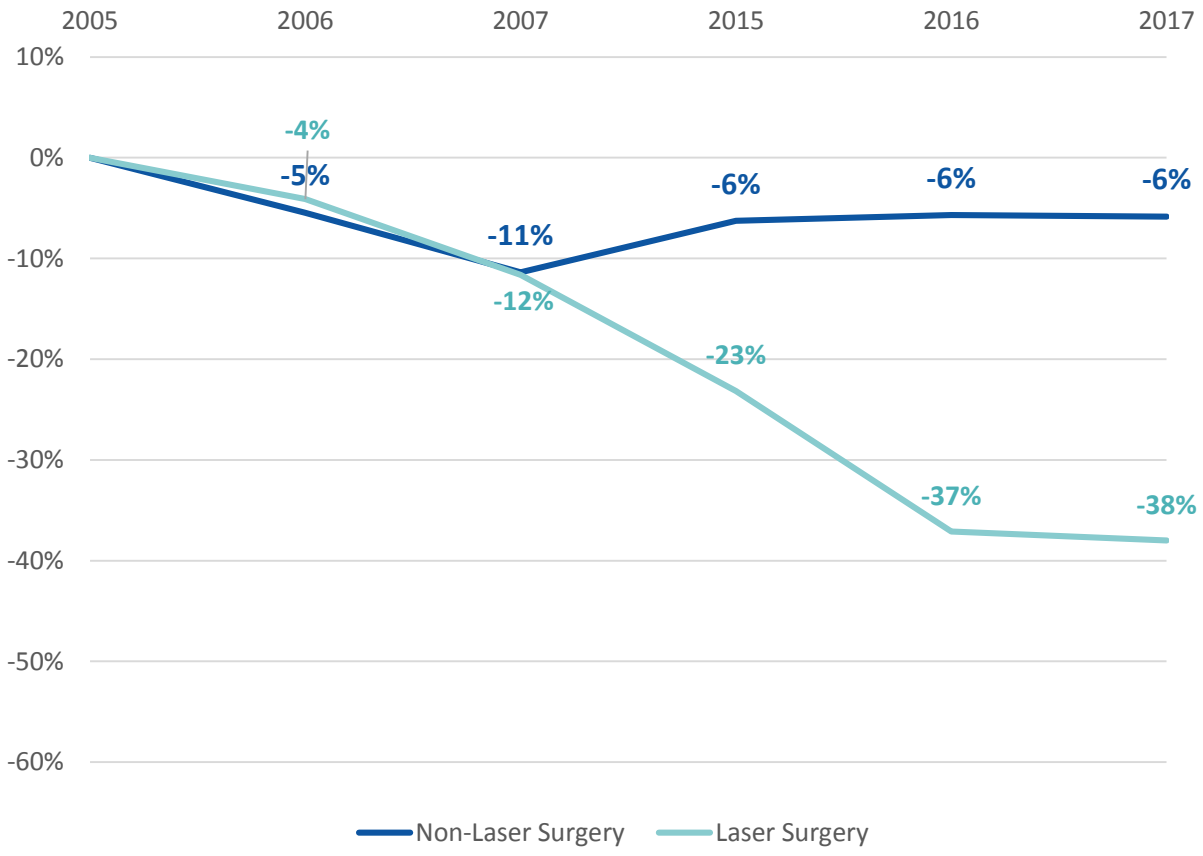
Efficiency – Profit Margin Across Services (Profit divided by revenue)



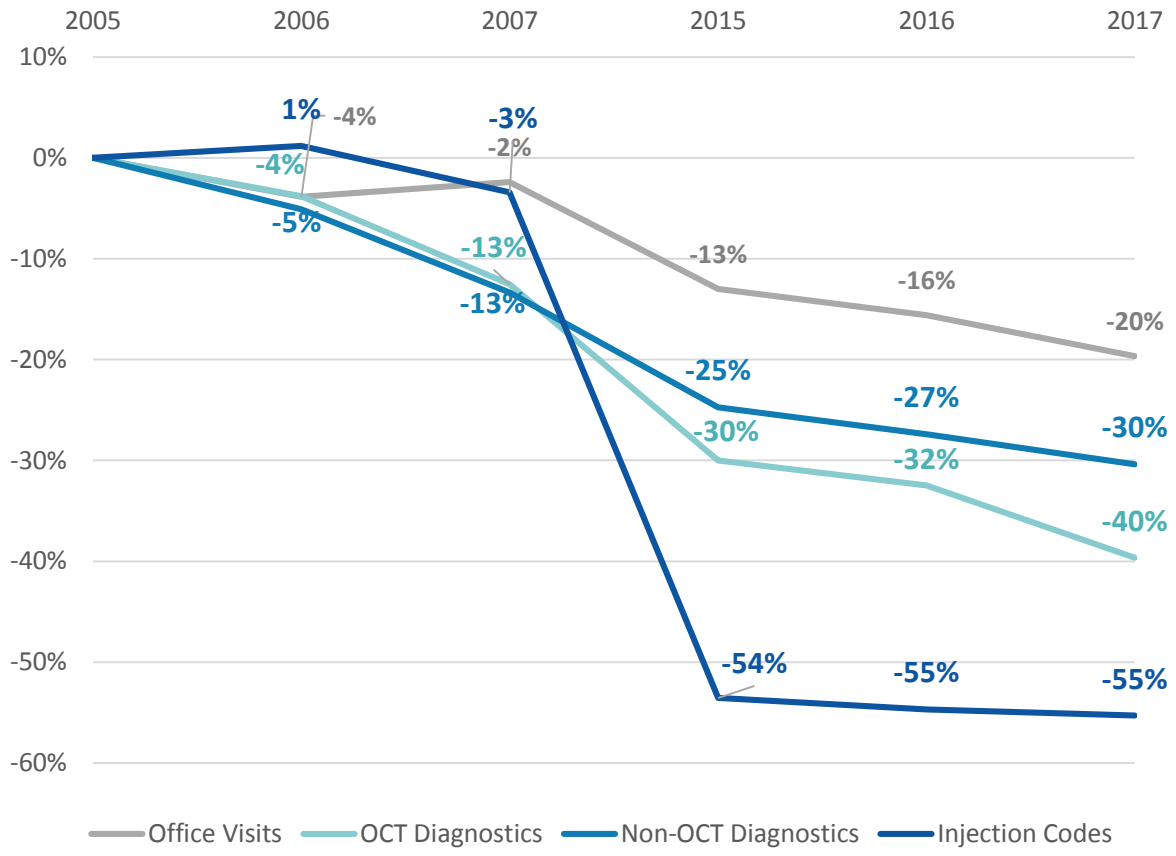
Source: Pravin U. Dugel and Kuo Bianchini Tong. Development of an Activity-based Costing Model to Evaluate Physician office Practice Profitability. Ophthalmology, 2011. Angiogenesis 2009; Clinical Ophthalmology 2011:5 913–925.

PERCENT CHANGE IN RETINA PHYSICIAN REIMBURSEMENT

Percent Change in Reimbursement (2005-2017) (Ophthalmic Surgery)



Percent Change in Reimbursement (2005-2017) (Office-based procedures and diagnostics)

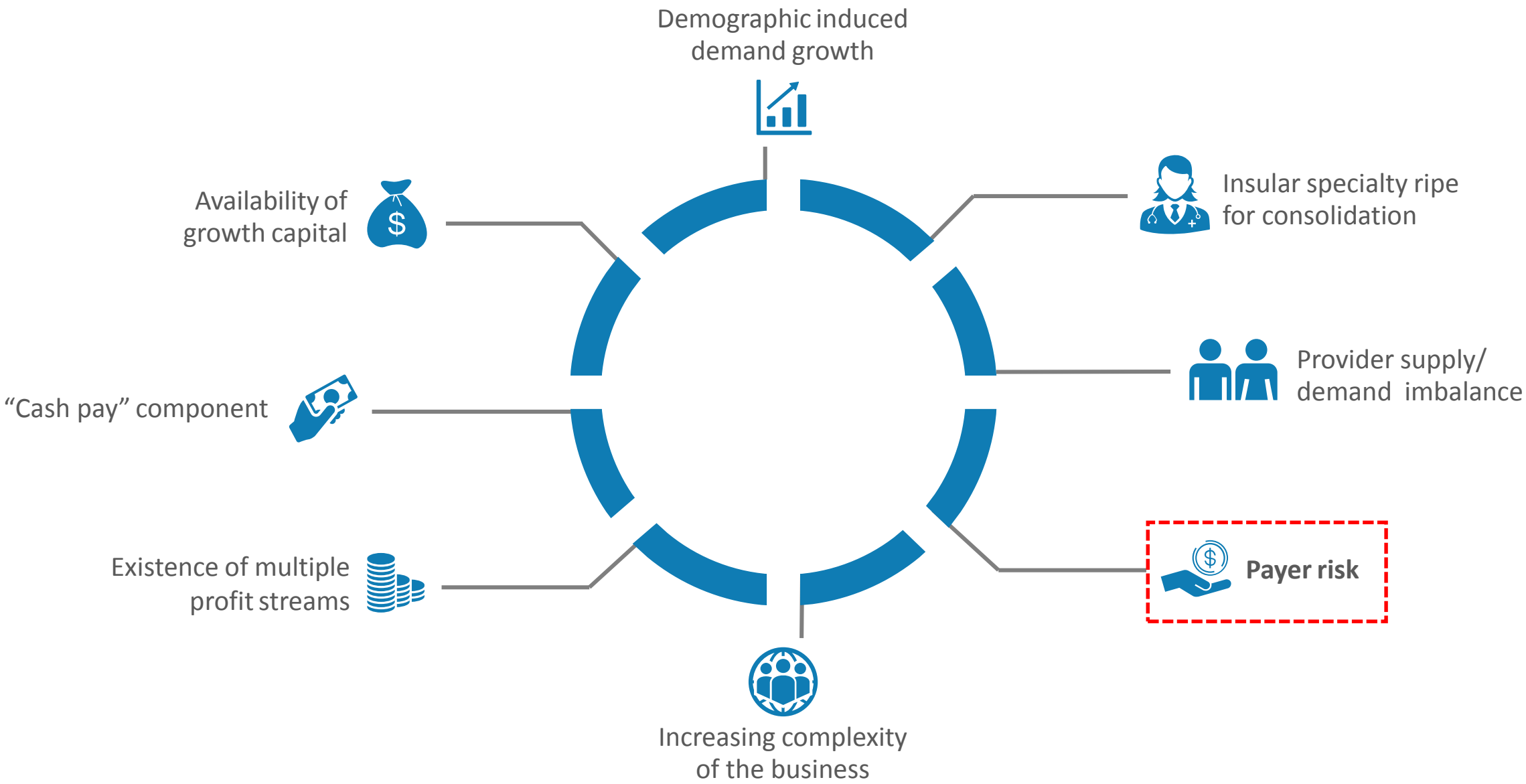


*2005 – 2007, 2015 – 2017 Physician Supplier Procedure Summary Data; 2005 – 2007, 2015 – 2017 Medicare ASC Facility Fee Schedule Amount
Dollars adjusted to 2017 US dollars using Bureau of Labor Statistics, medical services consumer price index

FUTURE TRENDS INFLUENCING CONSOLIDATION OF OPHTHALMIC CARE

- Increased reimbursement for surgery and ASCs
- Explosion of baby boomer senior population
- Relative shortage of physicians
- Increasing population with diabetes
- New surgical treatments for AMD, dystrophies, damaged retinal tissue
  - Gene therapy
  - Implantable devices and prosthesis
  - Stem cell therapy
- Reimbursement pressures and escalating malpractice premiums
- Large capital need for investment into back office functions

OPHTHALMIC CARE CONSOLIDATION DRIVERS



INCREASING NUMBER OF PRIVATE EQUITY LED TRANSACTIONS IN OPHTHALMOLOGY

Original Transaction Date	PE Firm(s)	MSO (if known)	Affiliated Practices**		States Located
1/1/2011	Candescent Partners; Sold Claris Vision to Undisclosed Strategic Acquirer 5/31/18	Claris Vision	Koch Eye Associates Eye Health Vision Centers	Southcoast Eye Care Seacoast Eye Associates	RI, MA
2014	Audax Private Equity, Charlesbank, Caisse de dépôt et placement du Québec, and Others	Vision Group Holdings	The LASIK Vision Institute TLC Laser Eye Centers Cataract Vision Institute QualSight LASIK Hale Vision Laser & Implant Center Advanced Laser & Cataract Center	Global Laser Vision Atlantic Eye Whiting Clinic LASIK + Eye Care Gordon Schanzlin New Vision Institute Global Eye & Laser Center Ken Moadel, M.D., New York Eye Specialists	AL, AZ, AR, CA, CO, CT,FL, GA, IL, IN, IA, KS, KY, LA, HI, MD, MA, MN, MI, MO, MS, MT, NE, NV, NJ, NM, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, UT, VA, WA, WA DC, WI,
5/12/2014	Varsity Healthcare Partners Sold MSO to Harvest Partners in May of 2017	EyeCare Services Partners	Katzen Eye Group Dulaney Eye Institute Delaware Eye Care Center Inland Eye Specialists Omni Eye Specialists (Denver) Spivak Vision Center Colorado Eye Center Milauskas Eye Institute Chicagoland Retinal Consultants Hauser-Ross Eye Institute	Lakeside Eye Group Delaware Eye Institute Eye Doctors of Washington Yavitz Eye Center Florida Vision Institute Smith-Perry Eye Center National Retina Institute Shasta Eye Medical Group EyeLux Optometry VZN Eye Care	MD, DE, CA, CO, IL, WADC, VA,
12/15/2016	Cortec Group	EVP EyeCare	ICON Eyecare Kleiman Evangelista Eye Center	Swagel-Wootton Hiatt Eye Center (Added 07/2017)	CO, TX, AZ
01/2017	Comvest Partners (Direct Investment)***	Acuity Eye Group *May be a DBA of Trilogy Eye Medical Group Inc.*	Acuity Eye Group Retina Institute Glendale Eye Medical Group Precision Eye Care Eye Associates of San Diego Grossmont Eye Center	West Coast Eye Care Trinity Surgical Solutions	
02/2017	Shore Capital	EyeSouth Partners	Georgia Eye Partners Georgia Retina		
02/07/2017	Waud Capital Partners	Unifeye Vision Partners	Minnesota Eye Consultants		

Original Transaction Date	PE Firm(s)	MSO (if known)	Affiliated Practices**		States Located
2/23/2017	Sterling Partners	Great Lakes Management Services Organization / Blue Sky Vision	Grand Rapids Ophthalmology Shoreline Vision (Added Later)	Vitro-Retinal Associates (Added Later) Michigan Optical Walker Surgical Center	MI
2/27/2017	FlexPoint Ford	SouthEast Eye Specialists	Eye Surgery Center of Chattanooga, LLC Pediatric Eye Specialists	The Retina Center SouthEast Eye Surgery Center	TN, GA
4/17/17	HIG Capital	American Vision Partners	Barnet Dulaney Perkins Eye Center Southwestern Eye Center	Miles Eye Center	AZ
7/6/2017	New Mainstream Capital	OMNI Ophthalmic Management Consultants (OOMC)	Omni Eye Services Phillips Eye Center (Added January of 2018)	Kremer Eye Center (Added April of 2018)	NJ, PA, DE
7/24/17	Centre Partners	Chesapeake Eye Care Company; Formed One Vision Eye Partners in Jan 2018	Whitten Laser Eye Chesapeake Eye Care and Laser Center	Arlington Eye Center (Added Later) Maryland "Vision Institute (Added March 2018)	MD, VA, WV
11/17/17	Blue Sea Capital	Spectrum Vision Partners	Ophthalmic Consultants of Long Island New Vision Cataract Center (Added Later)	Ophthalmic Consultants of Connecticut (Added Later) Huntington Eye Care	NY, CT
2/20/2018	Gauge Capital	Comprehensive EyeCare Partners ("CompEye" originally formed in 2016)	Nevada Eye Physicians New Eyes of Southern Nevada	Shepherd Eye Center	NV
3/21/18	LLR Partners	Eye Health America	Clemson Eye	The Eye Associates	SC, FL
5/23/2018	Firmament Group (formerly McLary Capital Partners)	Vision Integrated Partners (VIP)	Practice Names Not Disclosed. Referred to as "The Founding Practices."		CA, FL
5/24/2018	Revelstoke Capital Partners	CEI Vision Partners (CEIVP)	Cincinnati Eye Institute		OH, KY, IN
2018	Undisclosed Investor	Seemingly Unannounced	Boston Eye Group The Eye & LASIK Center	Eye Care Specialists	MA, NH, RI
2018	Zenyth Partners	ReFocus Eye Health	Newly formed; no acquisitions announced		

