Alnylam R&D Day 2021

November 19, 2021

Alnylam PHARMACEUTICALS

Agenda

Time	Topic	Speaker
8:30 – 8:35	**Welcome**	• Christine Lindenboom, *SVP, Investor Relations and Corporate Communications*
8:35 – 8:50	**RNAi Therapeutics: Past, Present and Future**	• John Maraganore, *CEO*
8:50 – 9:15	**Delivering Sustainable Innovation with RNAi Therapeutics**	• Akshay Vaishnaw, *President of R&D*
9:15 – 10:00	**Expanding Alnylam's TTR Franchise**	• John Vest, *Vice President, Clinical Research* • SriniVas Sadda, M.D., *Professor of Ophthalmology Doheny Eye Institute, David Geffen School of Medicine, UCLA*
10:00 – 10:30	**Reimagining the Treatment of Hypertension**	• Weinong Guo, *SVP, Clinical Research*
10:30 – 11:00	**Q&A**	• Pushkal Garg, *Chief Medical Officer*
11:00 – 11:10	**Break**	
11:10 – 12:00	**Beyond the Liver with RNAi Therapeutics**	• Kevin Fitzgerald, *Chief Scientific Officer* • Sharon Cohen, M.D. *FRCPC, Medical Director, Toronto Memory Program*
12:00 – 12:20	**Next Wave RNAi Therapeutics**	• Pushkal Garg, *Chief Medical Officer*
12:20 – 12:30	**Progress Towards P^5x25**	• Yvonne Greenstreet, *President and Chief Operating Officer*
12:30 – 1:00	**Q&A**	• Akshay Vaishnaw, *President of R&D*

Reminders

- Event scheduled to end ~1:00 p.m. ET.
- Two moderated Q&A sessions during meeting.
- To submit a question, type your question in the ‘Ask a Question’ field.
- Replay will be available on Investors page of our website later today.

Alnylam Forward Looking Statements

This presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934, including expectations regarding our aspiration to become a leading biotech company and the planned achievement of our "Alnylam P^{5}x25" strategy, the CEO leadership transition planned for year end, the potential of our platform to yield RNAi therapeutics for rare and prevalent diseases and to address multiple disease targets and tissue types, the potential for improved product profiles to emerge from our IKARIA and GEMINI platforms. plans for additional global regulatory filings and the continuing product launches of our approved products, new product opportunities for patisiran, vutrisiran and lumasiran, the achievement of additional pipeline milestones and data, including relating to ongoing clinical studies of patisiran, vutrisiran, lumasiran, zilebesiran, fitusiran, ALN-HBV02 (Vir 2218), ALN-HSD and cemdisiran, the initiation of additional clinical studies for zilebesiran, lumasiran and the combination of cemdisiran and pozelimab, the potential for zilebesiran to be a safe and effective treatment for hypertension, the expected timing for filing a CTA for each of ALN-APP and ALN-XDH, a JNDA for vutrisiran for the treatment of hATTR amyloidosis with polyneuropathy and supplemental regulatory filings with the FDA and EMA for lumasiran, the multiple development opportunities within our preclinical portfolio and our plans to advance potential treatments for oncology indications. Actual results and future plans may differ materially from those indicated by these forward-looking statements as a result of various important risks, uncertainties and other factors, including, without limitation: the direct or indirect impact of the COVID-19 global pandemic or any future pandemic on our business, results of operations and financial condition and the effectiveness or timeliness of our efforts to mitigate the impact of the pandemic; the potential impact of the planned leadership transition at year end on our ability to attract and retain talent and to successfully execute on our "Alnylam P^{5}x25" strategy; our ability to discover and develop novel drug candidates and delivery approaches, including using our IKARIA and GEMINI platforms, and successfully demonstrate the efficacy and safety of our product candidates; the pre-clinical and clinical results for our product candidates; actions or advice of regulatory agencies and our ability to obtain and maintain regulatory approval for our product candidates, including vutrisiran, as well as favorable pricing and reimbursement; successfully launching, marketing and selling our approved products globally; delays, interruptions or failures in the manufacture and supply of our product candidates or our marketed products; obtaining, maintaining and protecting intellectual property; our ability to successfully expand the indication for ONPATTRO (and potentially vutrisiran, if approved) in the future; our ability to manage our growth and operating expenses through disciplined investment in operations and our ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; our ability to maintain strategic business collaborations; our dependence on third parties for the development and commercialization of certain products, including Novartis, Sanofi, Regeneron and Vir; the outcome of litigation; the potential impact of current and the risk of future government investigations; and unexpected expenditures; as well as those risks more fully discussed in the "Risk Factors" filed with our most recent Quarterly Report on Form 10-Q filed with the SEC and in our other SEC filings. If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance, timelines or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.

Acknowledgments and Disclosures

All speakers are employees of Alnylam Pharmaceuticals except for Drs. SriniVas Sadda and Sharon Cohen, who are paid consultants to Alnylam. Alnylam Pharmaceuticals and the speakers at this event wish to thank patients, families, caregivers and dedicated researchers at their affiliated as well as other entities for their contributions to the findings presented.

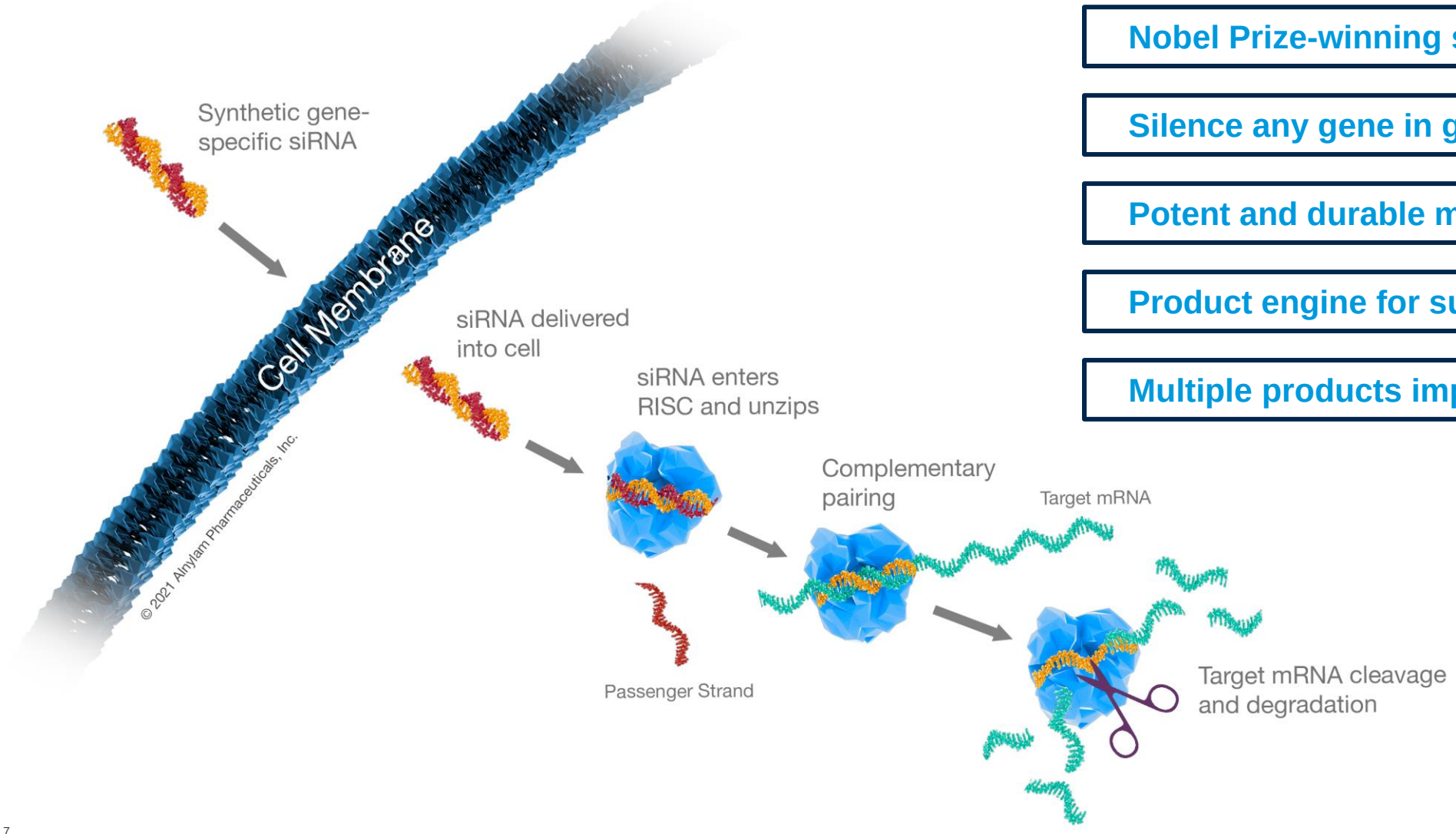
RNAi Therapeutics
Past, Present and Future

John Maraganore, Ph.D.
Chief Executive Officer

Alnylam PHARMACEUTICALS

RNAi Therapeutics: New Class of Innovative Medicines

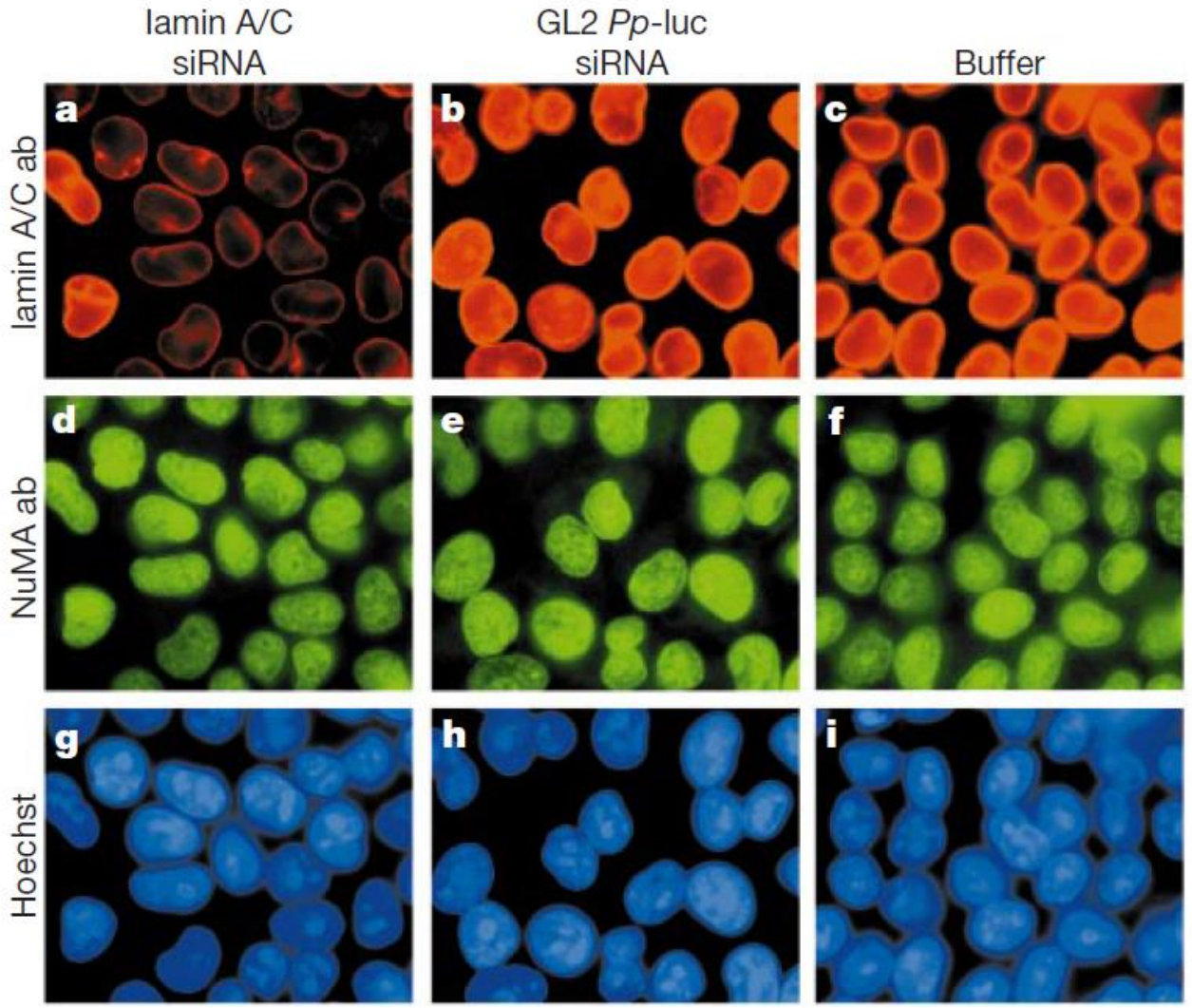
Clinically and Commercially Established Approach with Transformational Potential