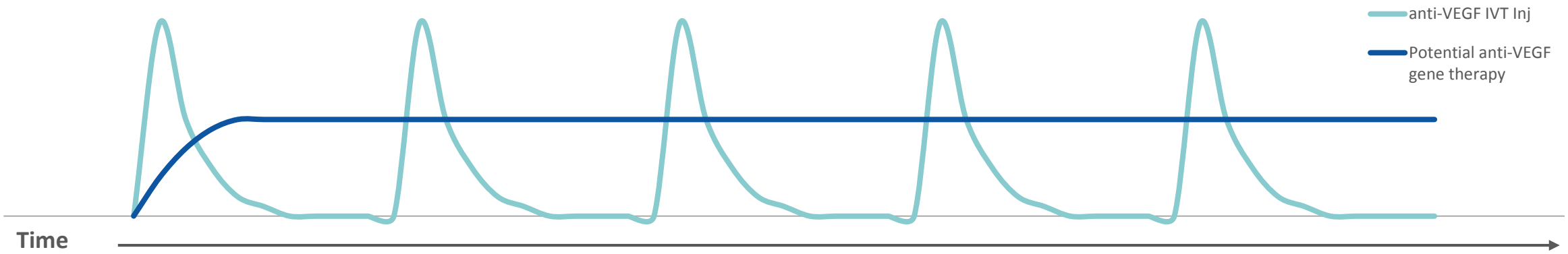
CONSOLIDATED OPHTHALMOLOGY PRACTICES

- Comprehensive EyeCare Partners
- Spectrum Vision Partners
- Blue Sky Vision
- Eye Health America
- American Vision Partners
- EVP EyeCare
- CEI Vision Partners
- Unifeye Vision Partners (UVP)
- OMNI Ophthalmic Management Consultants
- EyeCare Services Partners (ESP)
- Century Vision Global (Formerly Claris Vision)
- One Vision Eye Partners
- Eye South Partners
- Acuity Eye Group
- SouthEast Eye Specialists
- Unannounced
- Vision Integrated Partners *(Unknown locations throughout Florida and California)*
- Vision Group Holdings *(LASIK: 1,000+ affiliate locations across est. 42 states)*

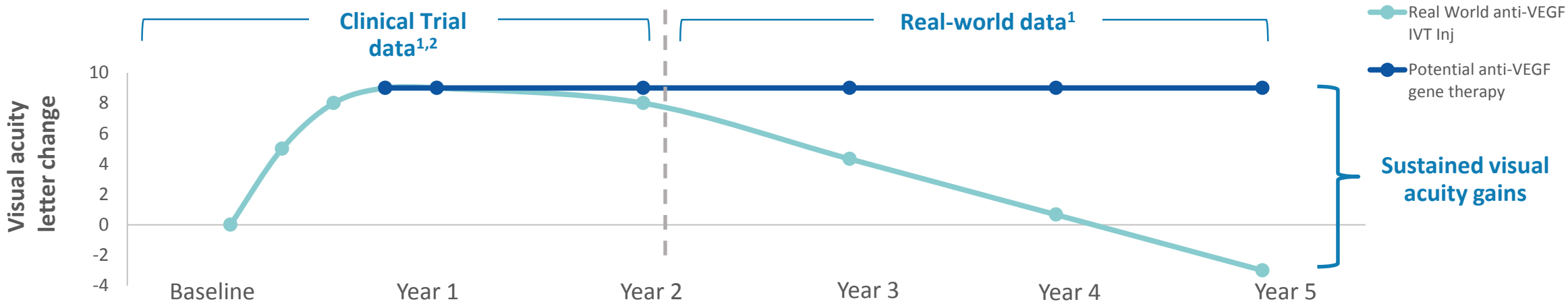
Source: BSM Consulting.
Note: Map may not include all ophthalmology practices. Location markers indicate presence in a given city, but may not represent number of physical locations in that city.

GENE THERAPY HAS THE POTENTIAL TO PROVIDE FOUNDATIONAL ANTI-VEGF THERAPY THAT MAY SUSTAIN VISON GAINS AND PREVENT BLINDNESS WITH A SINGLE TREATMENT

Anti-VEGF Exposure (Illustrative)



Visual Acuity



1. CATT Research Group, Martin DF, Maguire MG, et al., Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011;364:1897–908.
2. Ho AC et al., HARBOR Study 2-Year Results. Ophthalmology 2014.

IMPLICATIONS FOR LONG-LASTING THERAPIES IN CONSOLIDATED PRACTICES

1

Highly profitable procedures that offer long term solutions to patients will be prioritized due to costly at-risk contracts

Potential to offer significant value proposition to all patients responsive to anti-VEGF therapy

2

Centrally managed patient referrals to facilitate immediate access to treatments with durable outcomes

Faster switch to durable surgical solutions for patients responsive to IVT anti-VEGF

3

Consolidation will solve individual physician reimbursement pressures

Ensure risk-free access to value-based treatments

GENE THERAPY IS A POTENTIAL SOLUTION TO THE CURRENT BURDEN OF CARE…

Facts about vitrectomies and subretinal delivery

Allen C. Ho, MD

FINANCIAL DISCLOSURES

Aerpio (C)

AGTC (G)

Alcon (C, G)

Allergan (C, G)

Apellis (G)

Asclepix (C)

Beaver EndoOptiks (C)

BioTime (C)

Covalent (O)

DigiSight (C, O)

Eloxx (C)

Genentech (C, G)

Iconic (G)

Iridex (C, G)

Janssen (C, G)

NEI/NIH (G)

Notal (C)

ONL (C, O)

Ophthotech (C, G)

Optovue (C)

Orbit Biomedical (C)

PanOptica (C, G)

PRN (C, O)

ProQR (C, G)

Regeneron (C, G, O)

RegenxBio (C, G)

Sanofi (C, G)

Second Sight (C, G)

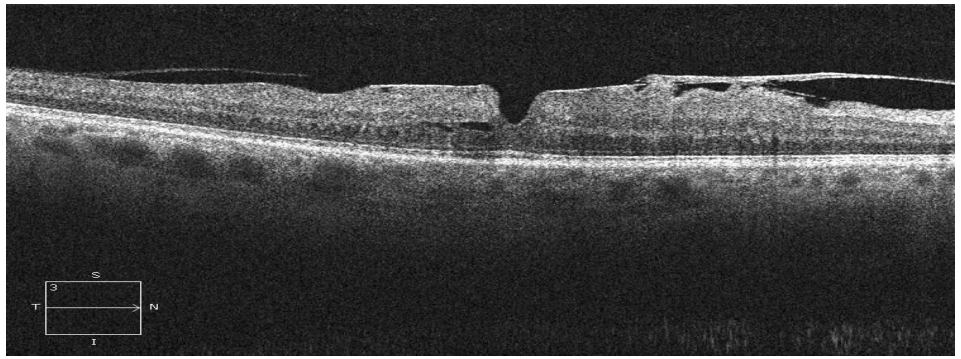
OVER 500,000 VITRECTOMIES PERFORMED ANNUALLY ON MEDICARE PATIENTS ALONE

Rank	ICD-10 Diagnosis Code/Description		Est. No. of vitrectomies	Est. No. of unique vitrectomy patients
1	H353x	Degeneration of macula and posterior pole (macular pucker)	259,340	210,125
2	H431x	Vitreous hemorrhage	73,141	58,637
3	H433x	Other vitreous opacities	35,207	28,637
4	E113x	Type 2 diabetes mellitus with ophthalmic complications	21,942	17,479
5	H590x	Disorders of the eye following cataract surgery	17,108	14,380
6	H438x	Other disorders of vitreous body	14,876	12,893
7	H330x	Retinal detachment with retinal break	12,521	10,041
8	H440x	Purulent endophthalmitis	11,653	9,050
9	H271x	Dislocation of lens	9,793	8,058
10	T852x	Mechanical complication of intraocular lens	9,793	8,182
ALL OTHER DIAGNOSES COMBINED			**48,967**	**39,918**
ALL DIAGNOSES			**514,342**	**417,399***

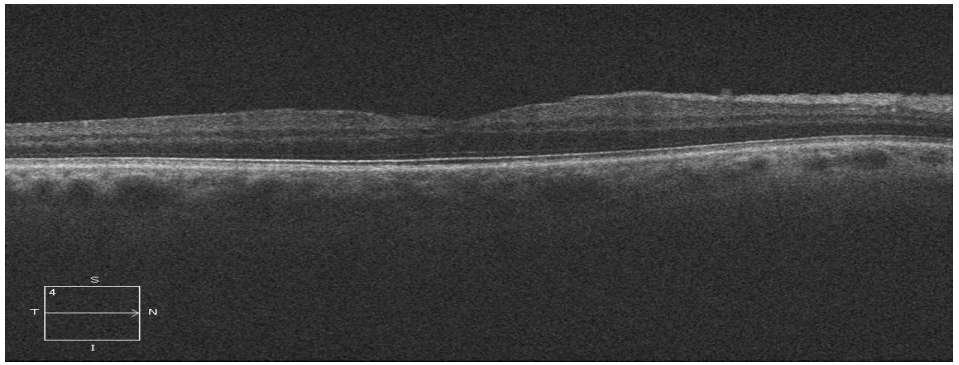
Source: CMS database, 2017
*2017 Standard Analytic Fails, adjusted for Medicare Advantage enrollment (Medicare Enrollment Dashboard) and payer mix (Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality) .
*Not corrected for double counting of patients with multiple diagnoses.

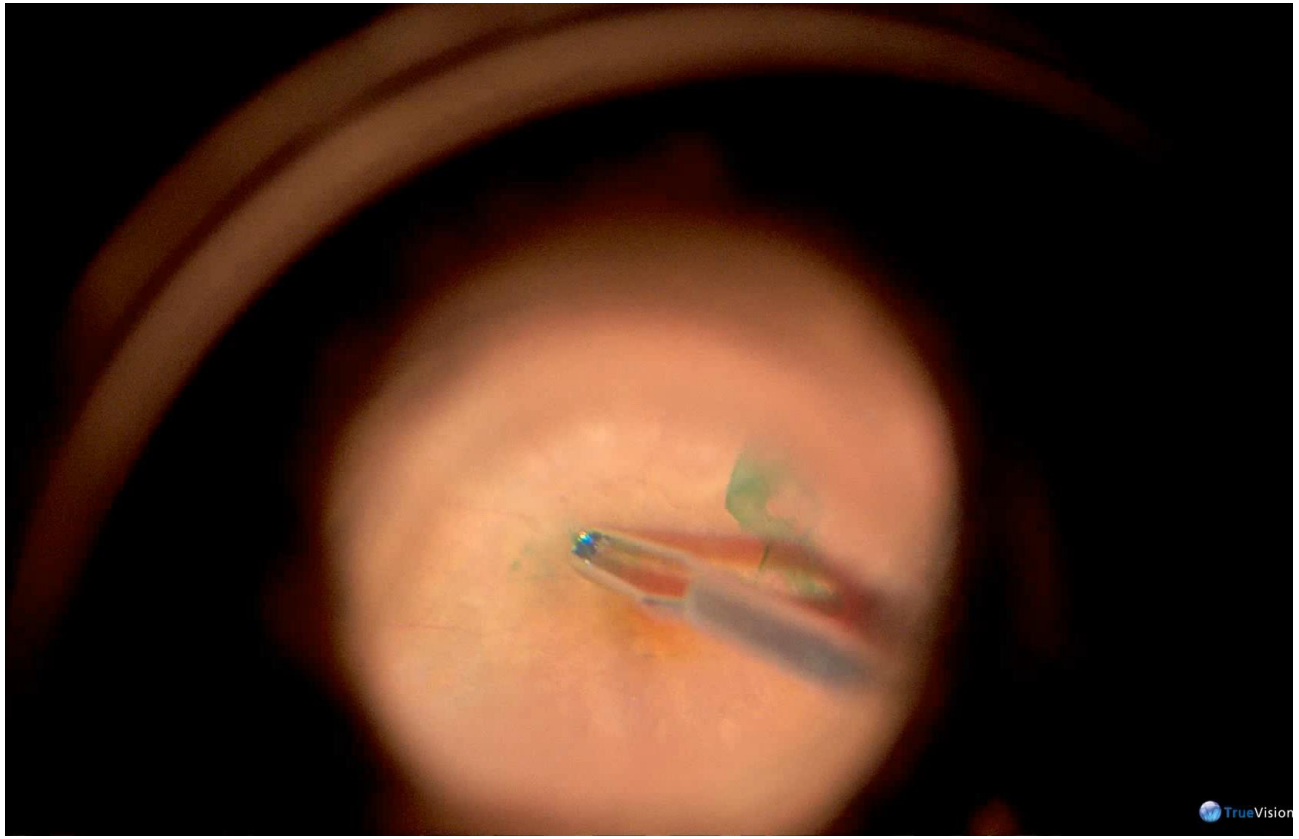
ERM PEELING IS A DELICATE SURGICAL PROCEDURE PERFORMED BY ALL RETINAL SURGEONS

Preoperative (20/50)



Postoperative at 6 months (20/25)



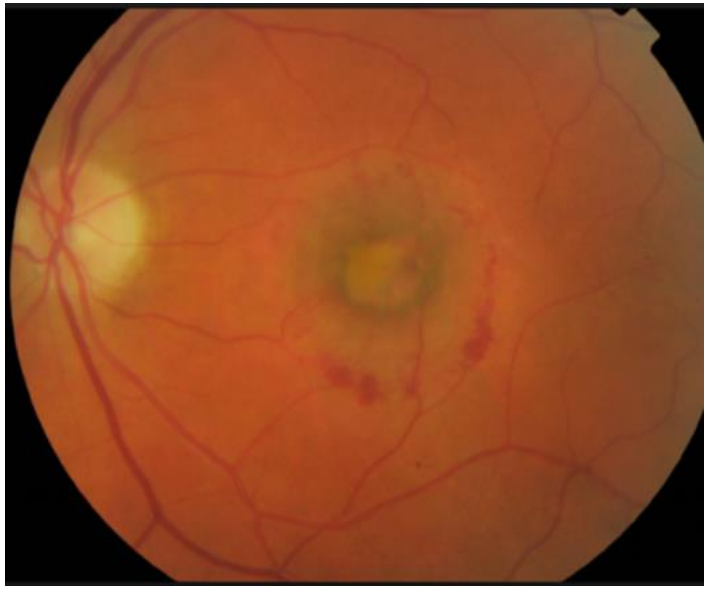


Vitrectomy and delicate membrane peeling from the surface of the macula and fovea

*Courtesy of Allen Ho, MD at Wills Eye Hospital; ERM = epiretinal membrane

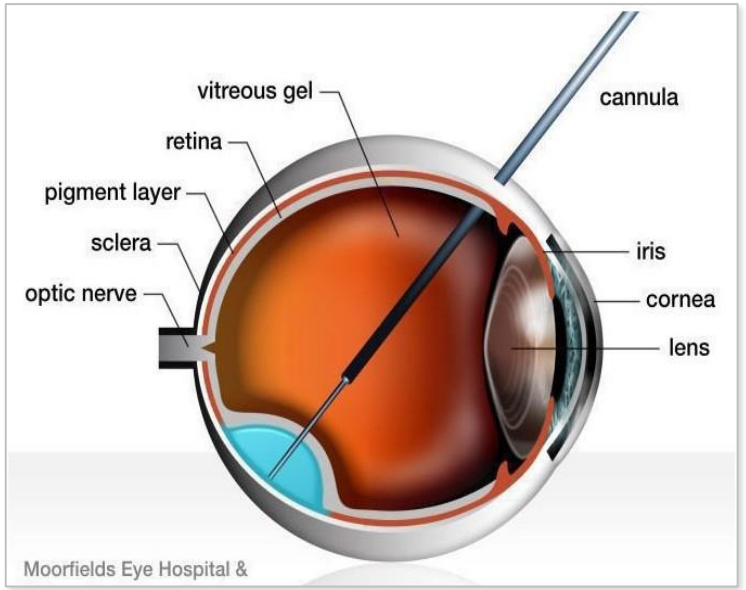
WET AGE RELATED MACULAR DEGENERATION

wet AMD



Fundus photography

Subretinal approach



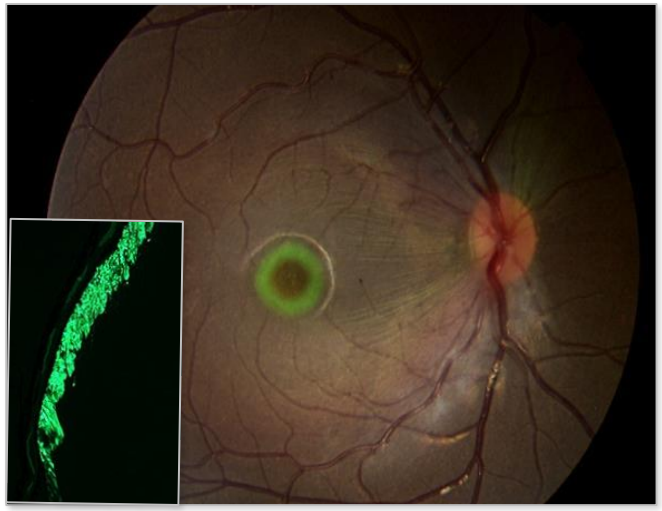
Subretinal, Intravitreal, Choroidal

Source: Moorfields Eye Hospital & University College London

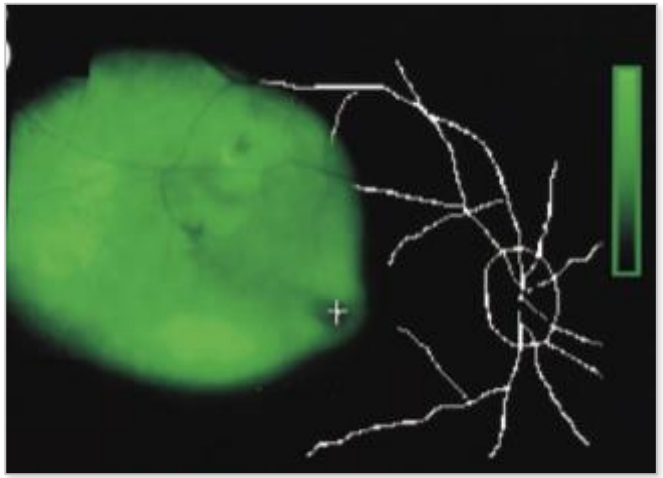
Courtesy of Allen Ho, MD at Wills Eye Hospital

EXPRESSION FOLLOWING SUBRETINAL VS. INTRAVITREAL GENE THERAPY WITH AAV

Intravitreal



Subretinal



Proc. Natl. Acad. Sci. USA
Vol. 96, pp. 9920–9925, August 1999
Neurobiology

Stable transgene expression in rod photoreceptors after recombinant adeno-associated virus-mediated gene transfer to monkey retina

JEAN BENNETT*†‡, ALBERT M. MAGUIRE*, ARTUR V. CIDECIYAN*, MICHAEL SCHNELL†§, ERNEST GLOVER†, VIBHA ANAND*, TOMAS S. ALEMAN*, NARENDRA CHIRMULE†§, ABHA R. GUPTA*, YIJUN HUANG*, GUANG-PING GAO†, WILLIAM C. NYBERG*, JOHN TAZELAAR†, JOSEPH HUGHES†, JAMES M. WILSON†§, AND SAMUEL G. JACOBSON*

*Department of Ophthalmology, F. M. Kirby Center for Molecular Ophthalmology, Scheie Eye Institute, University of Pennsylvania, 51 North 39th Street, Philadelphia, PA 19104; and †Institute for Human Gene Therapy and §Department of Cellular and Molecular Engineering, University of Pennsylvania, 204 Wistar, Philadelphia, PA 19104

Edited by Jeremy Nathans, Johns Hopkins University School of Medicine, Baltimore, MD, and approved June 22, 1999 (received for review May 10, 1999)

ABSTRACT **Recombinant adeno-associated virus (rAAV) is a promising vector for therapy of retinal degenerative diseases. We evaluated the efficiency, cellular specificity, and safety of retinal cell transduction in nonhuman primates after subretinal delivery of an rAAV carrying a cDNA encoding green fluorescent protein (EGFP), rAAV.CMV.*EGFP*. The treatment results in efficient and stable *EGFP* expression lasting >1 year. Transgene expression in the neural retina is limited exclusively to rod photoreceptors. There is neither electroretinographic nor histologic evidence of photoreceptor toxicity. Despite significant serum antibody responses to the vector, subretinal readministration results in additional transduction events. The findings further characterize the retinal cell tropism of rAAV. They also support the development of studies aimed ultimately at treating inherited retinal degeneration by using rAAV-mediated gene therapy.**

Retinal degenerative diseases are the most common human inherited eye disorders causing blindness. This broad group of diseases includes age-related macular degeneration, affecting 1 in every 10 people over the age of 60, retinitis pigmentosa, which affects ≈1 in 3,000 people in all ethnic groups (1–4), and conditions that are more rare but that cause blindness in infancy or childhood (such as Leber congenital amaurosis and Stargardt disease (5, 6). Retinal degenerative diseases are costly in terms of lost work productivity, need for social support, and individual suffering. There is no treatment available for the vast majority of patients with retinal degeneration.

Progress in understanding the pathogenesis of retinal degenerative diseases has been aided by the discovery of naturally occurring animal strains with retinal degeneration and creation of genetically engineered animal models of the human diseases. Gene therapy approaches have been used successfully to treat retinitis pigmentosa-like disease in a number of these animals (7–13).

As in all gene therapy studies, a critical factor appears to be the vector. Different vectors vary in their ability to target specific cell types efficiently, their ability to deliver genes in a stable fashion, their toxicity, and their elicitation of immune response. One of the most promising vectors for gene therapy aimed at retinal degenerative disease is recombinant adeno-associated virus (rAAV). Although there is a significant time delay between exposure to this virus and onset of transgene expression, rAAV transduces photoreceptors and retinal pigment epithelium (rpe) cells efficiently and in a stable fashion (14–16).

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PNAS is available online at www.pnas.org.

One drawback of the available animal models for inherited retinal degenerations is that their ocular and retinal anatomy differ substantially from those of the human. The nonhuman primate (monkey, for example), however, possesses ocular anatomic features virtually identical to those of the human. The monkey eye is of similar size as a human eye, its components are of similar proportion, and it possesses a macula. There are two main reasons why it is important to evaluate promising gene transfer techniques in the eye of a monkey: (*i*) It is essential to demonstrate that neither the treatment nor the vector result in toxicity to this human-like retina; and (*ii*) it is important to demonstrate that the vectors under consideration for human gene therapy clinical trials deliver transgenes efficiently and in a stable fashion to human-like retina.

This report describes the ability to deliver foreign genes specifically to the retina of a primate. The procedure produces no long-term toxicity and results in transgene expression in up to 100% of the retinal rod photoreceptors at the site of administration lasting >1 year. Subretinal injection of rAAV can be repeated in the same animal to obtain additional transduction events. The results indicate that rAAV is an ideal vector for delivery of genes to rod photoreceptors and for development of gene therapy approaches for treatment of human retinal disease.

METHODS

Preparation of Virus for Injection. pAAV.CMV.*EGFP* contains the "enhanced" version of the green fluorescent protein (EGFP)-encoding cDNA (CLONTECH) driven by the immediate-early cytomegalovirus (CMV) enhancer-promoter and contains a simian virus 40 splice site donor-acceptor and polyadenylation signal. High titer virus free of replication-competent AAV was produced by using a rep-cap expressing cell line and an adenovirus (Ad)-AAV hybrid virus as described (17, 18). In brief, B-50 cells, cells that contain the p5 promoter driving expression of a rep-cap gene, were infected with Sub100r, an E2b-defective Ad5 mutant, at an MOI of 10 for 24 hr. This served to induce high levels of rep-cap expression. The cells then were infected with the Ad.rAAV.CMV.*EGFP* hybrid vector at an MOI of 10 for an additional 48 hr. The cells were harvested, and CsCl gradient purification through three successive gradients was performed to isolate and purify the rAAV. The hybrid virus, Ad.rAAV.CMV-

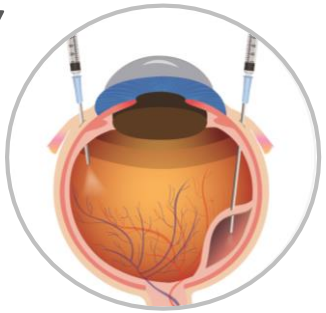
This paper was submitted directly (Track II) to the *Proceedings* office.

Abbreviations: rAAV, recombinant adeno-associated virus; EGFP, enhanced green fluorescent protein; rAAV-EGFP, rAAV carrying cytomegalovirus-driven EGFP; rpe, retinal pigment epithelium; CMV, cytomegalovirus; GCs, genome copies; ERG, electroretinogram; RT, reverse transcriptase; NAbs, neutralizing antibodies; Ad, adenovirus.

‡To whom reprint requests should be addressed at: F. M. Kirby Center; 310 Stellar-Chance Labs, 422 Curie Boulevard, University of Pennsylvania, Scheie Eye Institute, Philadelphia, PA 19104-6069. E-mail: jebennet@mail.med.upenn.edu.

Bennett, J., et al., 1999; *PNAS,* 96(17), 9920–9925.

MULTIPLE TRIALS HAVE DEMONSTRATED THE SAFETY OF SUBRETINAL DELIVERY



Choroideremia Gene Therapy Phase 2 Clinical Trial: 24-Month Results

BYRON L. LAM, JANET L. DAVIS, NINEL Z. GREGORI, ROBERT E. MACLAREN, ANIZ GIRACH,

Articles

Gene therapy with recombinant adeno-associated vectors for neovascular age-related macular degeneration: 1 year follow-up of a phase 1 randomised clinical trial

EBioMedicine

journal homepage: www.ebiomedicine.com

Research Paper

Phase 2a Randomized Clinical Trial: Safety and Post Hoc Analysis of Subretinal rAAV.sFLT-1 for Wet Age-related Macular Degeneration

RESEARCH ARTICLE

Lentiviral Vector Gene Transfer of Endostatin/Angiostatin for Macular Degeneration (GEM) Study

CHANGES IN RETINAL SENSITIVITY AFTER GENE THERAPY IN CHOROIDEREMIA

Results at 5 Years After Gene Therapy for RPE65-Deficient Retinal Dystrophy

Mark E. Pennesi,[1] Richard G. Weleber,[1] Paul Yang,[1] Chris Whitebirch,[1] Beverly Thean,[1] Terence R. Flotte,[2] Margaret Humphries,[2] Elvira Chegarnov,[1] Kathleen N. Beasley,[3] J. Timothy Stout,[4] and Jeffrey D. Chulay[3,*]

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Ophthalmology. 2016 March ; 123(3): 558–570. doi:10.1016/j.ophtha.2015.10.025.

Gene Therapy for Leber Hereditary Optic Neuropathy:

Initial Results

Articles

Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with *RPE65*-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial

Summary

nature medicine

LETTERS

Beneficial effects on vision in patients undergoing retinal gene therapy for choroideremia

Kanmin Xue[1,2], Jasleen K Jolly[1,2], Alun R. Barnard[1,2], Anna Rudenko[3], Anna P. Salvetti[1,2], Maria I. Patricio[1,2], Thomas L. Edwards[1,2], Markus Groppe[1,2], Harry O. Orlans[1,2], Tanya Tolmachova[3], Graeme C. Black[4], Andrew R. Webster[6,4], Andrew J. Lotery[7], Graham E. Holder[6,4,8], Susan M. Downes[1,2], Miguel C. Seabra[4,9] and Robert E. MacLaren[1,2,5,*]

CLINICAL PROTOCOL

Development of Methodology and Study Protocol: Safety and Efficacy of a Single Subretinal Injection of rAAV.hCNGA3 in Patients with *CNGA3*-Linked Achromatopsia Investigated in an Exploratory Dose-Escalation Trial

Nadine A. Kahle,[1,*] Tobias Peters,[1] Ditta Zobor,[1] Laura Kuehlewein,[1] Susanne Kohl,[1] Ahmad Zhour,[1] Annette Werner,[1] Immanuel P. Seitz,[1] Vithiyanjali Sothilingam,[1] Stylianos Michalakis,[2] Martin Biel,[2] Marius Ueffing,[1] Eberhart Zrenner,[1] Karl U. Bartz-Schmidt,[1] M. Dominik Fischer,[1,†] Barbara J.C. Wilhelm,[3,†] and the RD-CURE Consortium[‡]

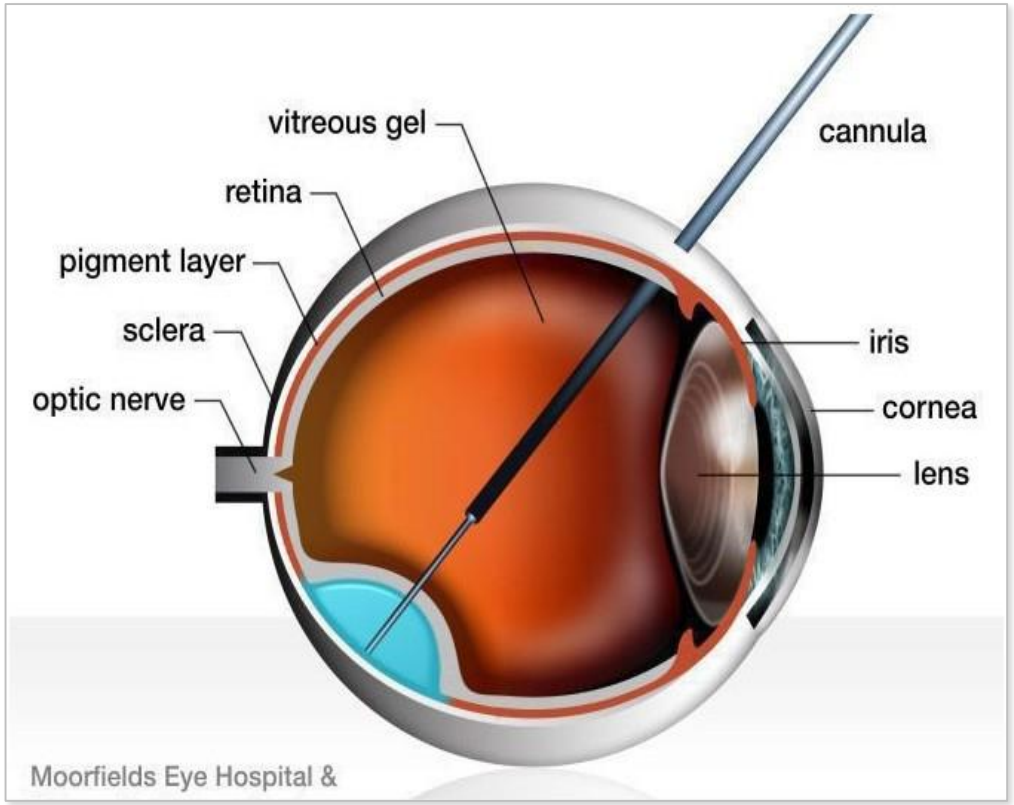
SUBRETINAL DELIVERY IS PREFERRED FOR GENE THERAPY

- **Broader retinal coverage and higher protein expression**
  - Broader transduction than intravitreal – IV only transduces cells in fovea due to ILM, which acts as a barrier[1]
  - 100 to 1,000x more efficient than intravitreal injection
- **Reduced sensitivity to neutralizing antibodies –seropositive patients can be treated with subretinal delivery**
  - Pre-existing AAV neutralizing antibodies (NAbs) may limit intravitreal gene therapy[2,3]
  - Intravitreal Nab prevalence: 30-50% for AAV8 and up to 70% for AAV2[4]
- **Procedure safety has been demonstrated in previous wet AMD trials[5,6]**
- **Bilateral administration is unaffected by prior treatment[7]**

[1] Yin L, et al. Intravitreal Injection of AAV2 Transduces Macaque Inner Retina. *IOVS* April 2011.
[2] Kotterman M, et al. Antibody Neutralization Poses a Barrier to Intravitreal Adeno-Associated Viral Vector Gene Therapy Delivery to Non-Human Primates. *Gene Therapy* April 2015.
[3] Heier JS, et al. Intravitreous injection of AAV2-sFLT01 in patients with advanced neovascular age-related macular degeneration: a phase 1, open-label trial. *Lancet* May 2016.
[4] Calcedo R, et al. Worldwide Epidemiology of Neutralizing Antibodies to Adeno-Associated Viruses. *Journal of Infectious Disease* October 2009
[5] Constable I, et al. Phase 2a Randomized Clinical Trial: Safety and Post Hoc Analysis of Subretinal rAAV.sFLT-1 for Wet Age-Related Macular Degeneration. *EBioMedicine* November 2016.
[6] Campochiaro P, et al. Lentiviral Vector Gene Transfer of Endostatin/Angiostatin for Macular Degeneration (GEM) Study. *Human Gene Therapy* 2016.
[7] Benett J et al., Safety and durability of effect of contralateral-eye administration of AAV2 gene therapy in patients with childhood-onset blindness caused by RPE65 mutations: a follow-on phase 1 trial. Lancet 2017.