- **Nobel Prize-winning science**
- **Silence any gene in genome with siRNAs**
- **Potent and durable mechanism of action**
- **Product engine for sustainable innovation**
- **Multiple products impacting patients globally**

In Vitro Data that Started Alnylam

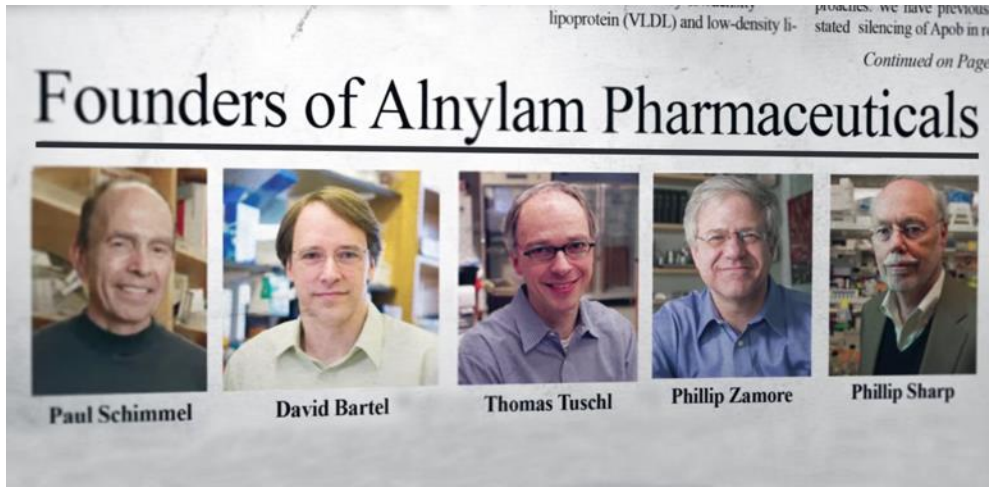
Elbashir et al., Nature, 2001;411:494-98



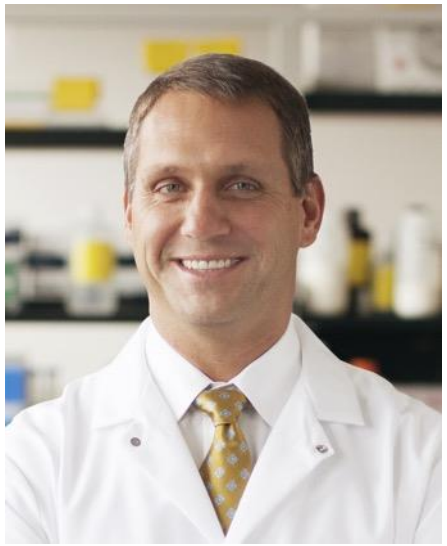
The Founding Team

A Conventional Biotech Company Start

Scientific Founders



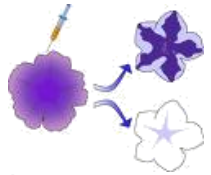
Venture Founders



CEO Founder

RNAi Therapeutics Timeline

From Observation to Nobel Prize to Innovative Medicines in ~3 Decades



Napoli and Jorgensen report that violet petunias turned white petunias instead of a deeper violet[1]

1990

Fire and Mello reported potent gene silencing effect in worms coined RNA interference[2]

1998

Alnylam founded

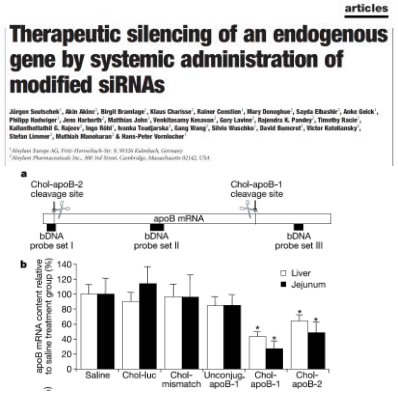
2002

Andrew Fire Craig Mello

Fire and Mello awarded the 2006 Nobel Prize in Physiology or Medicine

RNAi Platform Technology

2004: First in vivo silencing of a gene after systemic administration



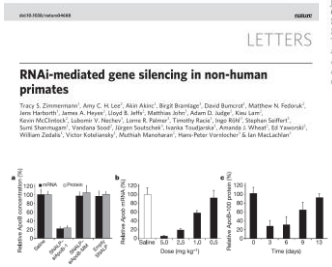
articles

Therapeutic silencing of an endogenous gene by systemic administration of modified siRNAs

Jürgen Soutschek, Akin Akinc, Birgit Bramlage, Klaus Charisse, Rainer Constien, Mary Donoghue, Sayda Elbashir, Anke Geick, Philipp Hadwiger, Jens Harborth, Matthias John, Venkitasamy Kesavan, Gary Lavine, Rajendra K. Pandey, Timothy Racie, Kallanthottathil G. Rajeev, Ingo Röhl, Ivanka Toudjarska, Gang Wang, Silvio Wuschko, David Bumcrot, Victor Koteliansky, Stefan Limmer, Muthiah Manoharan & Hans-Peter Vornlocher

Alnylam Europe AG, Fritz-Hornschuch-Str. 9, 95326 Kulmbach, Germany
Alnylam Pharmaceuticals Inc., 300 3rd Street, Cambridge, Massachusetts 02142, USA

2006: First silencing of a gene using LNPs

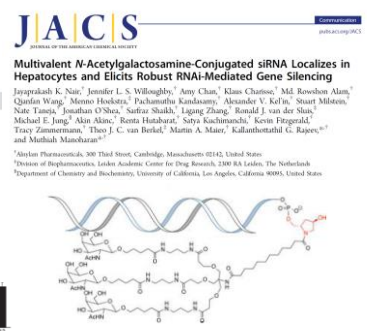


LETTERS

RNAi-mediated gene silencing in non-human primates

Tracy S. Zimmermann, Amy C. H. Lee, Akin Akinc, Birgit Bramlage, David Bumcrot, Matthew N. Fedoruk, Jens Harborth, James A. Heyes, Lloyd B. Jeffs, Matthias John, Adam D. Judge, Kieu Lam, Kevin McClintock, Lubomir V. Nechev, Lorna R. Palmer, Timothy Racie, Ingo Röhl, Stephan Seiffert, Sunit Shanmugam, Vandana Sood, Jürgen Soutschek, Ivanka Toudjarska, Amanda J. Wheat, Ed Yaworski, William Zedalis, Victor Koteliansky, Muthiah Manoharan, Hans-Peter Vornlocher & Ian MacLachlan

2014: First silencing of a liver gene with GalNAc conjugate



J|A|C|S

Communication

Multivalent *N*-Acetylgalactosamine-Conjugated siRNA Localizes in Hepatocytes and Elicits Robust RNAi-Mediated Gene Silencing

Jayaprakash K. Nair, Jennifer L. S. Willoughby, Amy Chan, Klaus Charisse, Md. Rowshon Alam, Qianfan Wang, Menno Hoekstra, Pachamuthu Kandasamy, Alexander V. Kel'in, Stuart Milstein, Nate Taneja, Jonathan O'Shea, Saifuz Shaikh, Lagang Zhang, Ronald J. van der Sluis, Michael E. Jung, Akin Akinc, Renta Hutabarat, Satya Kuchimanchi, Kevin Fitzgerald, Tracy Zimmermann, Theo J. C. van Berkel, Martin A. Maier, Kallanthottathil G. Rajeev, and Muthiah Manoharan

2018: Improved off target safety with ESC+

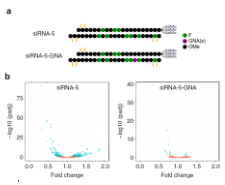
nature COMMUNICATIONS

ARTICLE

OPEN

Selection of GalNAc-conjugated siRNAs with limited off-target-driven rat hepatotoxicity

Maja M. Janas, Mark K. Schlegel, Carole E. Harbison, Vedat O. Yilmaz, Yongfeng Jiang, Rubina Parmar, Ivan Zlatev, Adam Castoreno, Huiles Xu, Svetlana Shulga-Morskaya, Kallanthottathil G. Rajeev, Muthiah Manoharan, Natalie D. Keirstead, Martin A. Maier & Vasant Jadhav



2018- 2020

onpattro

first RNAi therapeutic APPROVED

GIVLAARI™ (givosiran) injection for subcutaneous use 189 mg/mL

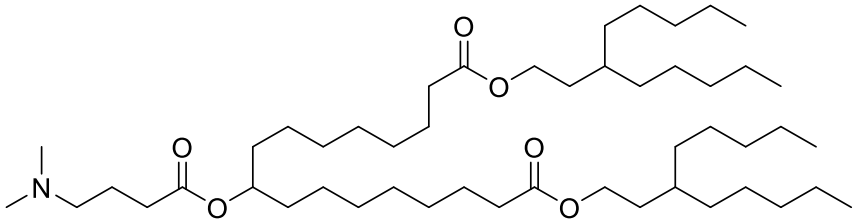
first GalNAc conjugate APPROVED

OXLUMO® (lumasiran) for injection 94.5mg/0.5mL

first pediatric RNAi therapeutic APPROVED

1. Napoli C et al. Plant Cell. 1990;2(4):279-289;
2. Fire A et al. Nature. 1998;391(6669):806-811

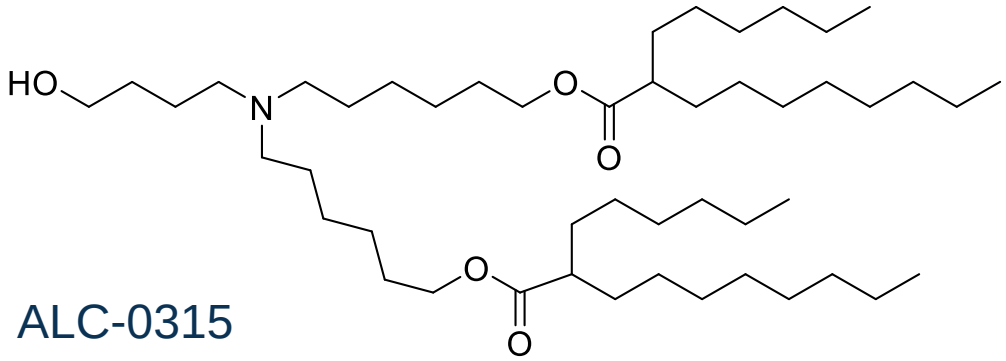
Alnylam LNPs Provide Foundation for mRNA Vaccines