RGX-314 TRANSVITREAL SUBETINAL DELIVERY

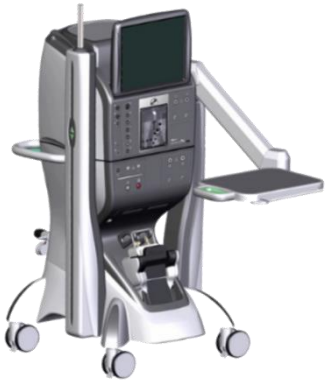
MicroDose Injection Kit Surgeon foot pedal control



Source: Moorfields Eye Hospital & University College London, MedOne Surgical, Inc.

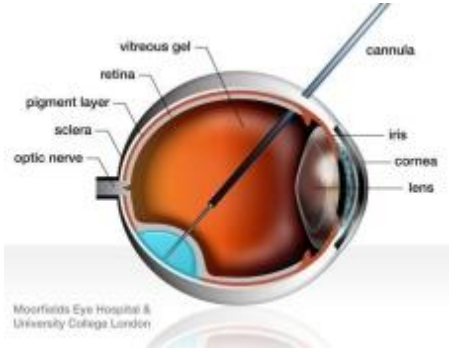
RGX-314 STANDARDIZED AUTOMATED SUBRETINAL DELIVERY PROCEDURE

Step 1 – Vitrectomy



Step 2 – Subretinal Injection

MedOne MicroDose Syringe



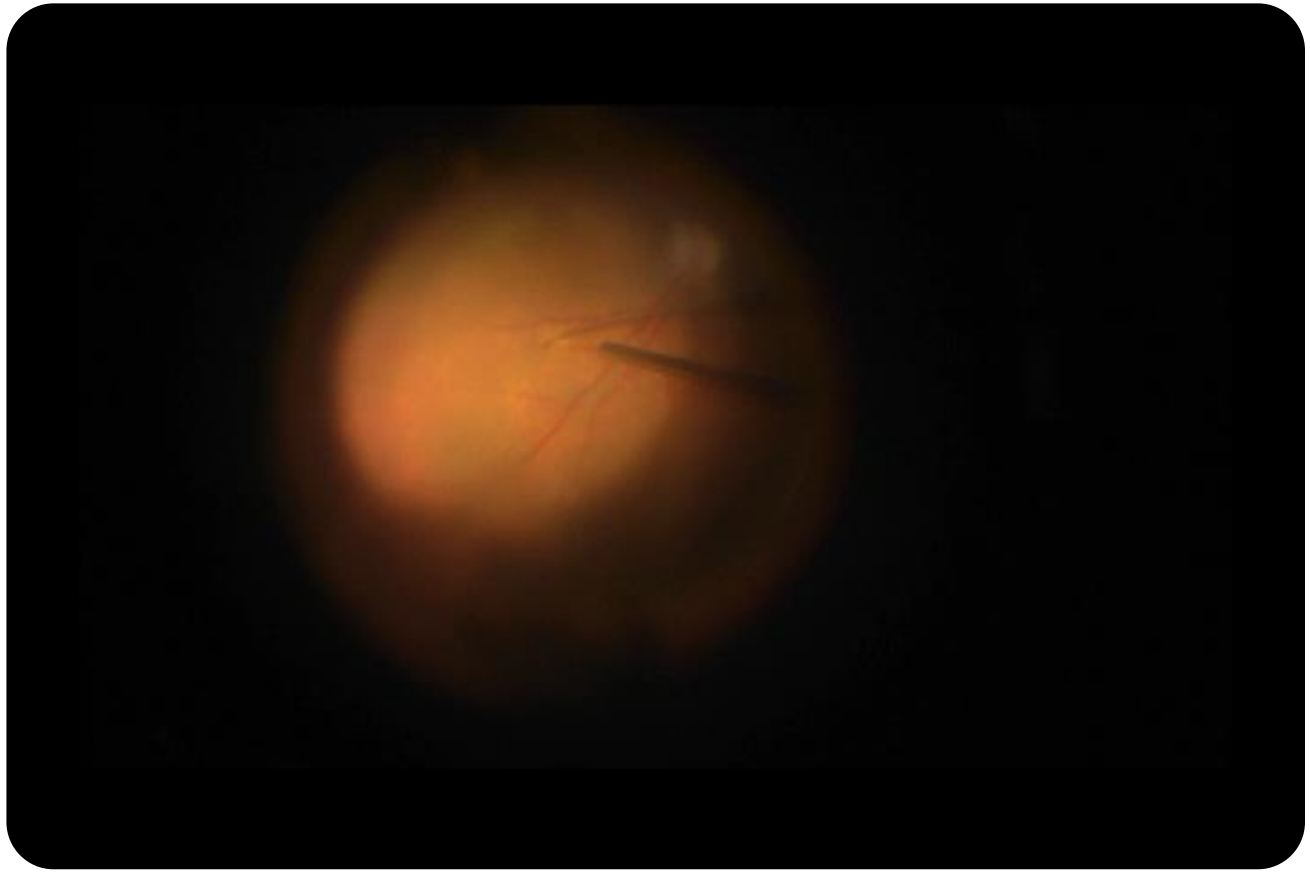
Performed Under Local Anaesthesia in the OR

Same Day Surgery - Patients go home, similar to cataract surgery

AUTOMATED SUBRETINAL INJECTION

Automated Delivery

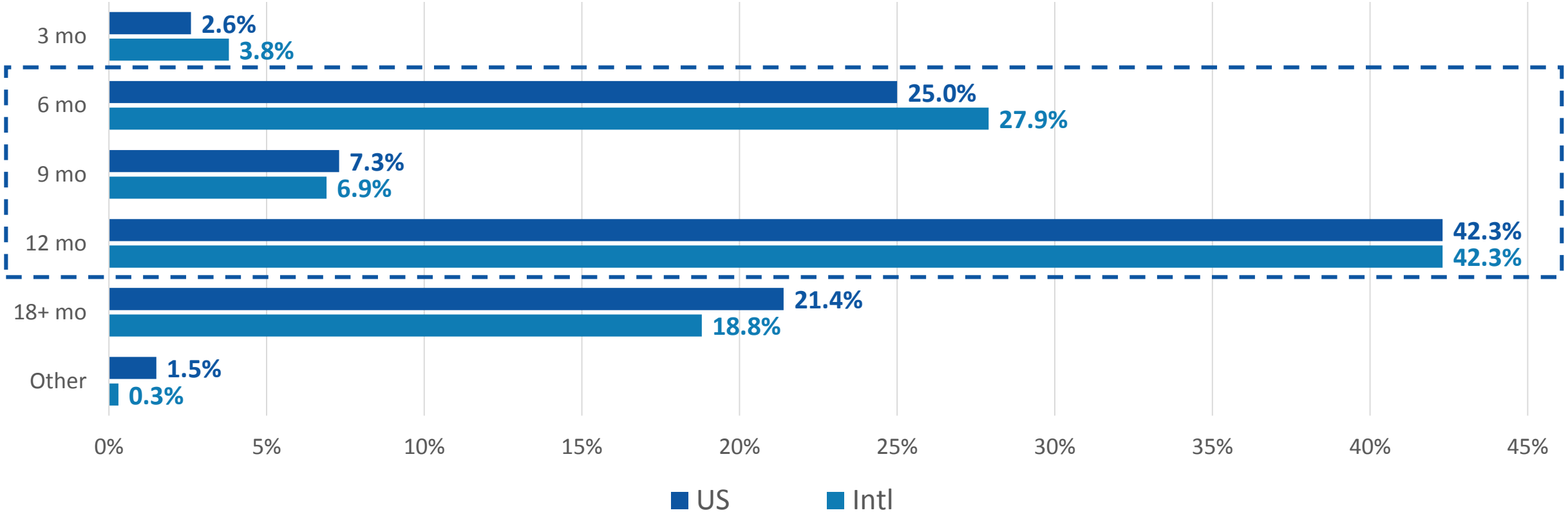
- Vitrectomy is performed
- Subretinal bleb is placed away from the macula in a healthy area of retina
- Air-fluid exchange is performed



*Courtesy of Allen Ho, MD at Wills Eye Hospital

RETINAL SPECIALISTS BELIEVE A DURABLE BENEFIT OF 6-12 MONTHS JUSTIFIES A SURGICAL PROCEDURE IN WET AMD

Durability needed for an anti-VEGF therapy to justify a 30 minute surgical procedure



ASRS American Society of Retina Specialists

Stone TW, ed. *ASRS 2018 Preferences and Trends Membership Survey*. Chicago, IL. American Society of Retina Specialists; 2018.

PAT Survey

SUMMARY

1

Almost all retina specialists are trained surgeons (~2100 retina specialists in US[1])

- Over 500,000 vitrectomies performed annually in Medicare patients alone

2

Retina specialists perform delicate surgical procedures routinely

- Subretinal gene therapy injection is standardized and performed peripheral to the macula and fovea

3

Majority of retina specialists report they would perform a 30 minute surgical procedure to treat wet AMD[2]

- A durable benefit of 6-12 months justifies a surgical procedure in wet AMD

1 Registered with American Academy of Ophthalmology; 2 ASRS 2018 Preferences and Trends Survey

RGX-314 phase I/IIa clinical data

Jeffrey Heier, MD

FINANCIAL DISCLOSURES

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INABILITY TO COMPLY WITH FREQUENT ANTI-VEGF INJECTIONS LEADS TO SIGNIFICANT LOSS OF VISION

AURA: Retrospective, Observational Trial

- Conducted in 8 countries
- 2227 patients

OPEN

Determinants of visual acuity outcomes in eyes with neovascular AMD treated with anti-VEGF agents: an instrumental variable analysis of the AURA study

CLINICAL STUDY

Abstract

Purpose To identify the strongest variable(s) linked with the number of ranibizumab injections and outcomes in AURA, and to identify ways to improve outcomes using this association.

Methods AURA was a large observational study that monitored visual acuity over a 2-year period in patients with neovascular age-related macular degeneration (AMD) who received ranibizumab injections. Baseline characteristics, resource use, and outcomes were analyzed using an instrumental variable approach and regression analysis.

Results Data were analyzed from 2227 patients enrolled in AURA. Optical coherence tomography (OCT) and ophthalmoscopy were the most common diagnostic tests used, and this combination was the strongest instrumental variable. Use of OCT and ophthalmoscopy affected the number of injections given and resulted in an increase in visual acuity gains from baseline of 17.6 letters in year 1 and 2.5 letters in year 2. Regression models using the instrumental variable (OCT and ophthalmoscopy combined) showed that ≥ 5.1 (95% CI: 3.3–11.4) ranibizumab injections were needed to maintain visual acuity from baseline in year 1 and ≥ 8.3 (95% CI: 5.3–18.8) injections were needed to maintain visual acuity from year 1 to year 2. To gain ≥ 15 letters, ≥ 7.9 (95% CI: 5.1–17.5) ranibizumab injections would be needed in year 1 and ≥ 16.1 (95% CI: 10.3–36.4) injections would be needed over 2 years.

Conclusions These findings highlight the role that regular monitoring plays in guiding neovascular AMD therapy and they showed that the number of ranibizumab injections needed to maintain visual acuity is higher than that administered in AURA.

Eye (2016) 30, 1063–1071; doi:10.1038/eye.2016.90; published online 20 May 2016

Introduction

Anti-vascular endothelial growth factor (VEGF) agents have become an important treatment option for neovascular age-related macular degeneration (AMD) since their introduction over a decade ago. These agents inhibit VEGF, a key factor in the development of underlying cell proliferation and neovascularization.[1]

Improvements in visual and anatomical outcomes following monthly injections of the anti-VEGF antibody fragment ranibizumab have been demonstrated in two key studies in neovascular AMD.[2,3] However, delivery of monthly dosing in clinical practice is challenging, and alternative dosing regimens of intravitreal ranibizumab are often used, including as-needed, quarterly, or treat-and-extend, although outcomes can be more variable.[4–6] Not surprisingly, observational studies have shown that ranibizumab may be underused in routine practice, resulting in poor long-term outcomes.[7–13]

AURA (a retrospective noninterventional study to assess the effectiveness of existing Anti-vascular endothelial growth factor treatment Regimen in patients with wet Age-related macular degeneration) monitored 2-year outcomes in patients with neovascular AMD who started treatment with ranibizumab between January 2009 and August 2010.[14]

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Accepted in revised form: 29 March 2016
Published online: 20 May 2016

FG Holz[1], R Tadayoni[2], S Beatty[3], AR Burger[4], MG Cereda[5], P Hykin[6], G Staurenghi[7], K Wittrup-Jensen[8], J Nilsson[8], K Kent[9] and S Sivaprasad[3,10]