ALNY-369

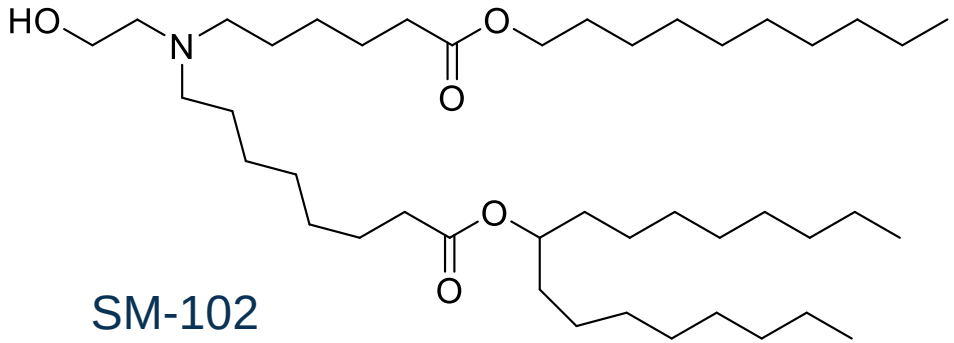
Patisiran Formulation:
Ionizable lipid/Chol/DPSC/PEG-lipid
50 / 38.5 / 10 / 1.5

Pfizer/BioNTech COVID vaccine



ALC-0315

Moderna COVID vaccine

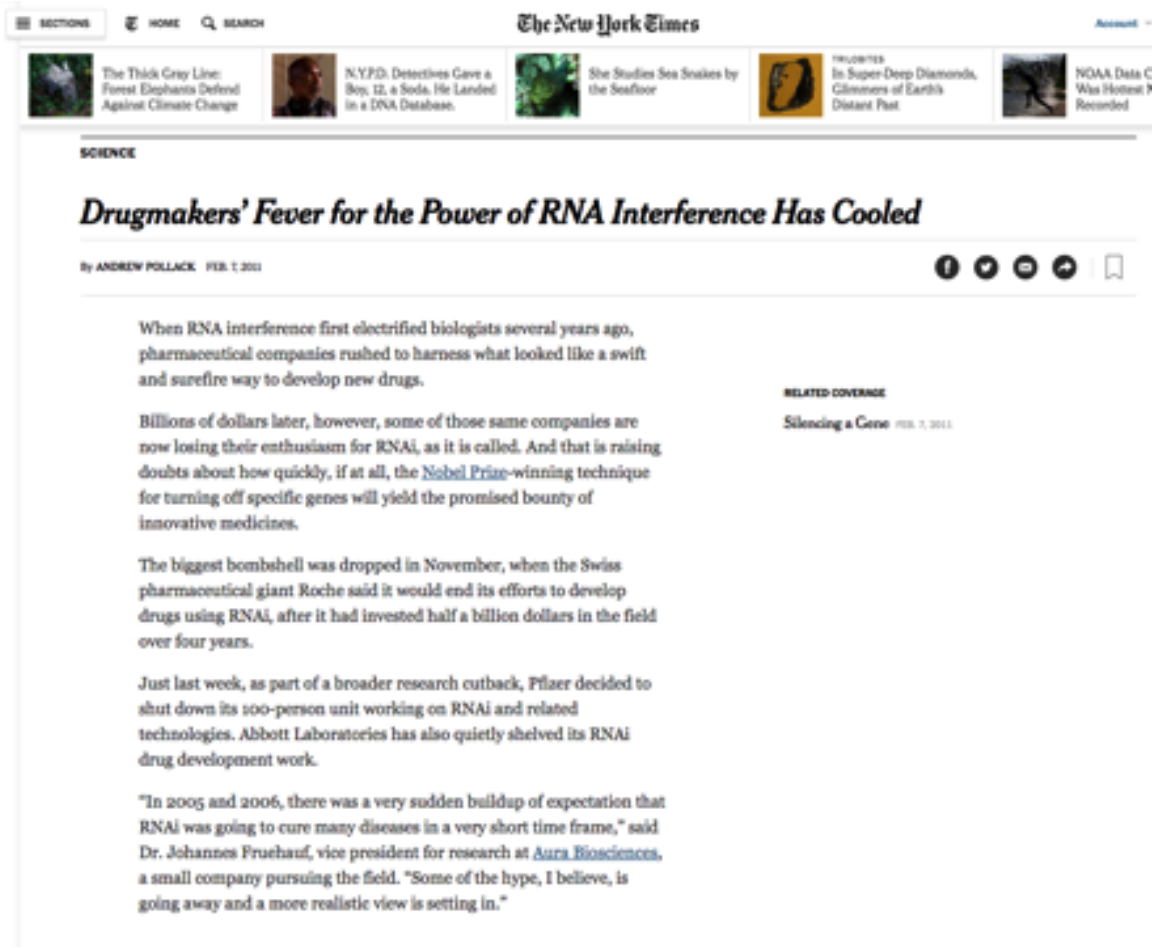


SM-102

COVID vaccine formulations:
Ionizable lipid/Chol/DPSC/PEG-lipid
50 / 38.5 / 10 / 1.5

Near Death Moments Made Us Stronger

Pharma Exits RNAi (2010-2012); Pipeline Setbacks (2016-2017)



The New York Times

SCIENCE

Drugmakers' Fever for the Power of RNA Interference Has Cooled

By ANDREW POLLACK FEB. 7, 2011

When RNA interference first electrified biologists several years ago, pharmaceutical companies rushed to harness what looked like a swift and surefire way to develop new drugs.

Billions of dollars later, however, some of those same companies are now losing their enthusiasm for RNAi, as it is called. And that is raising doubts about how quickly, if at all, the Nobel Prize-winning technique for turning off specific genes will yield the promised bounty of innovative medicines.

The biggest bombshell was dropped in November, when the Swiss pharmaceutical giant Roche said it would end its efforts to develop drugs using RNAi, after it had invested half a billion dollars in the field over four years.

Just last week, as part of a broader research cutback, Pfizer decided to shut down its 100-person unit working on RNAi and related technologies. Abbott Laboratories has also quietly shelved its RNAi drug development work.

"In 2005 and 2006, there was a very sudden buildup of expectation that RNAi was going to cure many diseases in a very short time frame," said Dr. Johannes Fruehauf, vice president for research at Aura Biosciences, a small company pursuing the field. "Some of the hype, I believe, is going away and a more realistic view is setting in."

RELATED COVERAGE

Silencing a Gene FEB. 7, 2011

xconomy

Alnylam Scraps RNAi Drug After Safety Problems, Shares Plunge

October 5, 2016

thepharmaletter

Up to date news for the Pharmaceutical and Biotechnology industries

Alnylam plunges on news of fatality in fitusiran study

July 7, 2017

Heritage of 5-Year Goals

Solid Track Record of Exceeding

RNAi Therapeutics: Transformational Medicines for Rare & Prevalent Diseases

Four Global Approvals in Just Over 2 Years

onpattro® (patisiran) lipid complex injection 10 mg/5 mL

Hereditary ATTR Amyloidosis with Polyneuropathy

U.S.
EU
Canada
Japan
Switzerland
Brazil
Israel
Taiwan

2018

GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

Acute Hepatic Porphyria

U.S.
EU
Brazil
Canada
Switzerland
Japan

2019

OXLUMO® (lumasiran) for injection 94.5 mg/0.5 mL

Primary Hyperoxaluria Type 1

EU
U.S.
Brazil

2020

Leqvio® (inclisiran)

Hypercholesterolemia

NOVARTIS

EU
Canada
Israel

2020

Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

- Genetic Medicines
- Cardio-Metabolic Diseases
- Infectious Diseases
- CNS/Ocular Diseases

		EARLY/MID-STAGE *(IND/CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION/ COMMERCIAL[1] (OLE/Phase 4/IIS/registries)	COMMERCIAL RIGHTS
onpattro (patisiran)	*hATTR Amyloidosis-PN*[2]			●	Global
GIVLAARI (givosiran)	*Acute Hepatic Porphyria*[3]			●	Global
OXLUMO (lumasiran)	*Primary Hyperoxaluria Type 1*[4]			●	Global
Leqvio® (inclisiran)	*Hypercholesterolemia*			●	Milestones & up to 20% Royalties[5]
Vutrisiran*	*hATTR Amyloidosis-PN*			●	Global
Patisiran	*ATTR Amyloidosis*		●		Global
Vutrisiran*	*ATTR Amyloidosis*		●		Global
Fitusiran*	*Hemophilia*		●		15-30% Royalties
Lumasiran	*Severe PH1* *Recurrent Renal Stones*	●	●		Global
Cemdisiran (+/- Pozelimab)[6]*	*Complement-Mediated Diseases*	●			50-50; Milestone/Royalty
Belcesiran[7]*	*Alpha-1 Liver Disease*	●			Ex-U.S. option post-Phase 3
ALN-HBV02 (VIR-2218)[8]*	*Hepatitis B Virus Infection*	●			50-50 option post-Phase 2
Zilebesiran (ALN-AGT)*	*Hypertension*	●			Global
ALN-HSD*	*NASH*	●			50-50
ALN-APP*	*Alzheimer's Disease;* *Cerebral Amyloid Angiopathy*	○			50-50
ALN-XDH*	*Gout*	○			Global

[1] Includes marketing application submissions; [2] Approved in the U.S. and Canada for the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy; [3] Approved in the U.S., Brazil and Canada for the treatment of adults with acute hepatic porphyria (AHP), and in the EU and Japan for the treatment of AHP in adults and adolescents aged 12 years and older; [4] Approved in the U.S., EU and Brazil for the treatment of primary hyperoxaluria type 1 in all age groups; [5] Novartis has obtained global rights to develop, manufacture and commercialize inclisiran; 50% of inclisiran royalty revenue from Novartis will be payable to Blackstone by Alnylam; [6] Cemdisiran and pozelimab are each currently in Phase 2 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics; [7] Dicerna is leading and funding development of Belcesiran; [8] Vir is leading and funding development of ALN-HBV02; * Not approved for any indication and conclusions regarding the safety or efficacy of the drug have not been established.

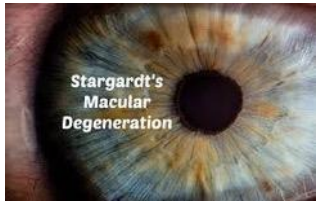
As of October 2021

Some New Themes for Today

Many Opportunities for Continued Pipeline Growth

POTENTIAL NEW INDICATIONS FOR EXISTING PRODUCTS AND PROGRAMS

Vutrisiran

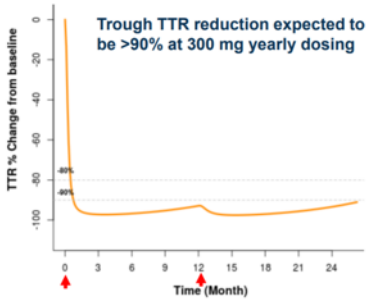


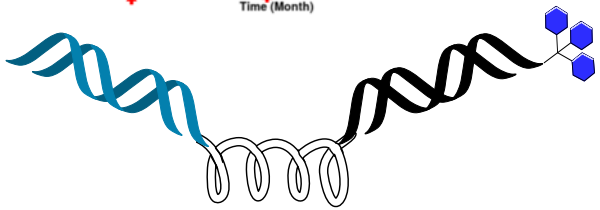
NEW TARGETS AND PLATFORM ADVANCES

- Human Genetics
- IKARIA
- GEMINI

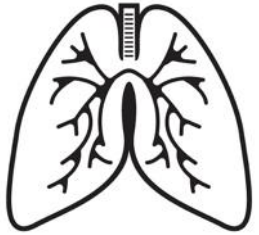
biobank uk

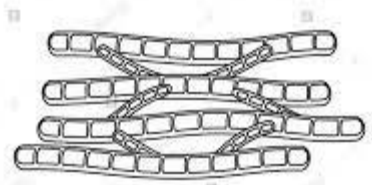
Human dose projection





UNLOCKING NEW TISSUES





Thank You!