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[2]Department of Ophthalmology, Hôpital Lariboisière, Paris, France
[3]Department of Ophthalmology, Institute of Eye Surgery, Waterford, Ireland
[4]Department of Ophthalmology and Vision Sciences, University of Toronto, and St Michael's Hospital, Toronto, Ontario, Canada
[5]Department of Biomedical and Clinical Sciences Luigi Sacco, Luigi Sacco Hospital, University of Milan, Milan, Italy
[6]NIHR Biomedical Centre for Research in Ophthalmology, Moorfields Eye Hospital, London, UK
[7]Bayer Pharmaceuticals, Berlin, Germany
[8]Adelphi Group, Real World Strategy and Analysis, Stockholm, Sweden
[9]Health Economics, AstraZeneca Nordic-Baltic, Södertälje, Sweden
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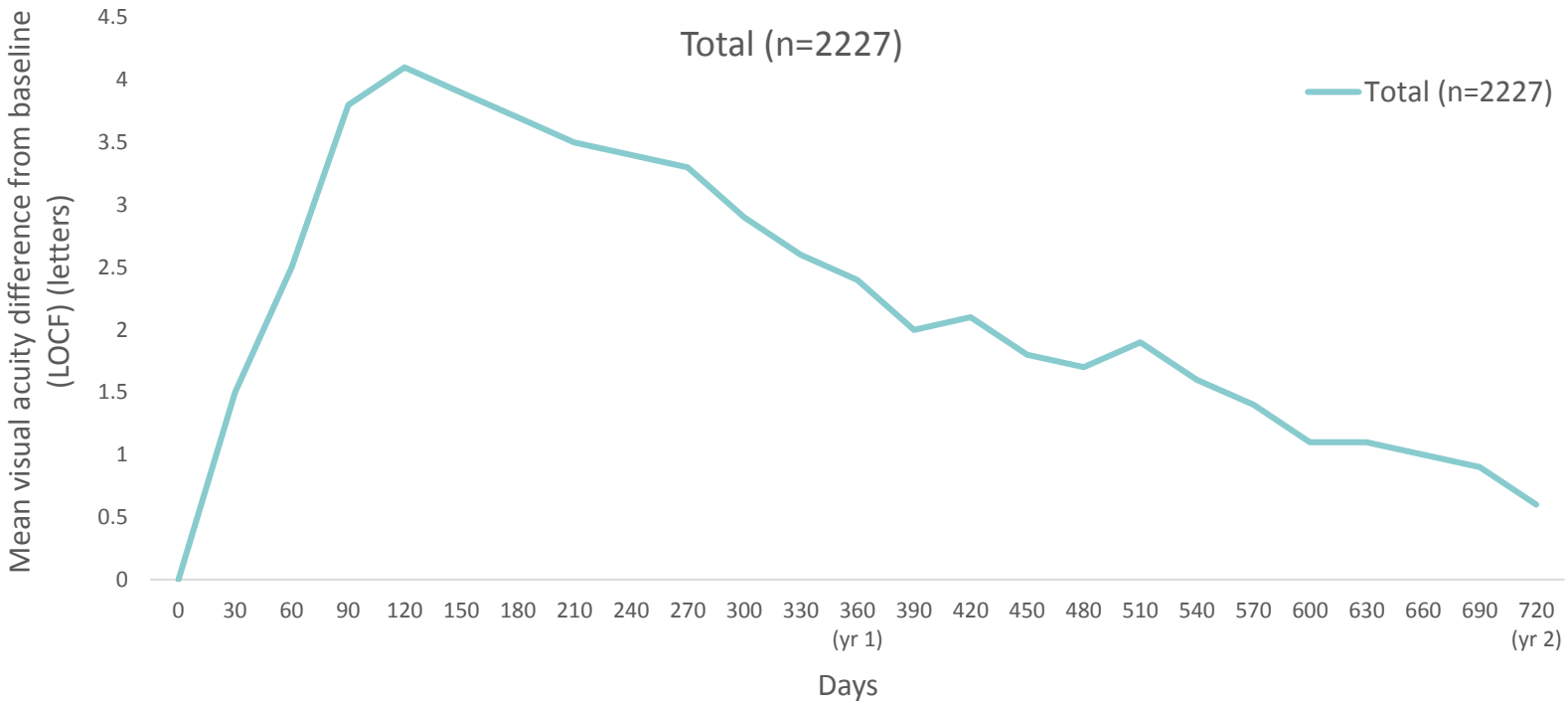
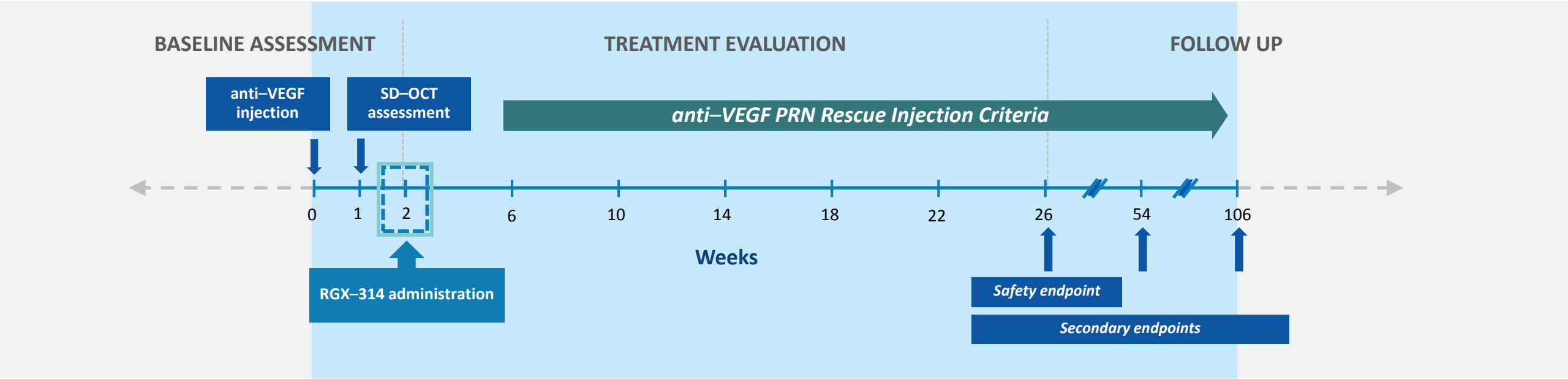
What did we learn?

- > 7.9 injections in year 1 needed to gain > 15 letters
- > 8.3 injections in year 2 needed to maintain visual acuity in year 2



RGX-314 PHASE I/IIA TRIAL: DESIGN



Previously Treated Subjects Requiring Frequent Injections

Dose 1 n = 6 ✓	Safety review[1]	Dose 2 n = 6 ✓	Safety review[1]	Dose 3 n = 6 ✓	Safety review[1]	Dose 4 n = 12	Safety review[1]	Dose 5 n = 12
$3x10^9$ GC/eye		$1x10^{10}$ GC/eye		$6x10^{10}$ GC/eye		$1.6x10^{11}$ GC/eye		$2.5x10^{11}$ GC/eye

Dosing Completed in 24 Subjects

[1] Dose escalation safety review to occur four weeks after final subject in each cohort has been dosed
Data cut Dec 3rd, 2018
SD-OCT = spectral domain optical coherence tomography

RGX-314 PHASE I/IIA: ELIGIBILITY CRITERIA

Key inclusion criteria

- Male or female ≥ 50 to 89 years of age
- Wet AMD subjects requiring ≥4 anti–VEGF injections in the 8 months prior to trial entry
- Documented response to anti–VEGF at trial entry (assessed by SD–OCT at week 1)
- Vision of 20/63 to 20/400 for the initial subject, then 20/40 to 20/400 for the rest of each cohort
- Pseudophakic (status post cataract surgery)

RGX-314: PHASE I/IIA TRIAL ANTI-VEGF RESCUE INJECTION CRITERIA

Anti-VEGF May Be Given **Beginning 4 Weeks**
Post-treatment with RGX-314 and **Every 4 Weeks Thereafter PRN**

Per the Investigator's Discretion
If One or More of the Following Criteria Apply:

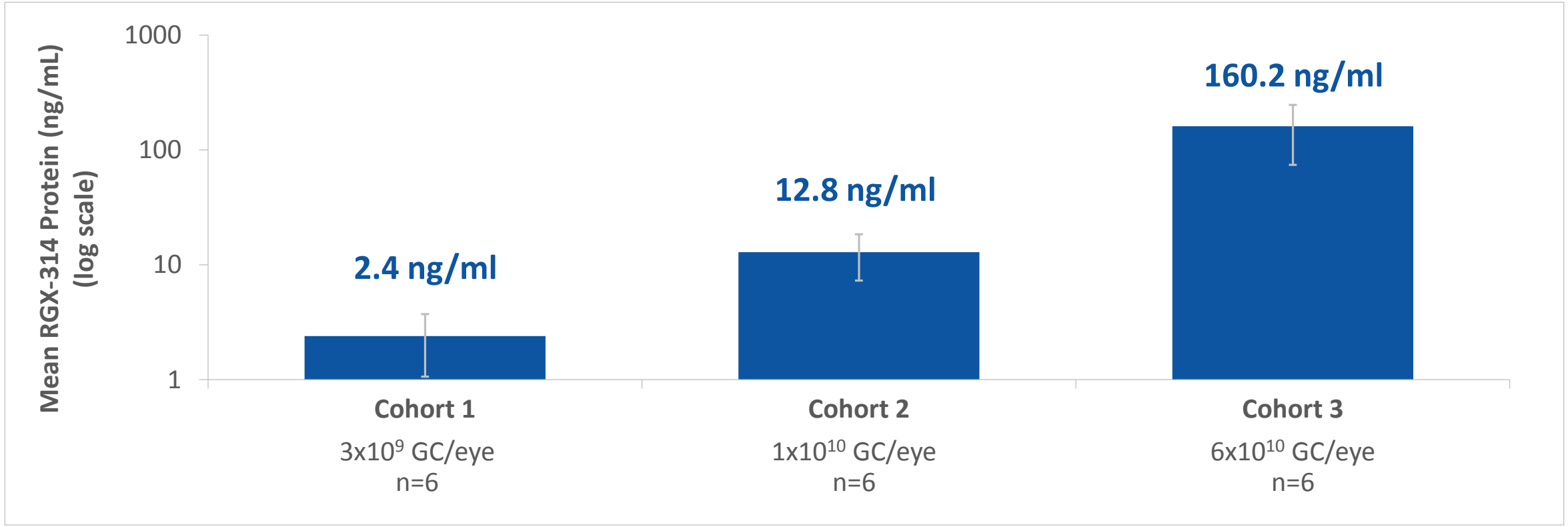
CNV-related increased, new, or persistent fluid	Vision loss of ≥5 letters associated w/ accumulation of fluid	New ocular hemorrhage

RGX-314: PHASE I/IIA TRIAL DEMOGRAPHICS & BASELINE FOR COHORTS 1-3

	Variable	Cohort 1 (n=6)	Cohort 2 (n=6)	Cohort 3 (n=6)	Total (n=18)
Demographics	Mean Age (Years)	78.2	78.0	80.0	78.7
	Female (Number, %)	4 (66.7%)	3 (50.0%)	2 (33.3%)	9 (50.0%)
	Caucasian, No. (%)	6 (100.0%)	6 (100.0%)	6 (100.0%)	18 (100.0%)
Baseline Characteristics	Months Since First anti-VEGF Injection	53.5	59.3	71.6	61.5
	# Injections Since Diagnosis (Mean)	40.7	32.5	34.2	35.8

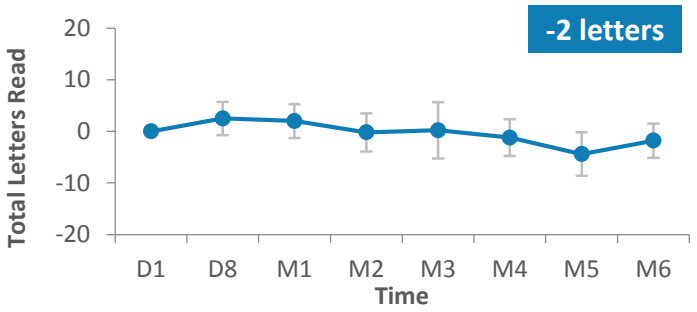
RGX-314: PHASE I/IIA TRIAL PROTEIN LEVELS AT ONE MONTH FOR COHORTS 1-3

RGX-314 Protein (as measured from aqueous samples by ECL-based assay)

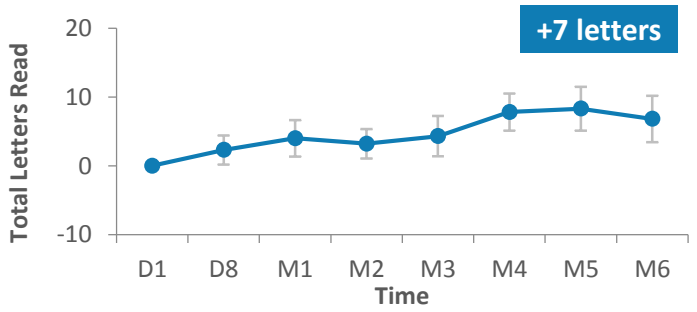


RGX-314: PHASE I/IIA TRIAL MEAN CHANGE IN BCVA, CRT AND AVERAGE INJECTIONS OVER SIX MONTHS, BY COHORT

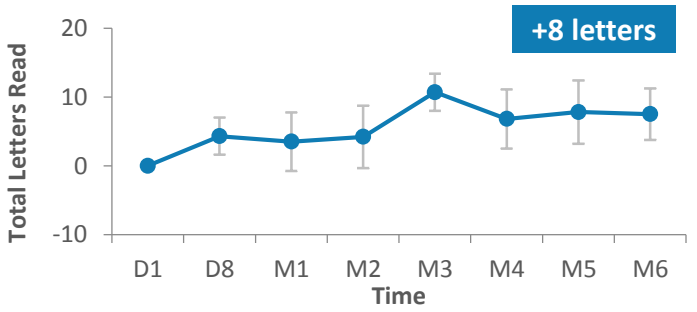
Best Corrected Visual Acuity (BCVA)



Cohort 1

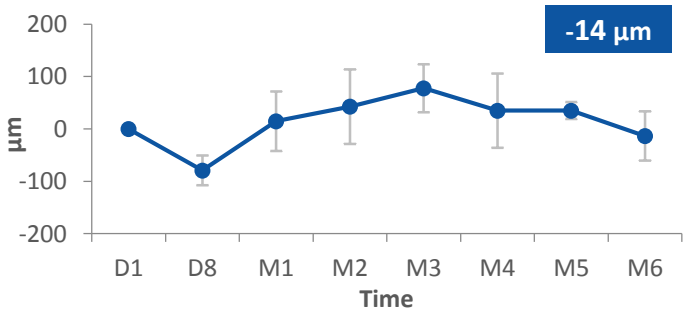


Cohort 2



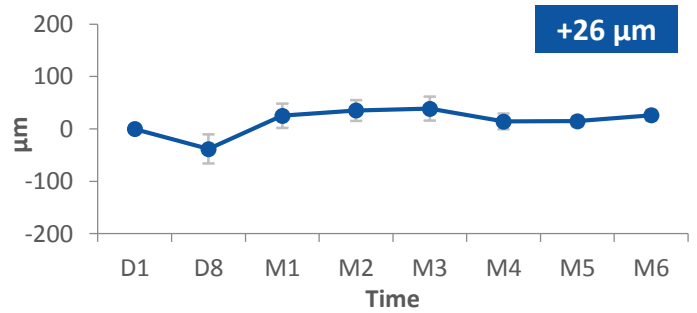
Cohort 3

Central Retinal Thickness (CRT) on SD-OCT



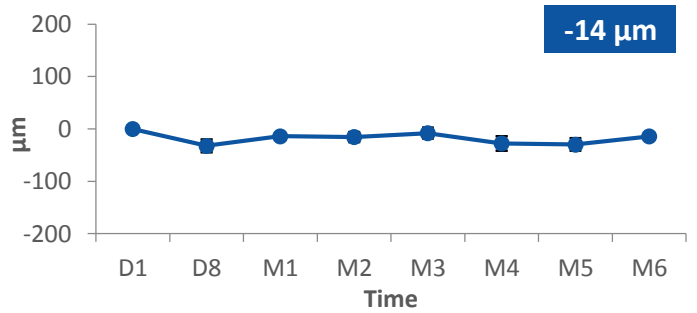
Average Injections: 4.7

Cohort 1



Average Injections: 3.8

Cohort 2



Average Injections: 1.3

Cohort 3

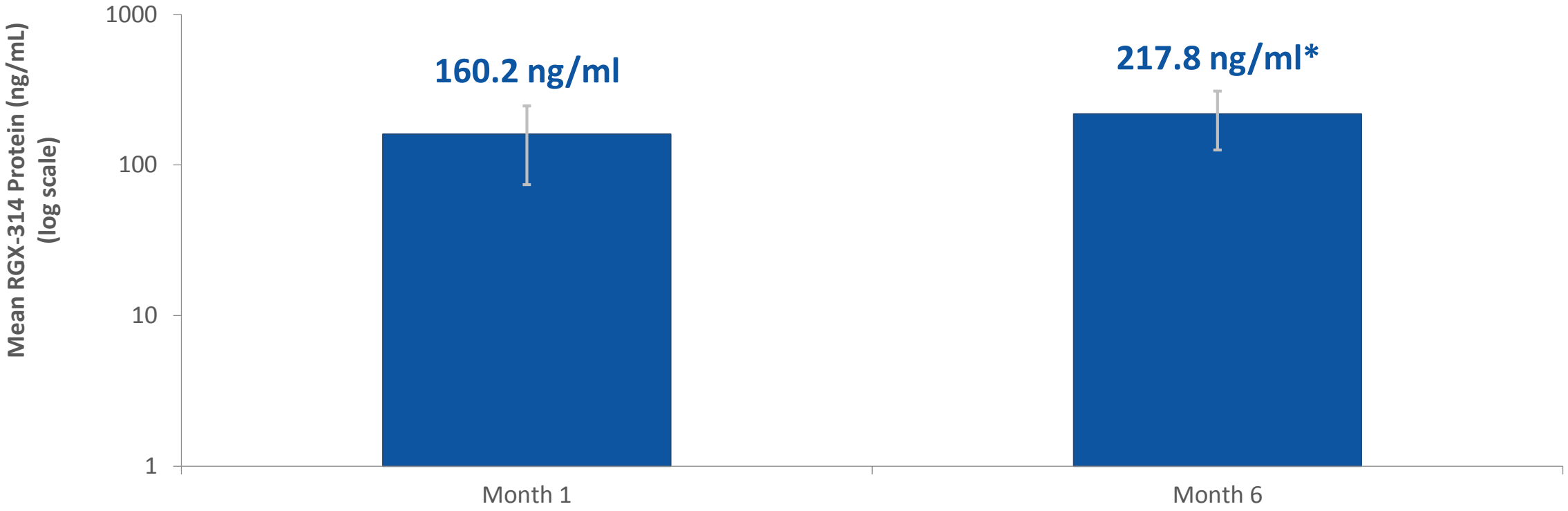
RGX-314: PHASE I/IIA TRIAL SUMMARY OF INTERIM RESULTS THROUGH SIX MONTHS

	Mean Aqueous RGX-314 Protein One Month Post-treatment	Mean # of Anti-VEGF Injections through Six Months	Mean Change in CRT through Six Months (Range)	Mean Change in BCVA through Six Months (Range)
Cohort 1 $3x10^9$ GC/eye (n=6)	2.4 ng/ml	4.7 inj*	-14 µm** (-181 to +92 µm)	-2 letters** (-8 to +10 letters)
Cohort 2 $1x10^{10}$ GC/eye (n=6)	12.8 ng/ml	3.8 inj	+26 µm (-7 to +62 µm)	+7 letters (-4 to +15 letters)
Cohort 3 $6x10^{10}$ GC/eye (n=6)	**160.2 ng/ml**	**1.3 inj**	**-14 µm** (-27 to +7 µm)	**+8 letters** (0 to +21 letters)

* One subject in Cohort 1 discontinued from the study at four months with four injections and was imputed as requiring six injections through six months
** n=5; one subject in Cohort 1 discontinued from the study at four months

RGX-314: SUSTAINED PROTEIN LEVELS AT SIX MONTHS

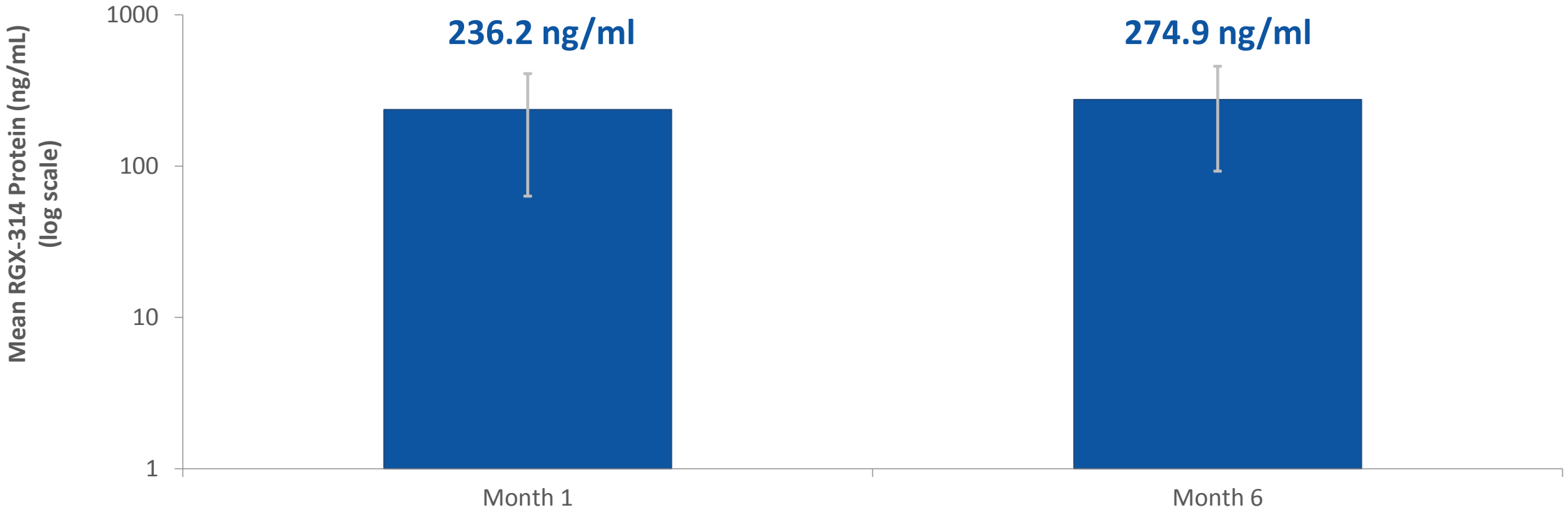
All Subjects (N=6) in Cohort 3 ($6x10^{10}$ GC/eye)



*One subject received an anti-VEGF rescue injection 1 month prior to sample.

RGX-314: SUSTAINED PROTEIN LEVELS AT SIX MONTHS

Subjects with **No Rescue Injections** (n=3) in Cohort 3 ($6x10^{10}$ GC/eye)

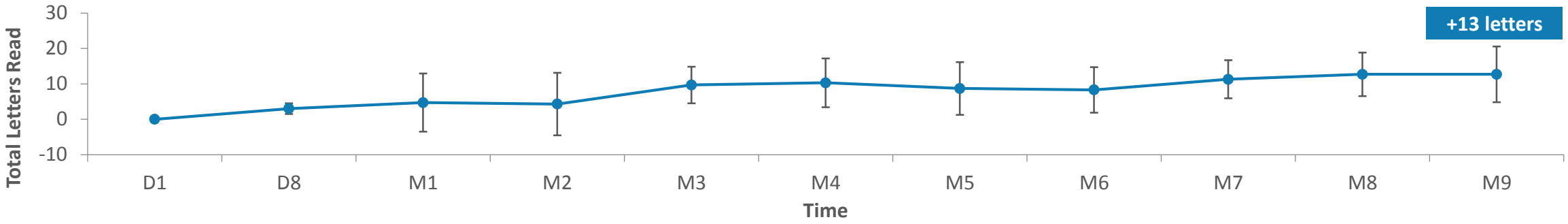


RGX-314 PHASE I/IIA TRIAL: COHORT 3 SUBJECTS WITH NO RESCUE INJECTIONS THROUGH NINE MONTHS (N=3)

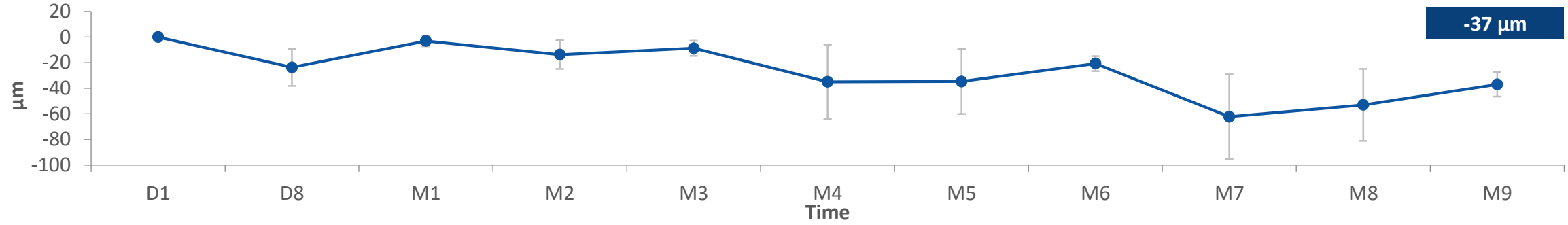
Previous Therapy	Study subjects received on average **>35 injections since wet AMD diagnosis**
Post-RGX-314 Anti-VEGF Injections	**0 injections** through nine months post-RGX-314
BCVA	Mean **gain in BCVA of +13 ETDRS** letters from baseline through nine months
SD-OCT	Maintained with a **mean change in CRT of -37 µm** from baseline through nine months

RGX-314 PHASE I/IIA TRIAL: MEAN CHANGE IN BCVA, CRT OVER NINE MONTHS IN COHORT 3 SUBJECTS WITH NO RESCUE INJECTIONS

Best Corrected Visual Acuity (BCVA)



Central Retinal Thickness (CRT) on SD-OCT



Cohort 3 with No Rescue Injections (n=3)

RGX-314 PHASE I/IIA TRIAL: SAFETY FOR COHORTS 1–4*

- RGX-314 was **well-tolerated** (n=24)
- **No drug-related AEs or drug-related SAEs**
- Most AEs were assessed as mild (Grade 1 – 83%)
- **No observed clinically-determined immune responses**, drug-related ocular inflammation, or any post-surgical inflammation beyond what is expected following routine vitrectomy
- **Six SAEs that were not drug-related were reported in four subjects**
  - One subject with a peripheral retinal detachment which was repaired and resolved without sequelae
  - One subject with a hospitalization related to a pre-existing condition that resulted in death
  - One subject with an event assessed mild in severity with no relationship to RGX-314
  - One subject with a diagnosis of cancer recurrence

* Data cut Dec 3rd, 2018

RGX-314: PHASE I/IIA TRIAL INTERIM RESULTS

RGX-314 was **well-tolerated** at all doses (n=24)

Cohort 3: **sustained RGX-314 protein at six months with stability in vision and anatomy** despite **few to no injections**

Cohort 3: **50% of subjects** continue to remain free of injections at **nine** months; **improved vision (+13 letters) and stable CRT (-37 µm)**

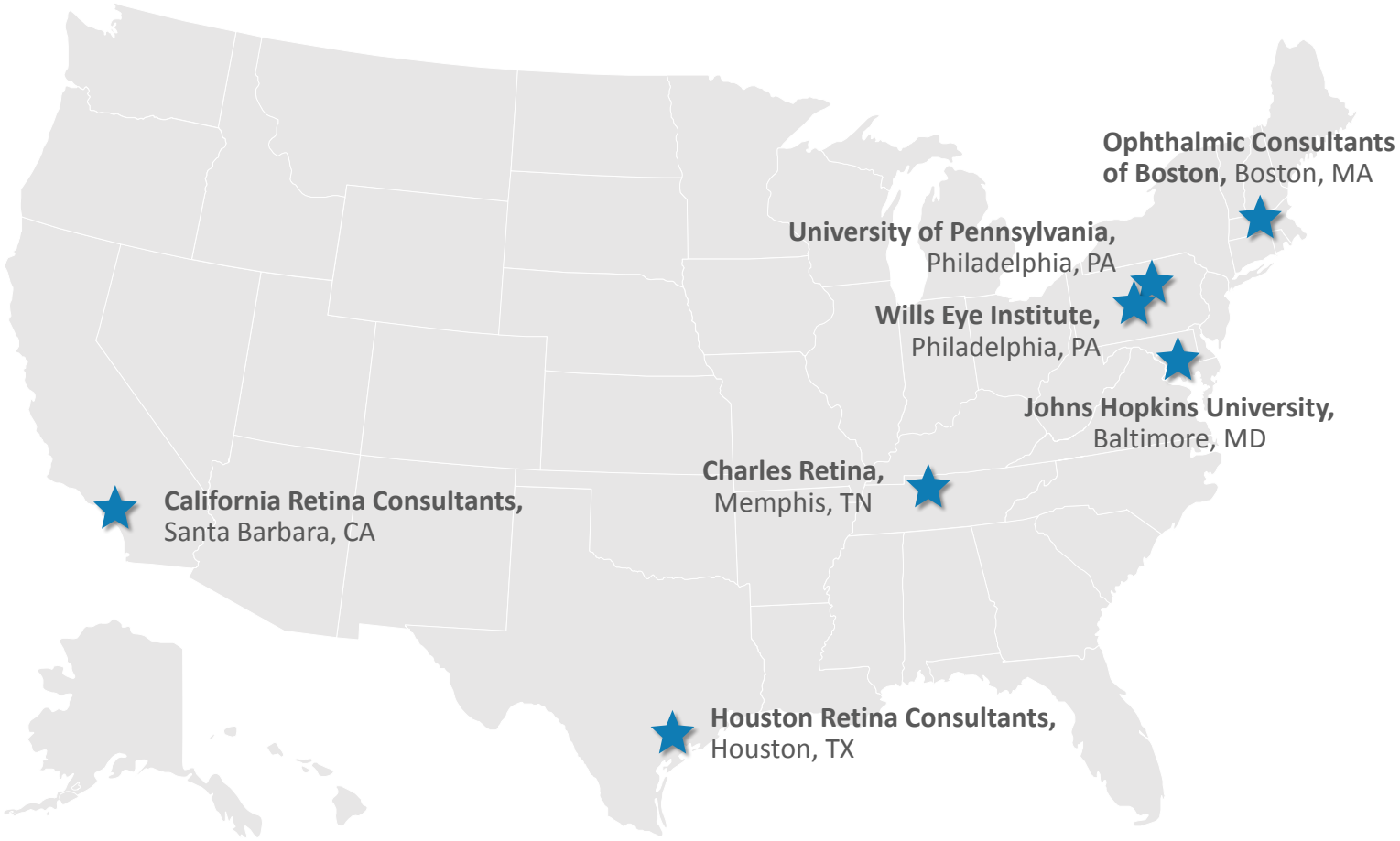
Dose dependent protein expression observed from Cohort 1 to Cohort 3

Recently reported Cohort 4: **detectable protein** at one month with a mean higher than Cohort 3

One-time gene therapy for wAMD offers the potential to **sustain clinical outcomes** while alleviating treatment burden

* Data cut Dec 3rd, 2018

RGX-314 ACKNOWLEDGMENTS



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David Brown, MD **(Houston, TX)**

Peter Campochiaro, MD **(Baltimore, MD)**

Jorge Calzada, MD **(Memphis, TN)**

Jeff Heier, MD **(Boston, MA)**

Allen Ho, MD **(Philadelphia, PA)**

Dante Pieramici, MD **(Santa Barbara, CA)**

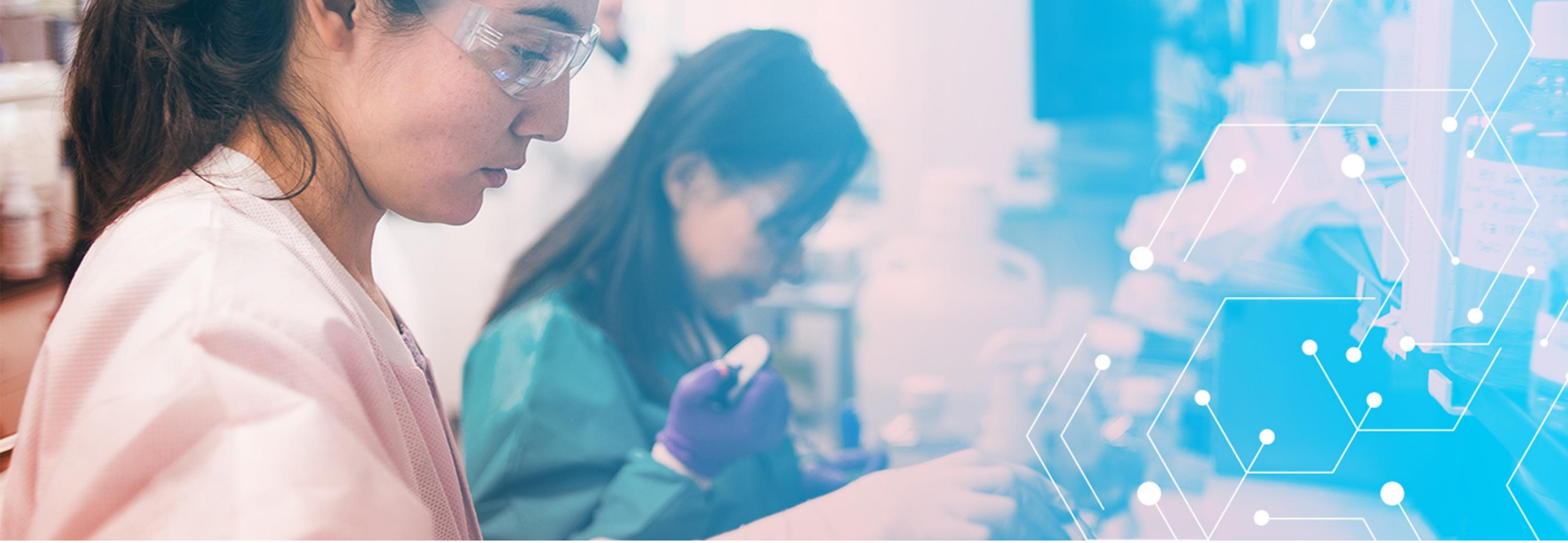
Charles Wykoff, MD PhD **(Houston, TX)**

Szilard Kiss, MD **(New York, NY)**

Albert Maguire, MD **(Philadelphia, PA)**

Sherri Van Everen, PharmD **(REGENXBIO)**

Darin Curtiss, PharmD **(REGENXBIO)**



RGX-314 Analyst and Investor Day
Market Opportunity

February 21, 2019

Ram Palanki
SVP, Commercial Strategy and Operations

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Topics

What is the current unmet need in wet AMD?