Our Mission Continues, Patients Are Waiting

After an incredible 19-year journey….I thank you for your confidence and support. Alnylam's brightest days are ahead!

Glaucienne
Diagnosed with AHP (Brazil)

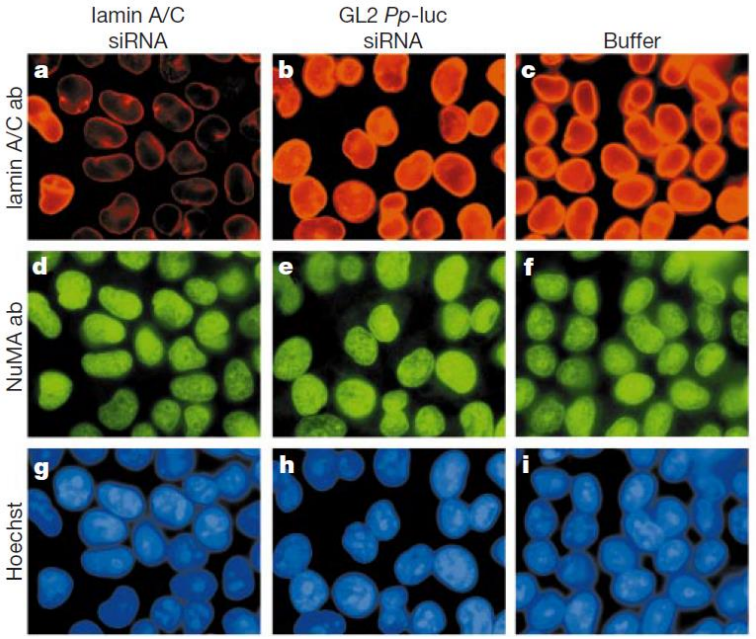
Delivering Sustainable Innovation with RNAi Therapeutics

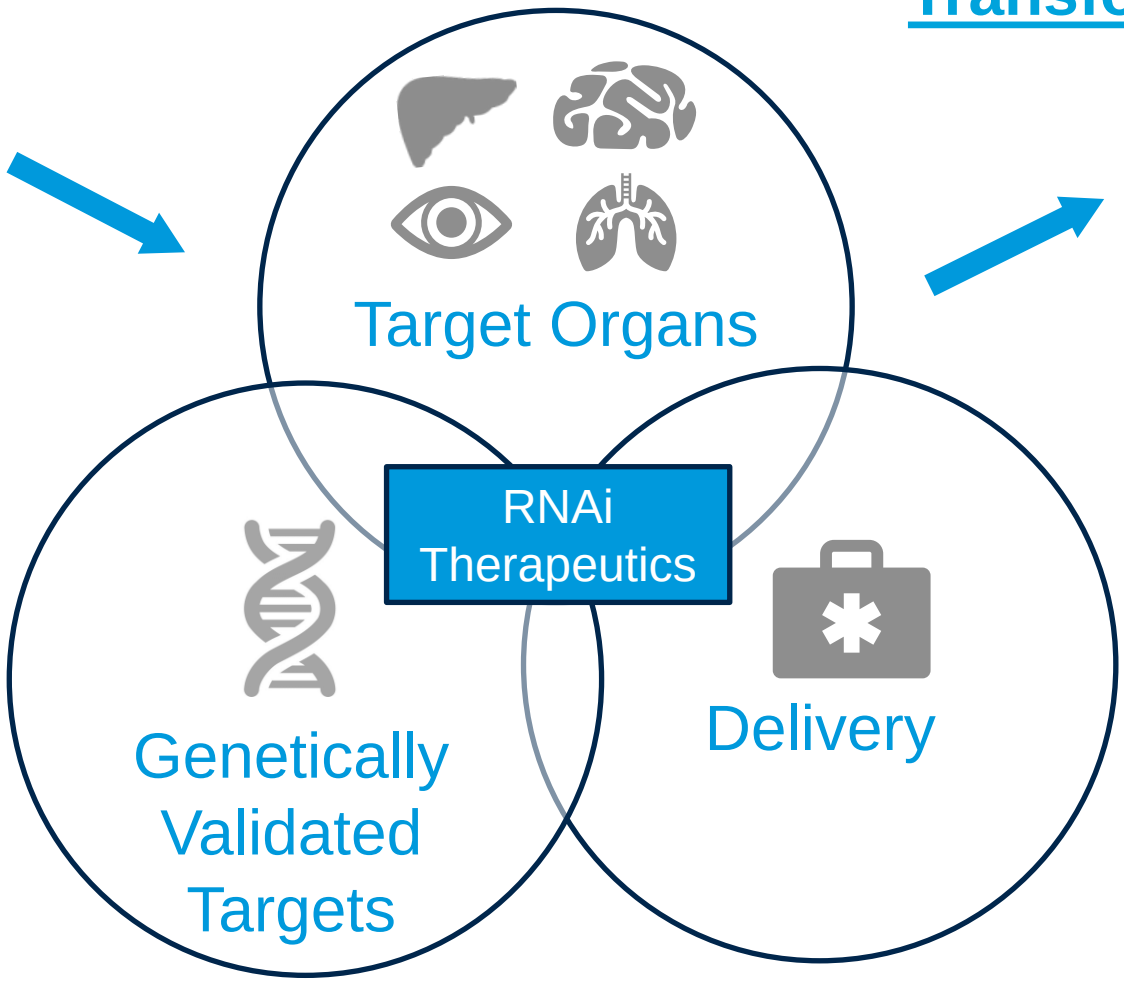
Akshay Vaishnaw, M.D., Ph.D.
President, Research & Development

Alnylam® PHARMACEUTICALS

Focused R&D Strategy

Turning an *In Vitro* Observation into a New Class of Transformative Medicines





Transformative Medicines

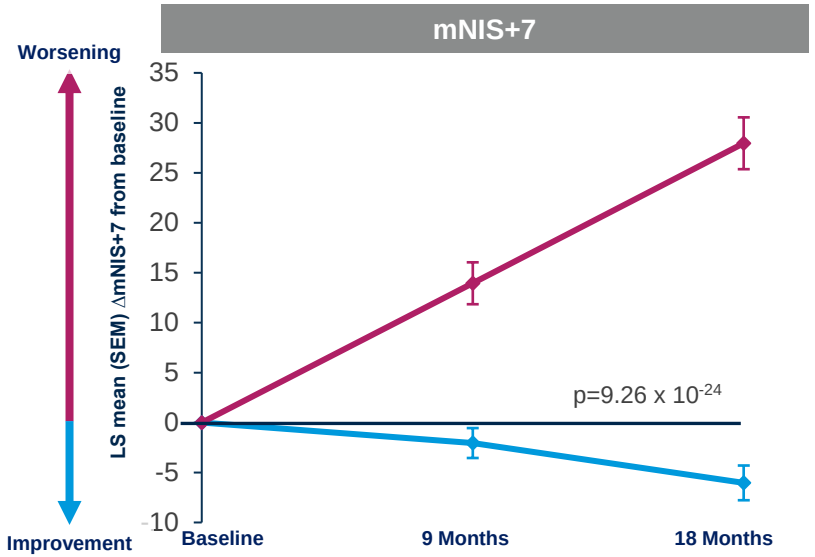
Agenda

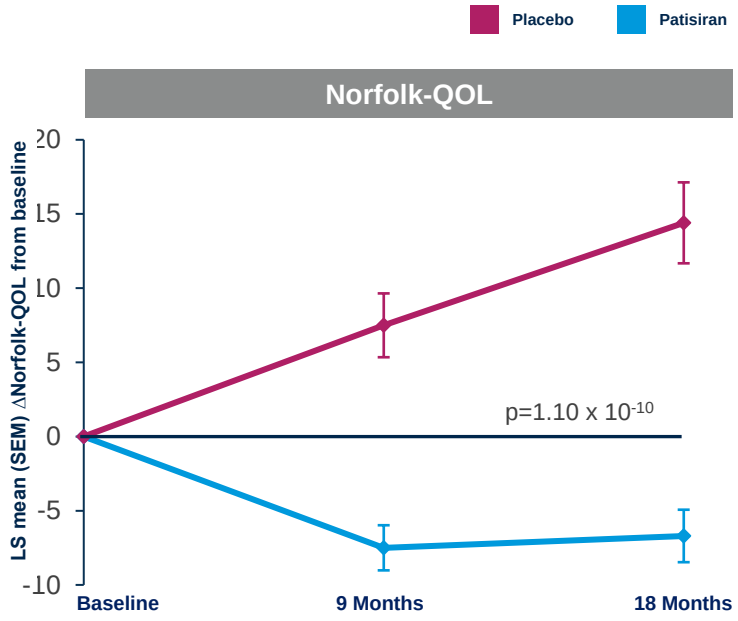
Products

Platform

P5x25 and Beyond

Patisiran APOLLO Phase 3 Study Results





At 18 months

- -6.0 point change relative to baseline
- 34.0 point difference relative to placebo
- 56.1% of patients improved*

At 18 months

- -6.7 point change relative to baseline
- 21.1 point difference relative to placebo
- 51.4% of patients improved*

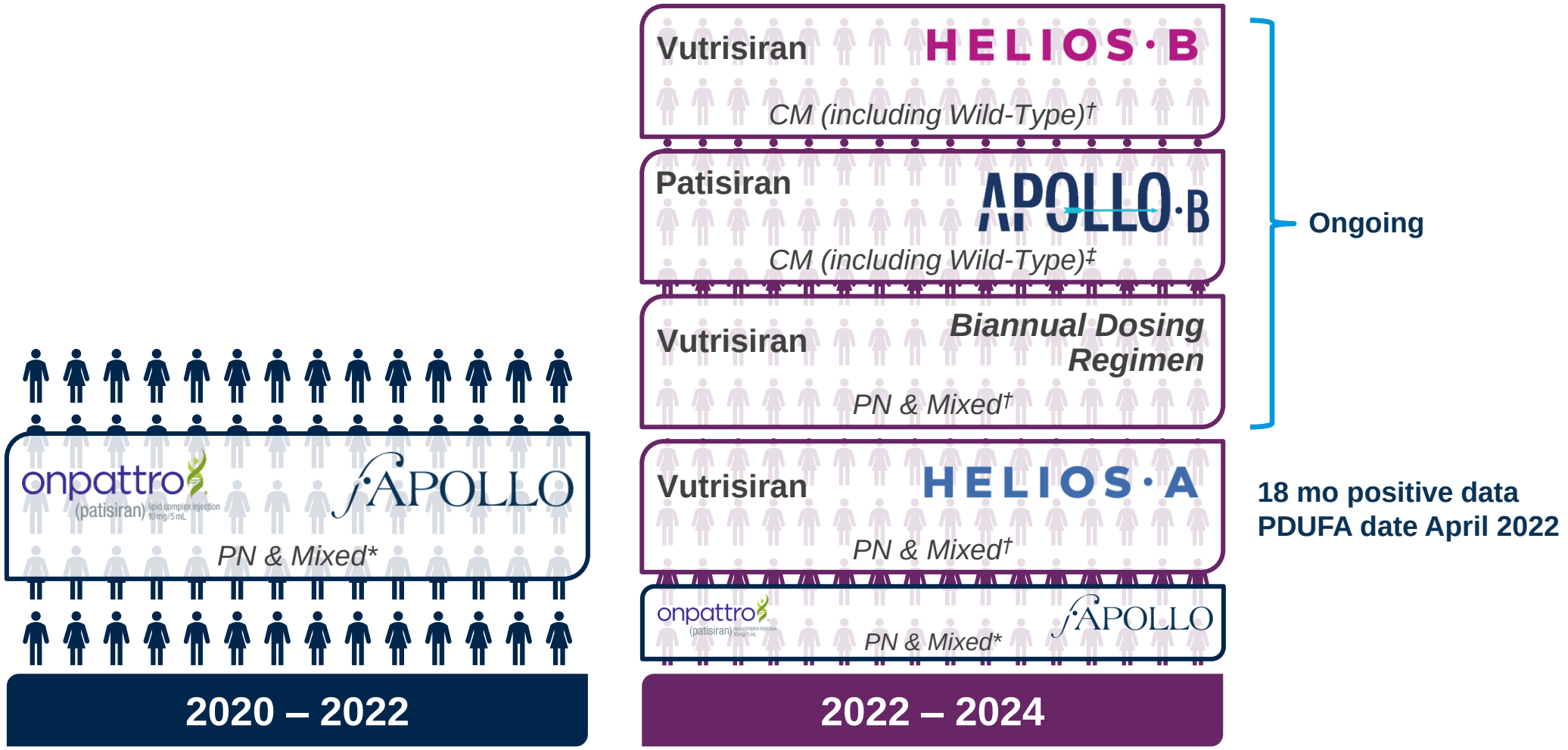
- Majority of AEs mild or moderate in severity
- No safety signals related to steroid pre-medication regimen or TTR reduction
- No hepatic, renal or hematologic (including platelet) safety signals