Where does RGX-314 fit in the clinical management of wet AMD?

Will a surgical solution for wet AMD be widely adopted?

What is the potential value of a one-time gene therapy for the treatment of wet AMD?

What is the overall market opportunity for RGX-314 in wet AMD and other retinal conditions?

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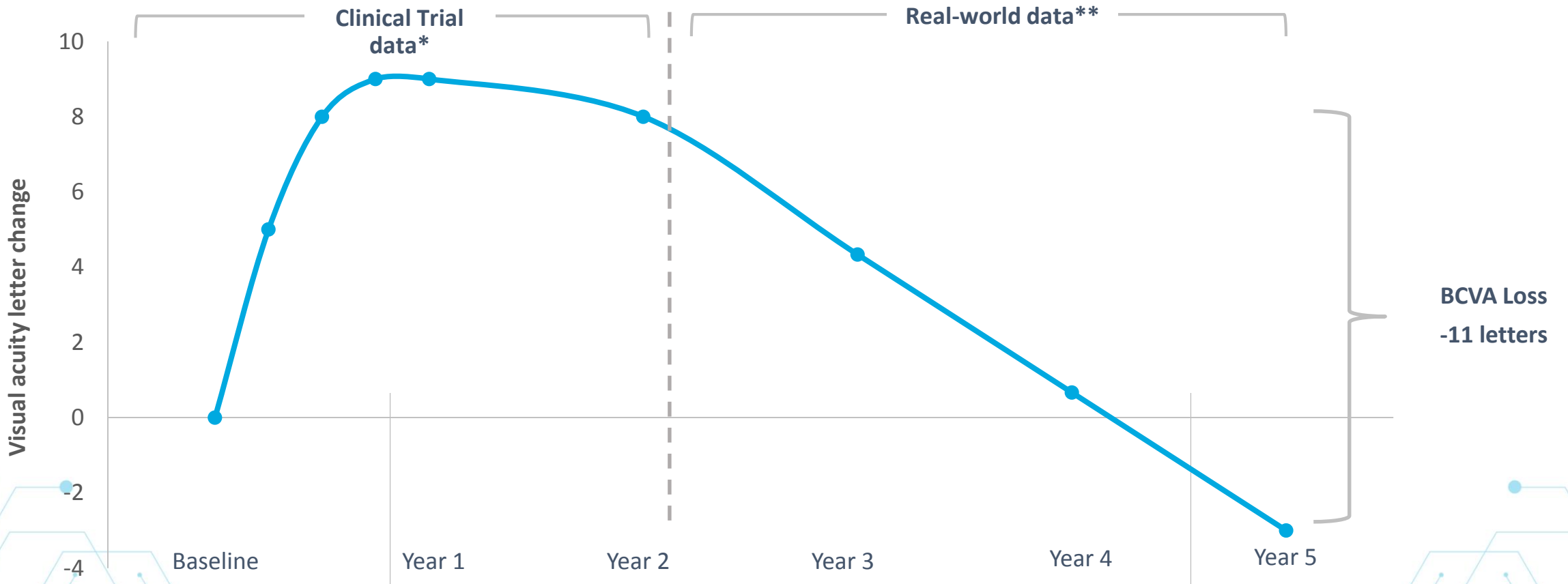
Real world data suggests patients on average lose visual acuity over time on current treatment regimens

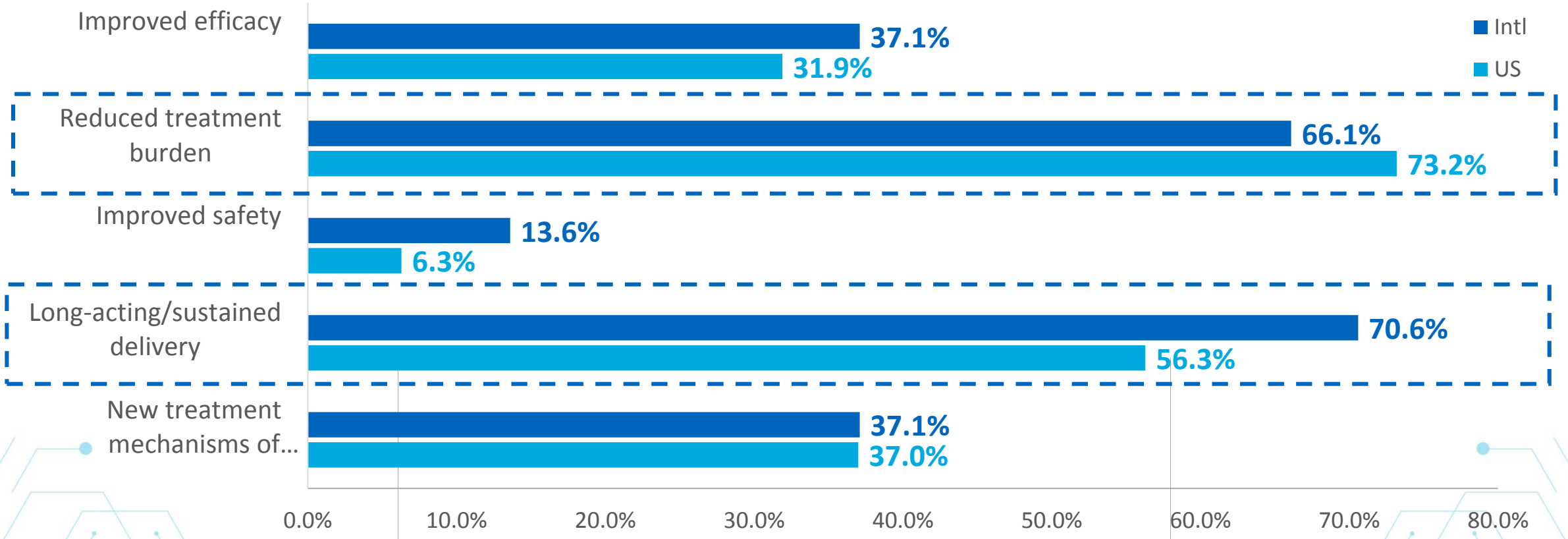
Visual Acuity



Source: *HARBOR and CATT data; **CATT data

Retina specialists confirm reduced treatment burden and long-acting treatment solutions as the greatest unmet needs

What are the greatest unmet needs regarding wet-AMD treatment?



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ASRS American Society of Retina Specialists

Stone TW, ed. *ASRS 2018 Preferences and Trends Membership Survey*. Chicago, IL. American Society of Retina Specialists; 2018.

PAT Survey

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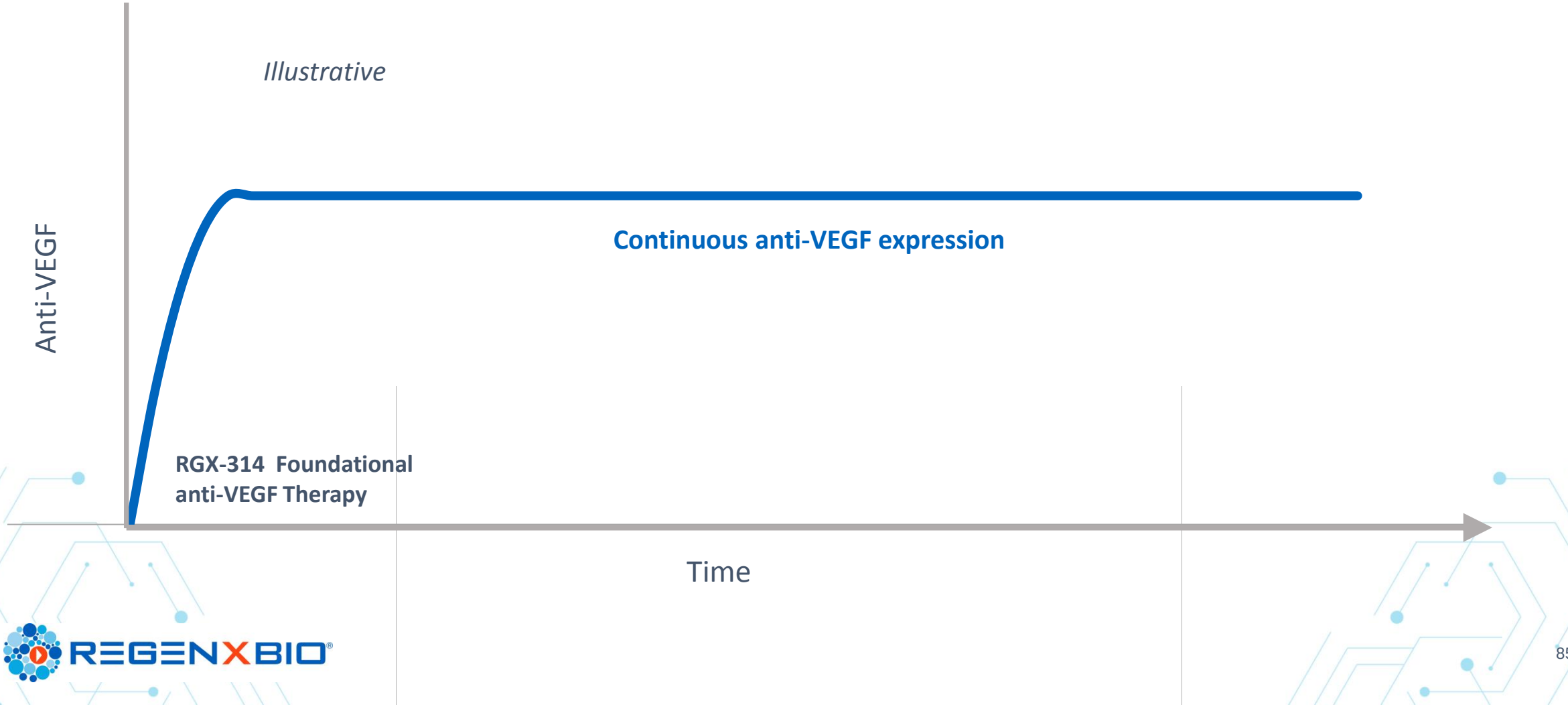
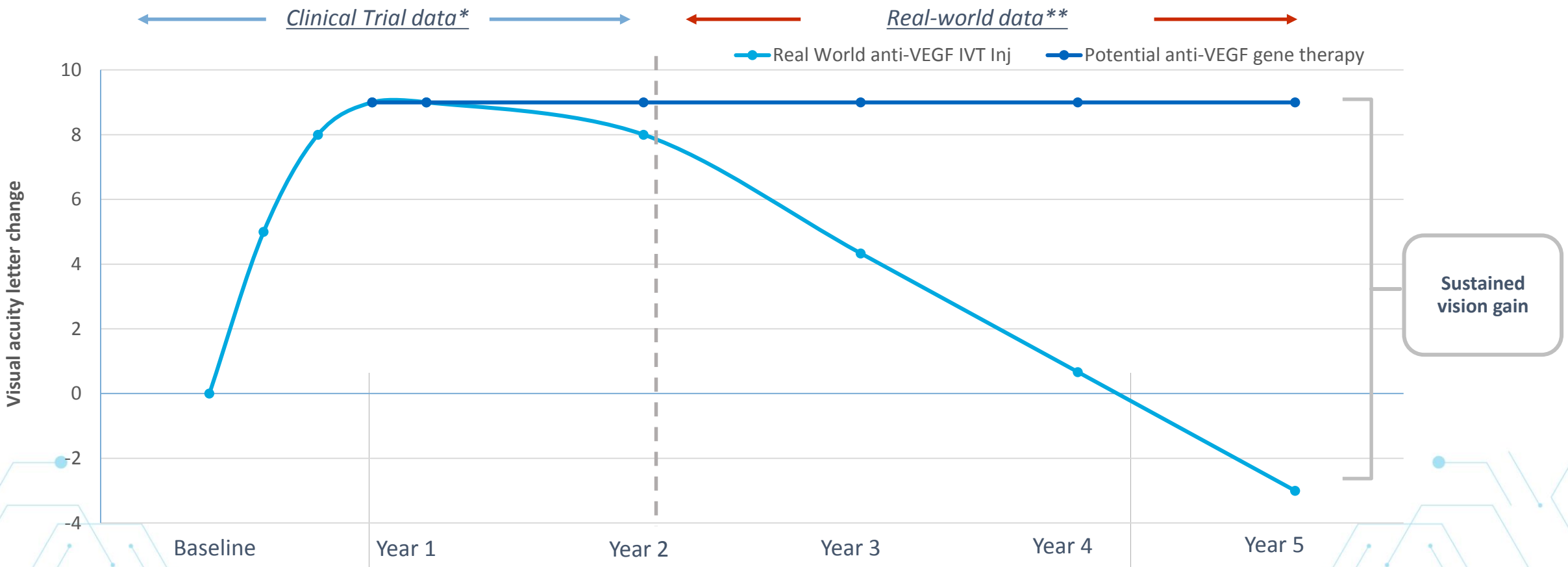
Single administration of RGX-314 can potentially establish foundational anti-VEGF therapy

RGX-314 positioning: Potential one-time anti-VEGF therapy could be sustained over time



Single treatment with RGX-314 has the potential to close the gap between randomized clinical trials and real world outcomes

Visual Acuity



Source: *HARBOR and CATT data; **CATT data
Potential anti-VEGF gene therapy curve hypothesized

Topics

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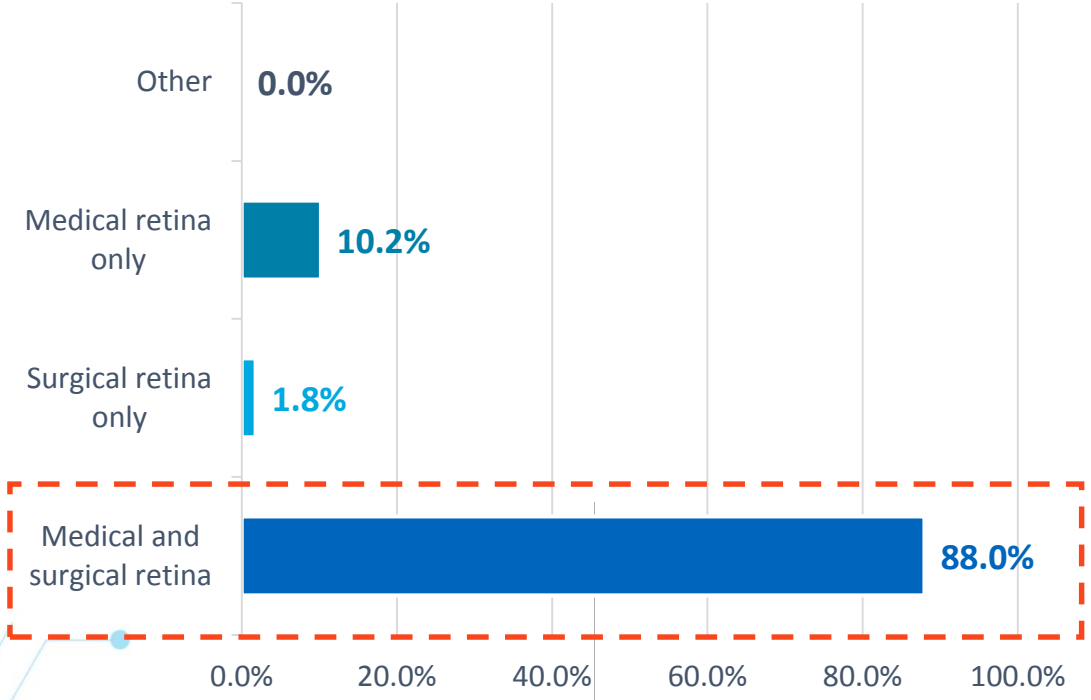
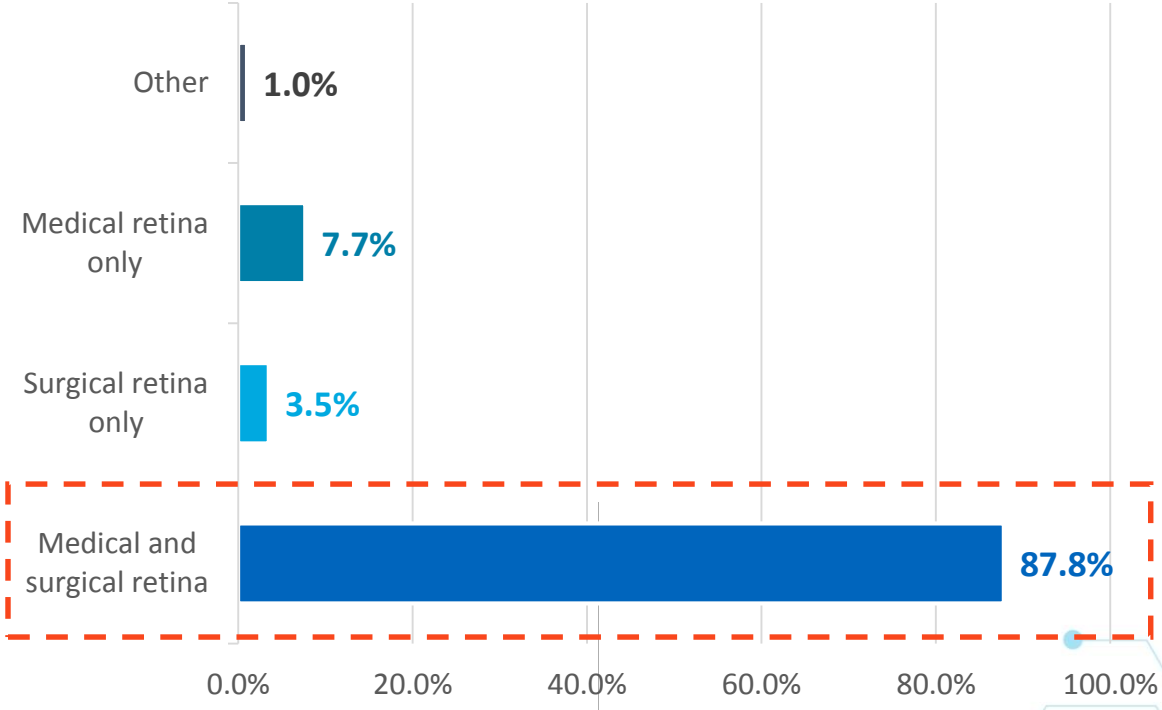
The majority of retina specialists are surgeons

Are you a medical retina specialist, a surgical retina specialist, or both?

United States



International



n = 1031

Stone TW, ed. *ASRS 2018 Preferences and Trends Membership Survey*. Chicago, IL. American Society of Retina Specialists; 2018.

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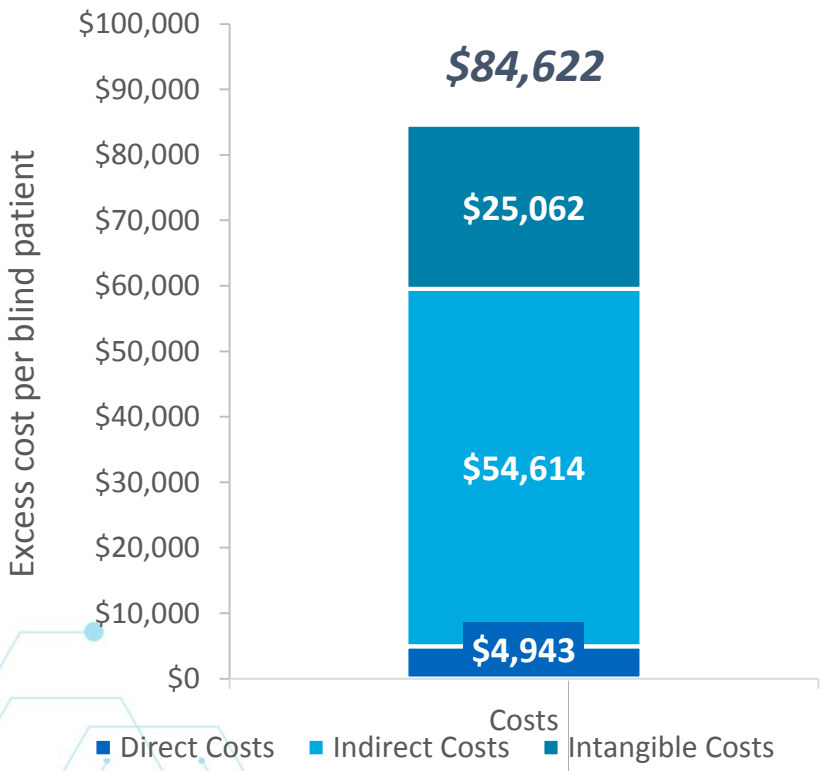
RGX-314 can potentially mitigate the social and economic impact of blindness

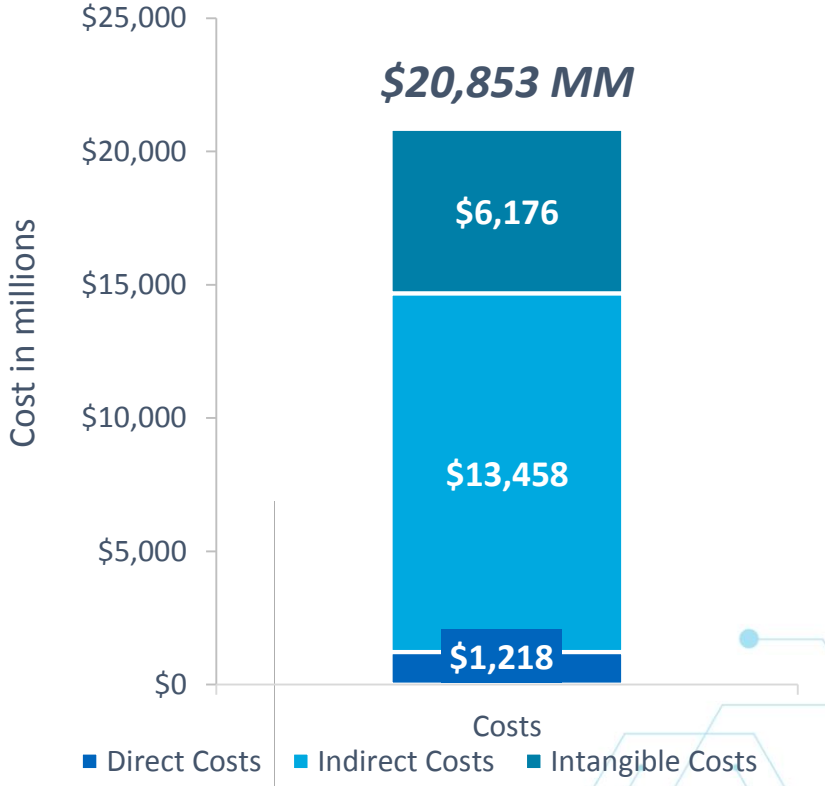
One in five cases of blindness in the US attributable to retinal disease characterized by angiogenic processes[1] that can be prevented with anti-VEGF treatment[2-7]

Annual cost per patient*, $



246,422 patients with bilateral blindness attributed to wAMD, DME, and PDR in 2020*

Aggregated annual costs*, $MM



Source: *DME, diabetic macular edema; PDR, proliferative diabetic retinopathy; RVO, retinal vein occlusion; wAMD,wet age-related macular degeneration. Moshfeghi et al, Angiogenesis 2019; [1]Flaxman et al. Lancet Glob Health 2017;5:e1221–34; [2]Stewart. Curr Diab Rep. 2014;14:510; [3]Martin et al. N Engl J Med. 2011;364:1897–1908; [4]Schmidt-Erfurth et al. Ophthalmology 2014;121:193–201; [5]Nguyen et al. Ophthalmology 2012;119:789–801; [6]Sivaprasad et al. Lancet 2017;389:2193–203; [7]Gross et al. J Am Med Assoc 2015;314:2137–46.

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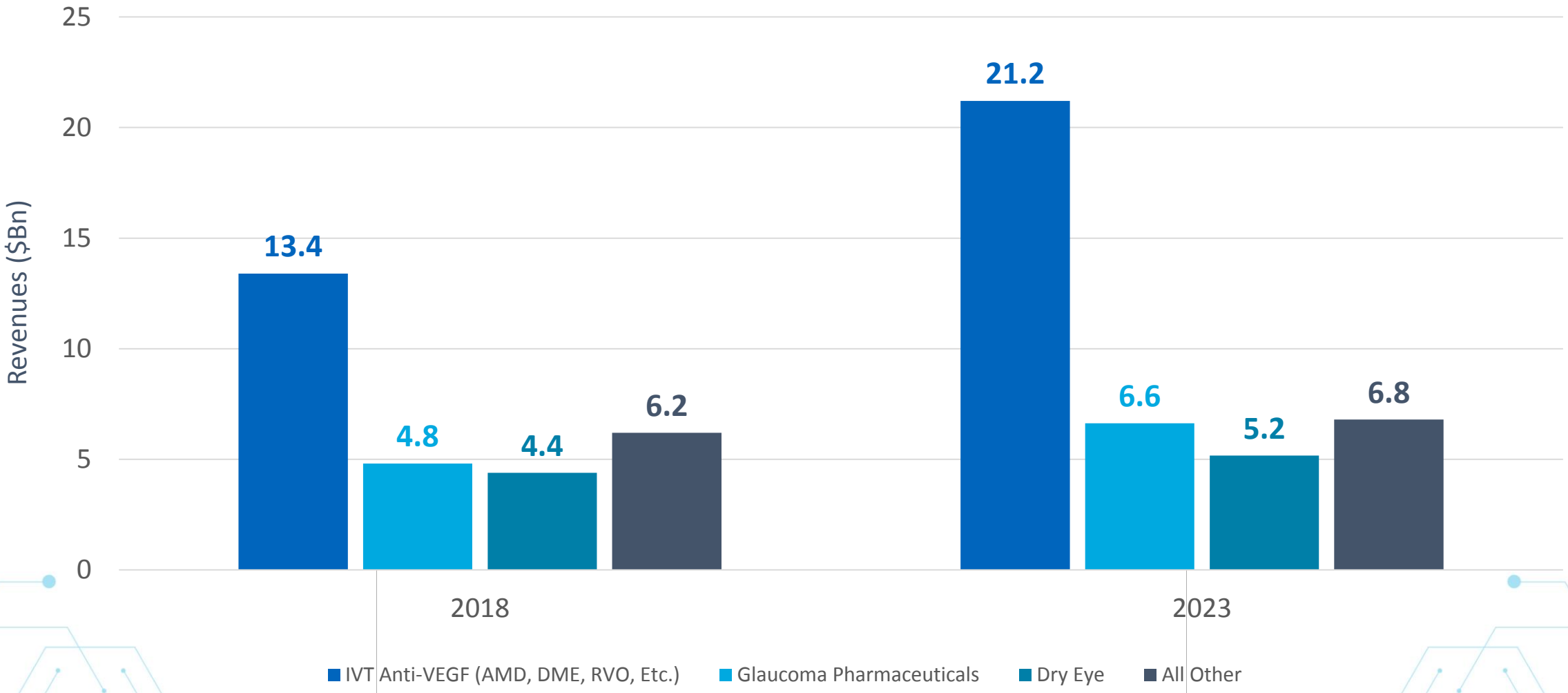
Anti-VEGF is the largest global ophthalmic pharmaceutical market



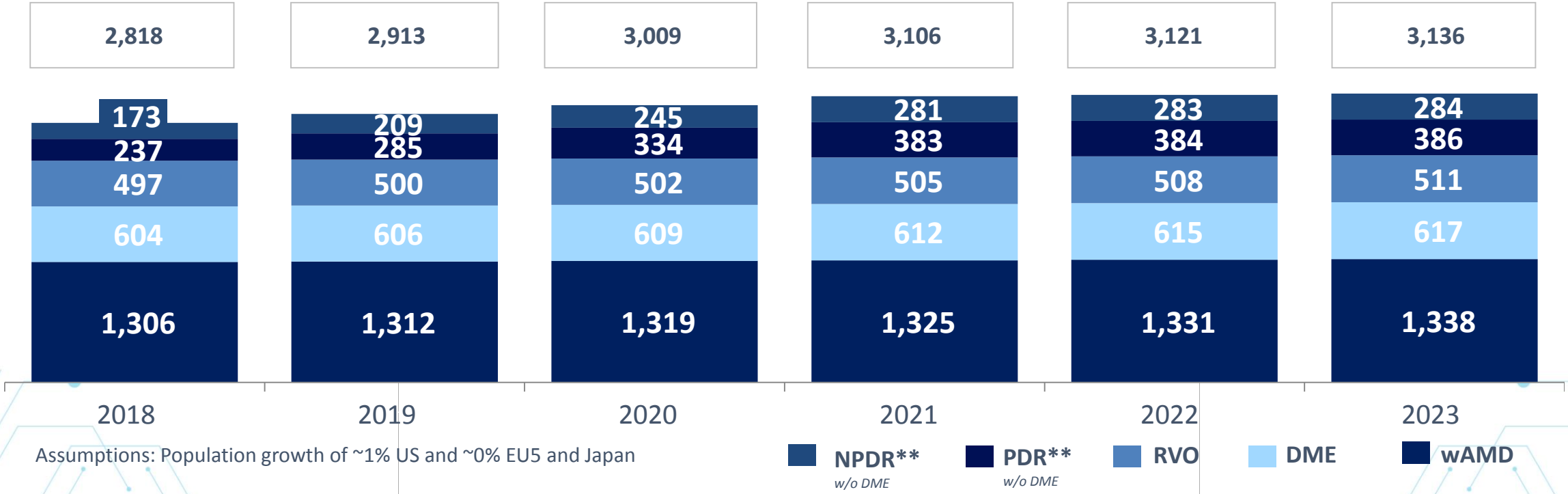
Source: Market Scope Estimates 2018; Courtesy Market Scope. http://market-scope.com/

Anti-VEGF market projected growth by indication (2018-2023)

*

- Almost all wet AMD patients are on chronic anti-VEGF Tx
- 50% of patients with DME are on chronic anti-VEGF Tx
- 50% of patients with RVO are on chronic anti-VEGF Tx
- Majority of patients with DR (NPDR and PDR) without DME require chronic anti-VEGF Tx

Number of patient eyes treated with IVT anti-VEGF injections annually (in '000s)



Assumptions: Population growth of ~1% US and ~0% EU5 and Japan

wAMD = wet AMD; DME = Diabetic Macular Edema; RVO = Retinal Vein Occlusion; NPDR = Non-Proliferative Diabetic Retinopathy; PDR = Proliferative Diabetic Retinopathy

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Source: epidemiology data based on literature, diagnosis rates based on Datamonitor Report, DRG Market Forecast Assumptions and REGENXBIO primary market research
According to https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5278808/ ; https://www.cdc.gov/diabetes/statistics/slides/long_term_trends.pdf
*US, EU5, Japan
**NPDR and PDR data only include US population; assuming increase from 50% to 80% aVEGF patient share among treated patients over 3 years

Thank you

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Q & A

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- Board of Trustees of EURETINA

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- Executive Committee of the Retina Society
- Investigator in the RGX-314 Phase I/IIa clinical trial

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- Principal Investigator of the RGX-314 Phase I/IIa clinical trial