Adams et al., EU-ATTR Meeting, Nov 2017

*Improvement defined as patients with <0 point increase from baseline to 18 months

Alnylam ATTR Amyloidosis Franchise

Expand Value to Patients Globally for Many Years to Come



* ONPATTRO is approved in the U.S. and Canada for the treatment of the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or 2 PN; ‡ ONPATTRO has not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in this population. APOLLO-B study of patisiran in ATTR patients with cardiomyopathy is ongoing.

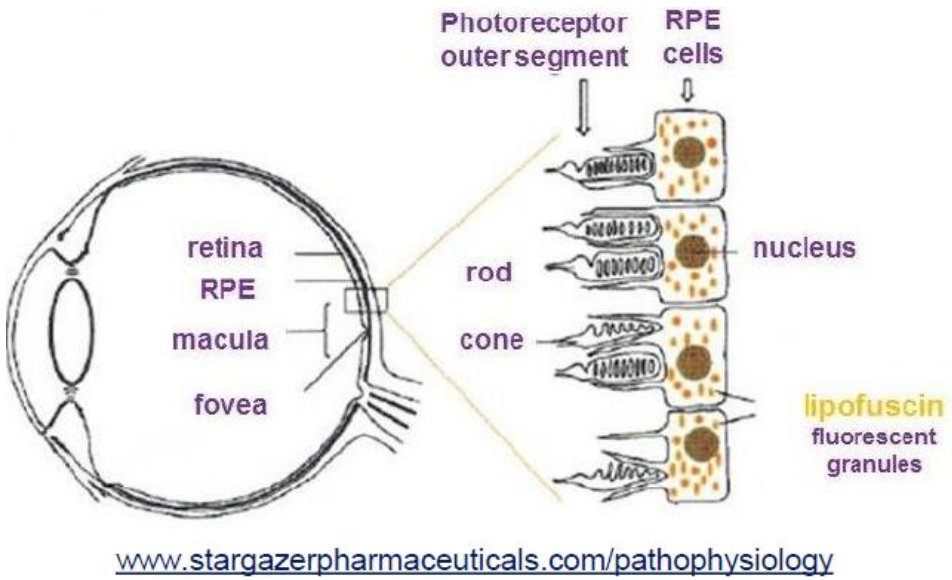
† Vutrisiran is an investigational agent and has not been approved by the FDA, EMA, or any other regulatory agency and no conclusions can or should be drawn regarding its safety or effectiveness; NDA accepted seeking approval of vutrisiran for the treatment of the polyneuropathy of hATTR amyloidosis in adults based on positive 9-Month results in HELIOS-A study; HELIOS-B study of vutrisiran in ATTR patients with cardiomyopathy is ongoing

Intended to be illustrative and not intended to represent specific estimates of patient numbers

Stargardt Disease, Most Common Inherited Retinopathy

Exciting New Opportunity for Vutrisiran

ABCA4 mutations lead to build up of toxic bisretinides (lipofuscin)



www.stargazerpharmaceuticals.com/pathophysiology

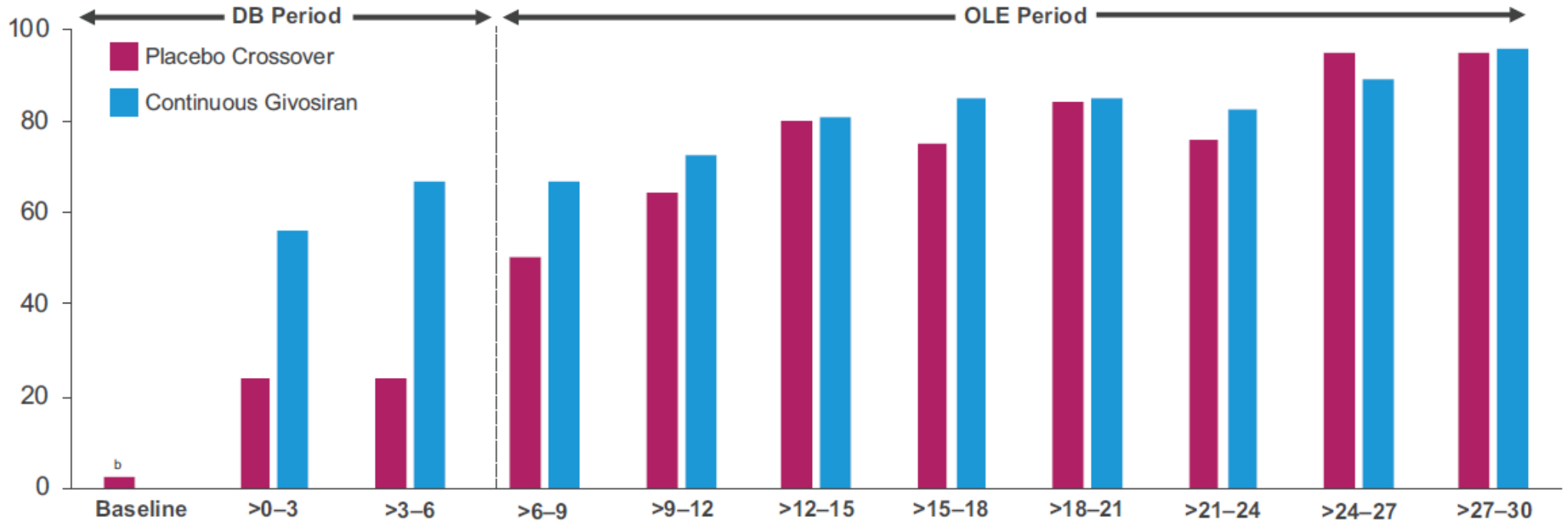
Central Vision Loss

Leading cause of blindness in children from an inherited, retinal disease

Incidence of 1 in 8,000-10,000 (~65,000 in U.S. & EU5)

Givosiran Phase 3 Population Shows Durable Efficacy at Two Years

Proportion of Composite Attack–Free Patients by 3-Month Interval during DB and OLE Periods



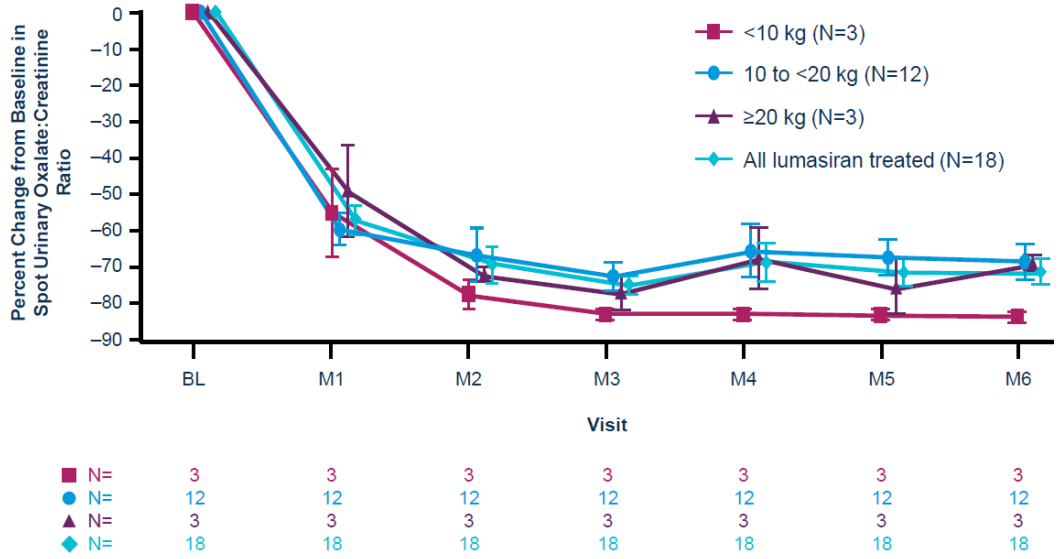
No. of patients	Baseline	>0–3	>3–6	>6–9	>9–12	>12–15	>15–18	>18–21	>21–24	>24–27	>27–30
Placebo/Givosiran	46	46	46	46	45	45	44	43	42	41	18
Givosiran/Givosiran	48	48	48	48	47	46	46	46	46	46	22

- The safety profile of givosiran remained acceptable with long-term treatment
- The majority of AEs continued to be mild to moderate in severity

Bonkovsky et al., UEG 2021

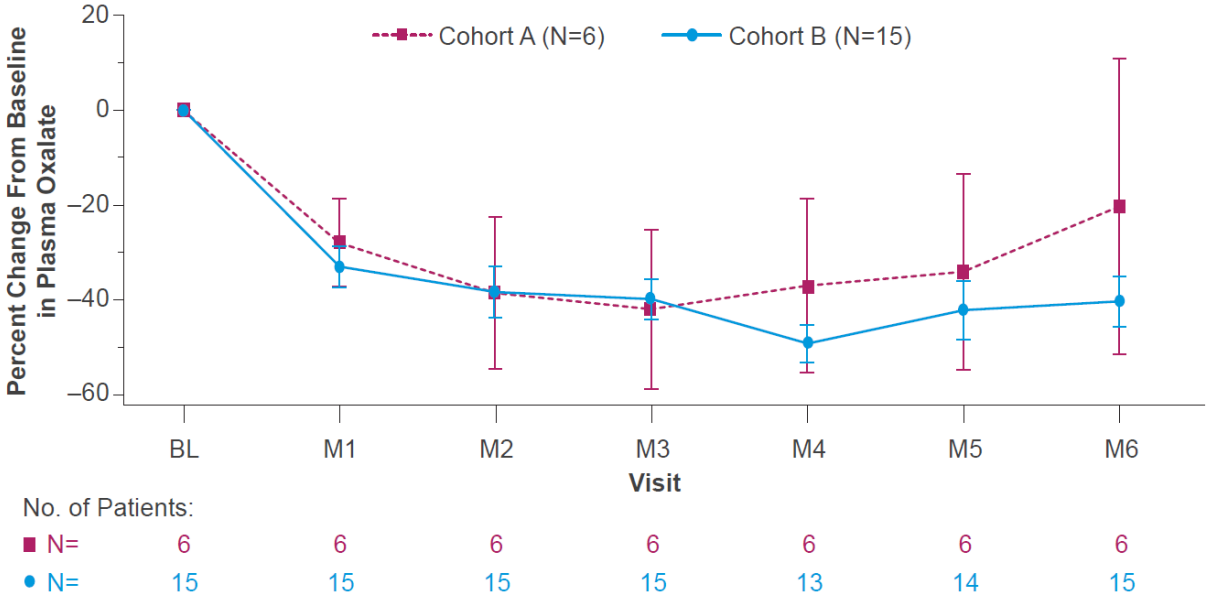
Lumasiran Impacts Urinary Oxalate Across PH1 Patient Population

Illuminate-B Study in Patients <6yrs age



- No deaths, discontinuations or withdrawals, or severe AEs
- One serious AE occurred which was not considered related to lumasiran

Illuminate-C Study in Patients With eGFR<45mL/min



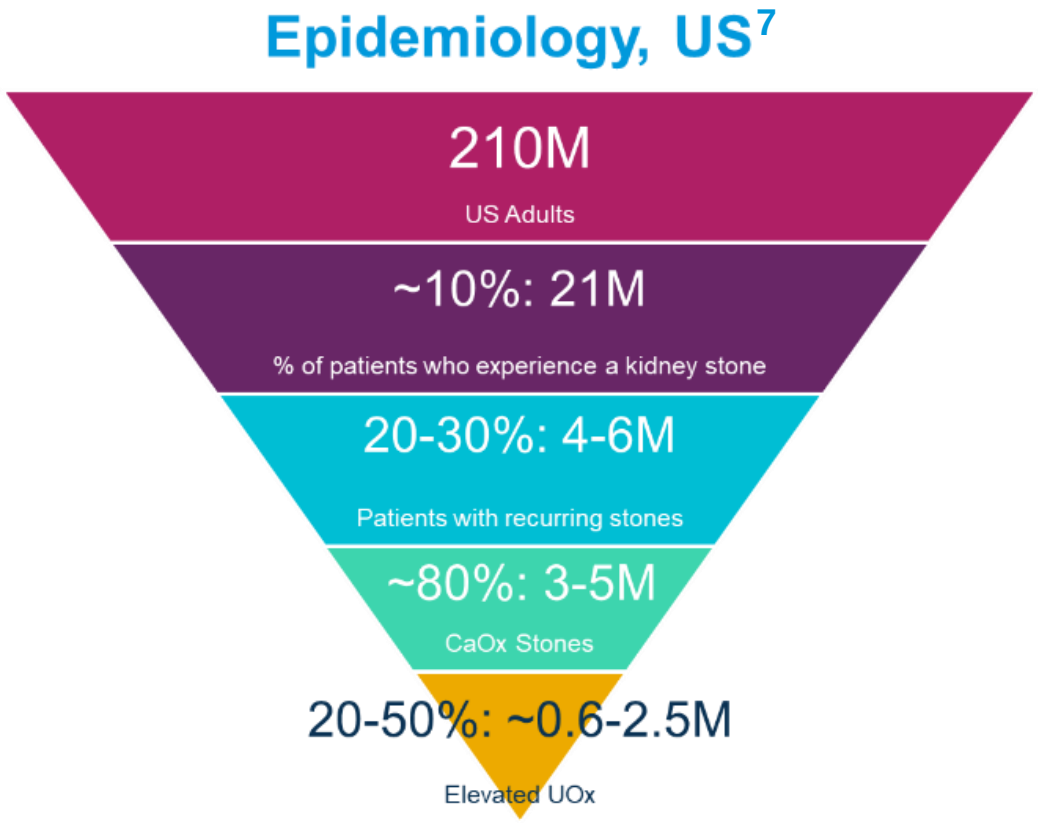
- Majority of AEs were mild or moderate in severity
- No serious or severe AEs related to lumasiran and no death of patients who received lumasiran

Prevention of Recurrent Calcium Oxalate Kidney Stone Disease

Exciting New Opportunity for Lumasiran[1]

- Recurrent kidney stone disease is associated with significant clinical burden including pain, infection/sepsis, hospitalizations, and a greater risk for developing chronic kidney disease (CKD) and end stage kidney disease[2-4]

- There are limited effective treatment options and despite best standard of care (dietary/lifestyle changes, citrate supplementation, thiazide diuretics, etc.) recurrent stones still occur[5,6]



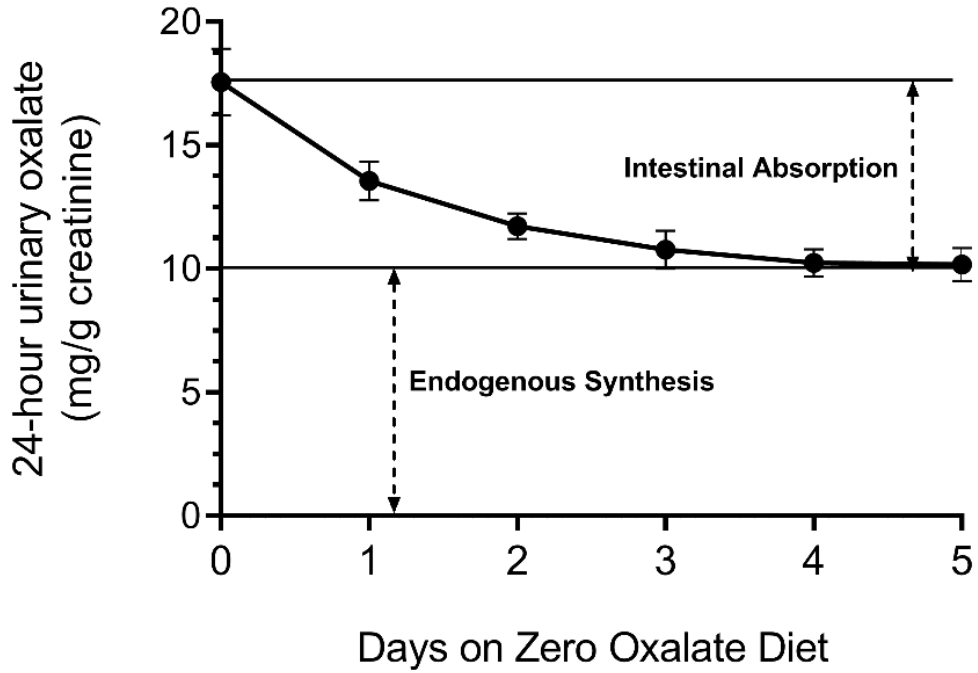
1. Beara-Lasic and Goldfarb, Clin J Am Soc Nephrol 2019. 2. Dhondup, Am J Kidney Dis, 2018. 3. Rule, Clin J Am Soc Nephrol, 2009. 4. Alexander et al., BMJ 2012. 5. Pearle et al., AUA Guideline 2014. 6. Türk et al., EAU Guidelines on Urolithiasis 2021. 6. Curhan, Urol Clin North Am, 2007. 7. Internal estimates based on multiple data sources.

CKD, chronic kidney disease; M, million; UOx, urinary oxalate

Lumasiran Life-Cycle Management

Proof-of-Concept Phase 2 Study in Recurrent Stone Former Population

Endogenous oxalate is >50% based on healthy volunteer study[4]



Rationale:

- Approximately 80% of kidney stones in adults are formed from calcium oxalate crystals[1-2]
- Stone formation occurs when a supersaturating level of calcium oxalate is present in the urine[3-4]
- Liver production of oxalate is expected to be a significant driver of high urinary oxalate based on a healthy volunteer study[4]
- Lumasiran is designed to reduce hepatic production of oxalate through inhibition of GO[5]

Population:

- Recurrent calcium oxalate kidney stone disease and elevated 24-hour urinary oxalate levels
  - Excludes patients with secondary causes of elevated urinary oxalate/recurrent kidney stones

Primary Endpoint:

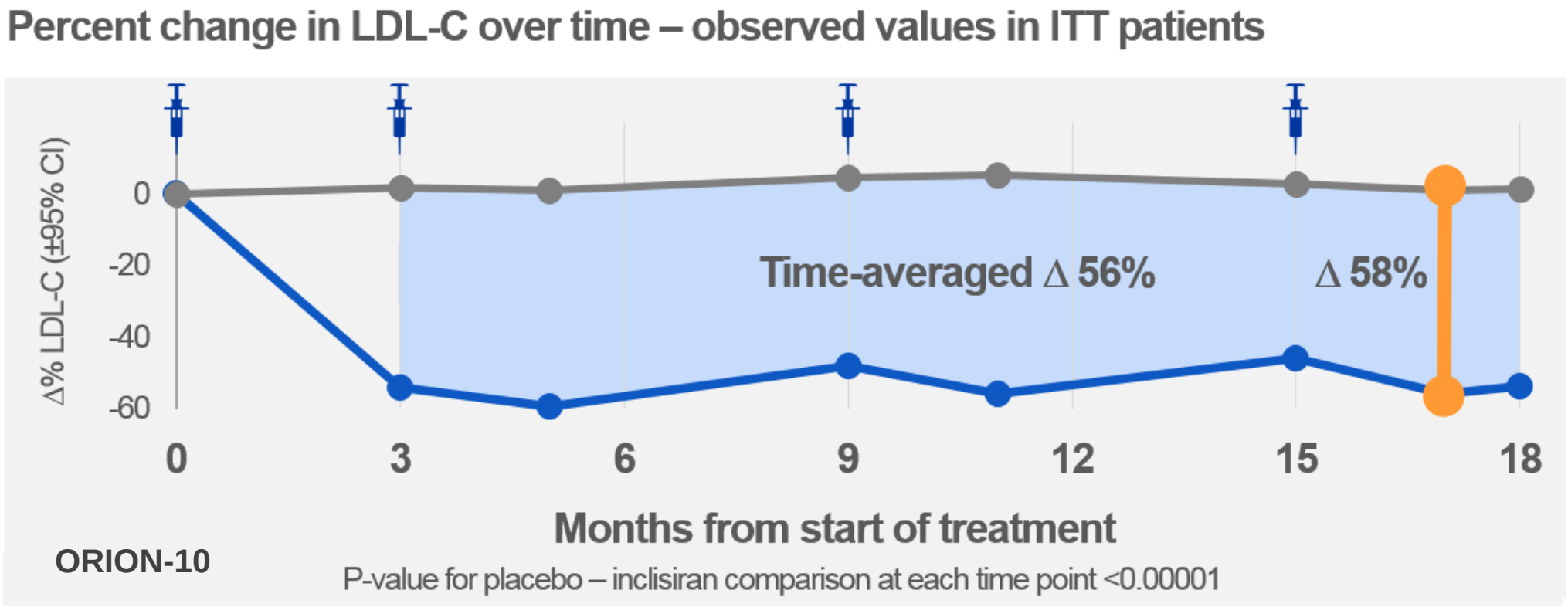
- Percent change in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)

Expected to initiate in 2021

1. Worcester and Coe, Prim Care 2008. 2. Worcester and Coe, NEJM 2010. 3. Coe et al., Nat Rev Nephrol 2016. 4. Mitchell et al., Am J Physiol Renal Physiol 2019. 5. Liebow et al., J Am Soc Nephrol 2017.
GO, glycolate oxidase

Inclisiran ORION-10+11 Results

Durable, Potent, and Consistent LDL-C Lowering Over 18 Months



- Inclisiran safety profile similar to placebo, with no adverse changes in laboratory markers
- Injection site events 2.6-4.7% - predominantly mild and none persistent
- ORION-10+11: Numerically fewer CV events reported for inclisiran than placebo (exploratory endpoint)

Wright et al., AHA 2019; Ray et al., ESC Congress 2019
All 95% confidence intervals are less than ±2% and therefore are not visible outside data points

RNAi Therapeutics Profile Supports Potential Expansion to Prevalent Diseases

- Durability
- Clamped pharmacology
- Safety profile evaluated in clinical trials
- Improved access

RARE

ONPATTRO: hATTR-PN[1]
GIVLAARI
OXLUMO
Vutrisiran: hATTR-PN[3]
Fitusiran
Belcesiran
ALN-APP
ALN-HTT

SPECIALTY

Patisiran: ATTR-CM[2]
Vutrisiran: ATTR-CM[3]
Cemdisiran

PREVALENT

Leqvio® (inclisiran)[4]
ALN-HBV02 (VIR-2218)
Zilebesiran (ALN-AGT)
ALN-HSD
ALN-XDH
ALN-KHK

[1] ONPATTRO is approved in the U.S. and Canada for the treatment of the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or 2 PN; [2] Patisiran has not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in this population. APOLLO-B study of patisiran in ATTR patients with cardiomyopathy is ongoing; [3] Vutrisiran is an investigational agent and has not been approved by the FDA, EMA, or any other regulatory agency and no conclusions can or should be drawn regarding its safety or effectiveness; NDA accepted seeking approval of vutrisiran for the treatment of the polyneuropathy of hATTR amyloidosis in adults based on positive 9-Month results in HELIOS-A study; HELIOS-B study of vutrisiran in ATTR patients with cardiomyopathy is ongoing; [4] Leqvio is approved in the EU for the treatment of adults with hypocholesterolemia or mixed dyslipidemia; in U.S., NDA for inclisiran resubmitted in response to Complete Response Letter.

RNAi Therapeutics Could Potentially Reimagine Treatment of Hypertension

Opportunity for Tonic Blood Pressure (BP) Control

Disease Overview

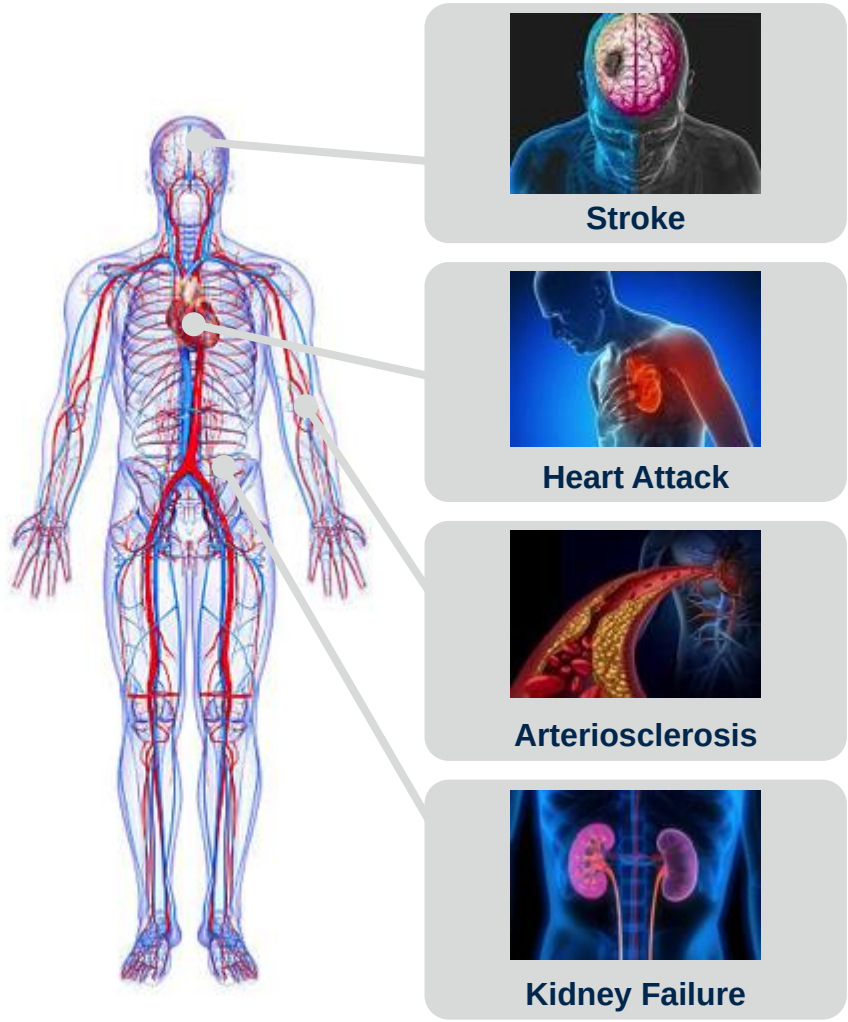
Primary Hypertension[1]	Hypertension at high CV risk[2]
~108 Million in U.S.	**~38 Million** in U.S.

>71% of patients have uncontrolled hypertension (>130/80 despite treatment)[3]

Hypertension risk further exacerbated by variability in BP **control**, lack of nighttime **dipping**, and poor medication **adherence**

Together, contribute to substantial risk of CV morbidity and mortality

Potential Complications of Uncontrolled Hypertension



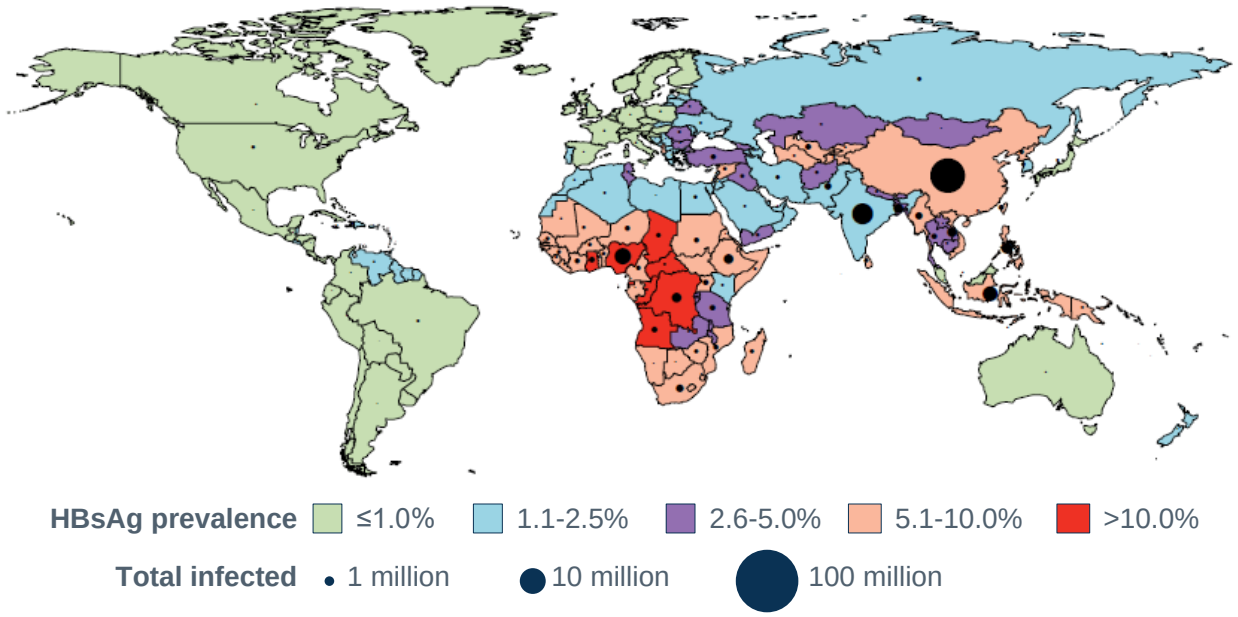
[1] Centers for Disease Control and Prevention (CDC). Hypertension Cascade: Hypertension Prevalence, Treatment and Control Estimates Among US Adults Aged 18 Years and Older Applying the Criter American College of Cardiology and American Heart Association's 2017 Hypertension Guideline—NHANES 2013–2016. Atlanta, GA: US Department of Health and Human Services; 2019.

[2] Estimated from multiple sources and internal estimates: Dorans. JAHA. 2018; Al Kibria. Hypertens Res. 2019; CDC Hypertension Cascade. 2019; High CV risk: ASCVD risk score ≥20% and/or history of CVD

[3] U.S. Department of Health and Human Services. The Surgeon General's Call to Action to Control Hypertension. Washington, DC: U.S. Department of Health and Human Services, Office of the Surgeon General; 2020.

HBV: Global Health Problem Impacting Developed and Developing Countries

HBV Prevalence Estimate: ~290 M
(diagnosed + undiagnosed)



~24M diagnosed patients
in top high-/middle-income countries*

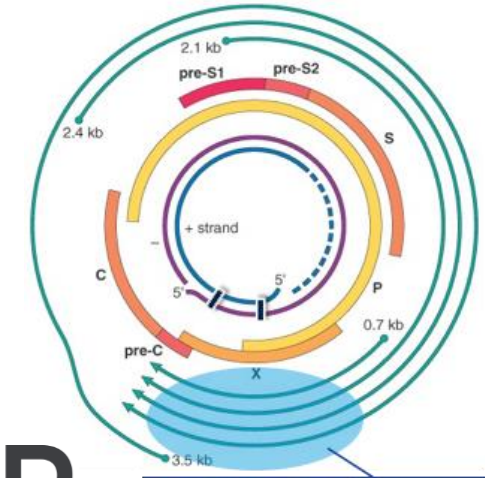
ALN-HBV02 (VIR-2218)
Investigational RNAi Therapeutic for Treatment of Chronic HBV Infection

Targets conserved region in X gene, upstream of integration hotspot, allowing for

- Single siRNA to suppress HBsAg from both intDNA and cccDNA
- Suppression of all HBV mRNAs, which overlap in this region

GalNAc-conjugated ESC+ siRNA

- Subcutaneous administration with GalNAc ligand for targeted delivery to liver and prolonged pharmacodynamic effect
- ESC+ technology: improved specificity of RNAi activity



siRNA targeting an overlapping region can silence all transcripts

*Main high-income countries (HICs) outside US/EU with high prevalence are S Korea, Taiwan, Canada, and Australia; HIC is defined per World Bank designations.
The Polaris Observatory Collaborators. Lancet Gastroenterol Hepatol 2018

Nonalcoholic Fatty Liver Disease (NAFLD)

Disorder of Over-Nutrition Leading to Accumulation of Hepatic Fat

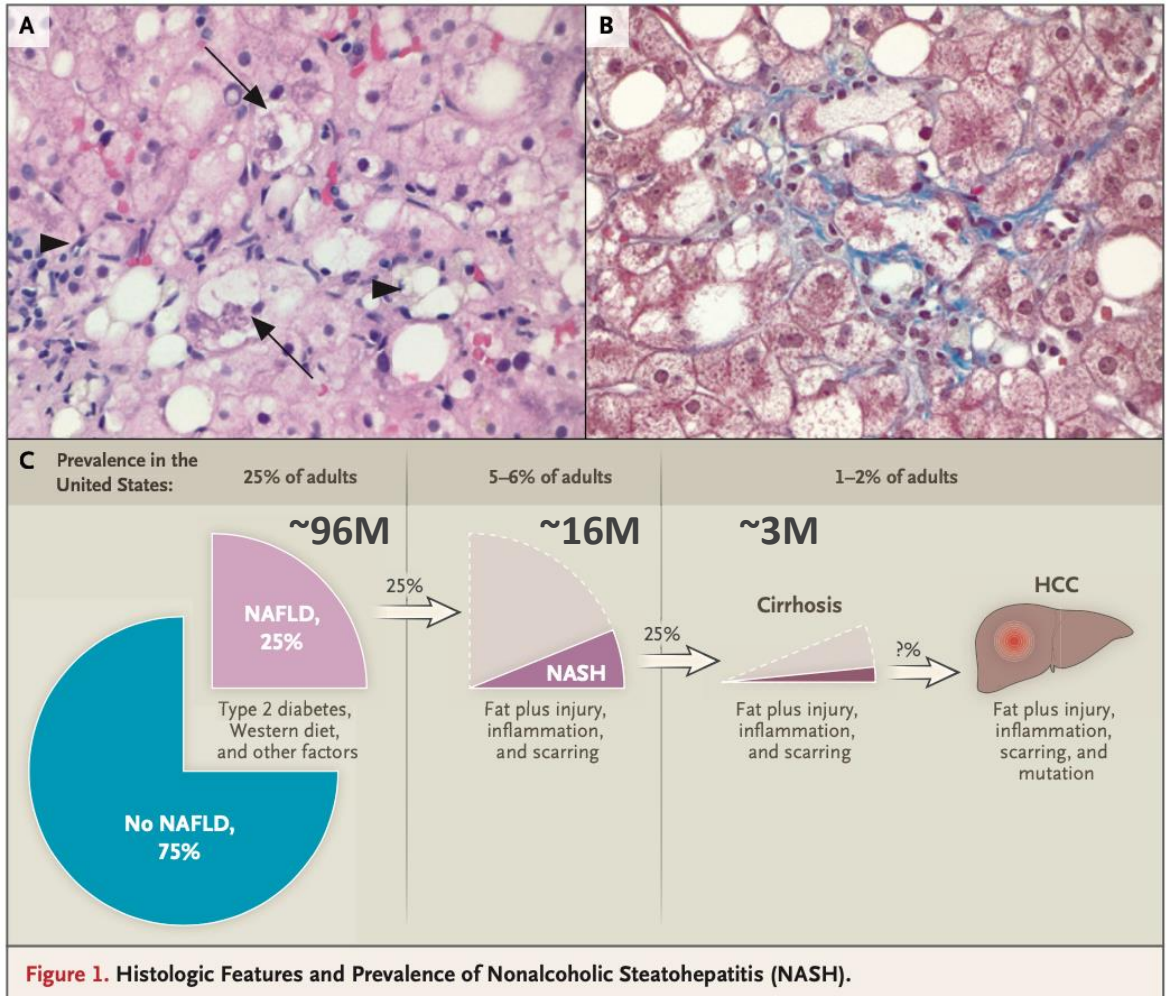


Figure 1. Histologic Features and Prevalence of Nonalcoholic Steatohepatitis (NASH).

Nonalcoholic steatohepatitis (NASH)

- Subset of NAFLD defined by presence of liver cell injury and inflammation
- Associated with progressive fibrosis, cirrhosis, and hepatocellular carcinoma
- Co-morbidities include obesity, metabolic syndrome, and type 2 diabetes

NASH treatment

- No approved medical therapies
- Weight loss is effective but difficult to achieve and generally not durable

Adapted from Diehl, A., Day, C. (2017). NEJM 377(21), 2063-2072.

Agenda

Products

Platform

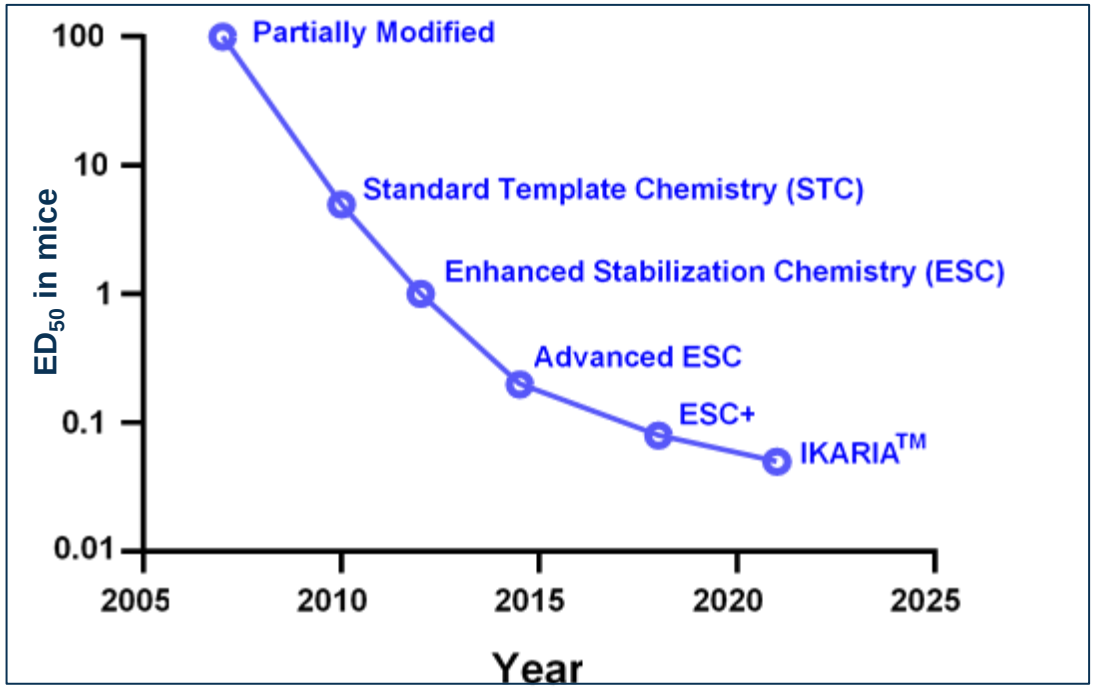
P5x25 and Beyond

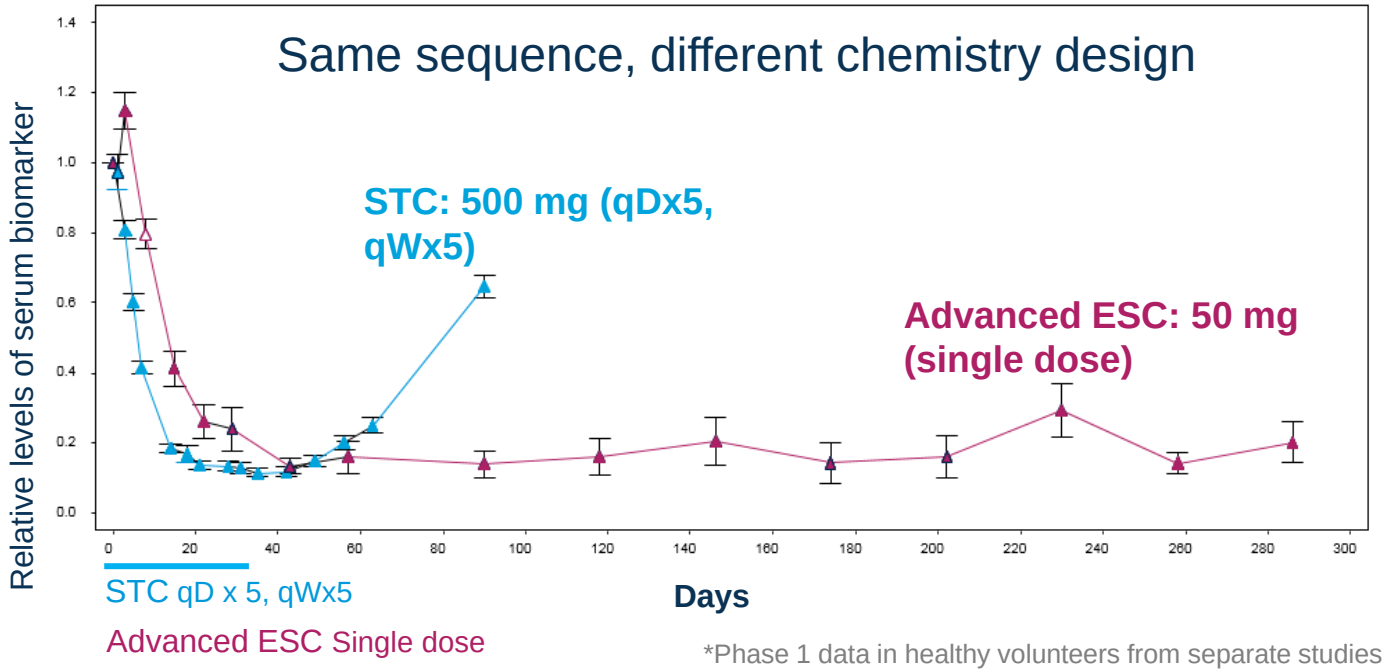
Evolution of Conjugate Chemistry Over Nearly Two Decades

Potency and specificity

Durability

ED_{50} Dose in mice for various designs





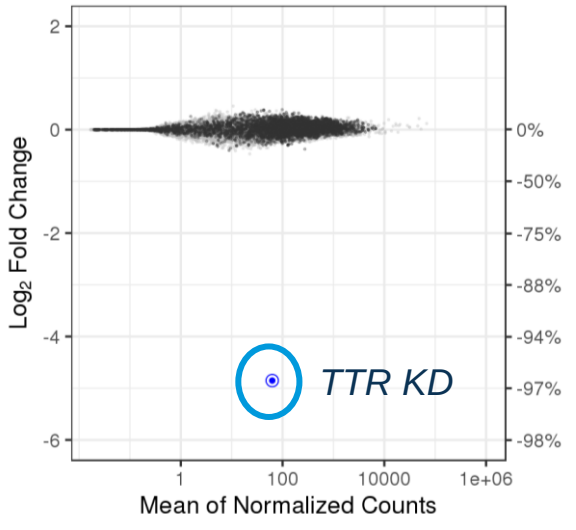
*Phase 1 data in healthy volunteers from separate studies

Zimmermann et al Nature 2006; Nair et al. JACS 2014; Foster et al. Mol. Ther. 2018; Janas et al. Nature Comm. 2018

IKARIA™ Platform: Proprietary siRNA Design with Novel Chemistry

Super-specific siRNAs May Enable Higher Doses to Achieve Annual Dosing

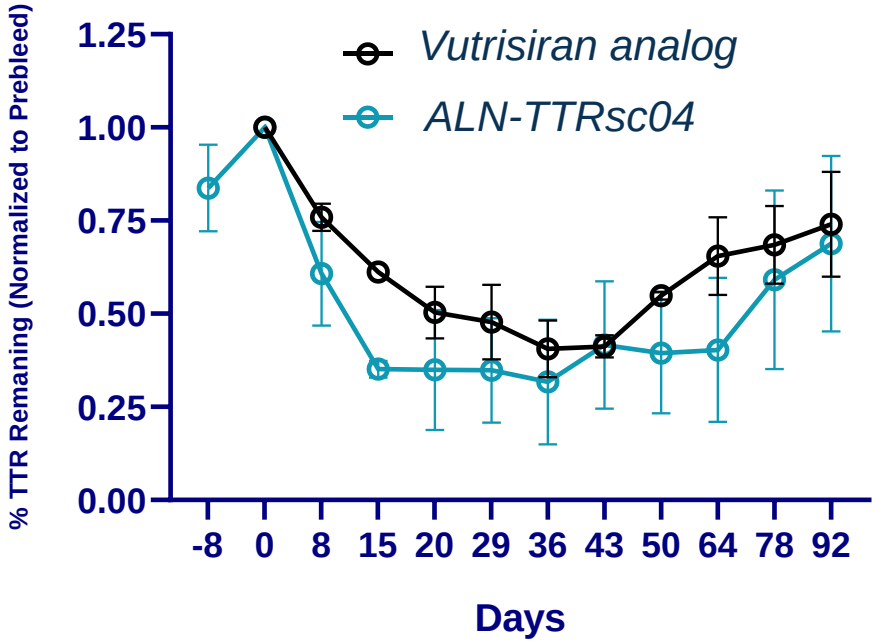
Exquisite specificity



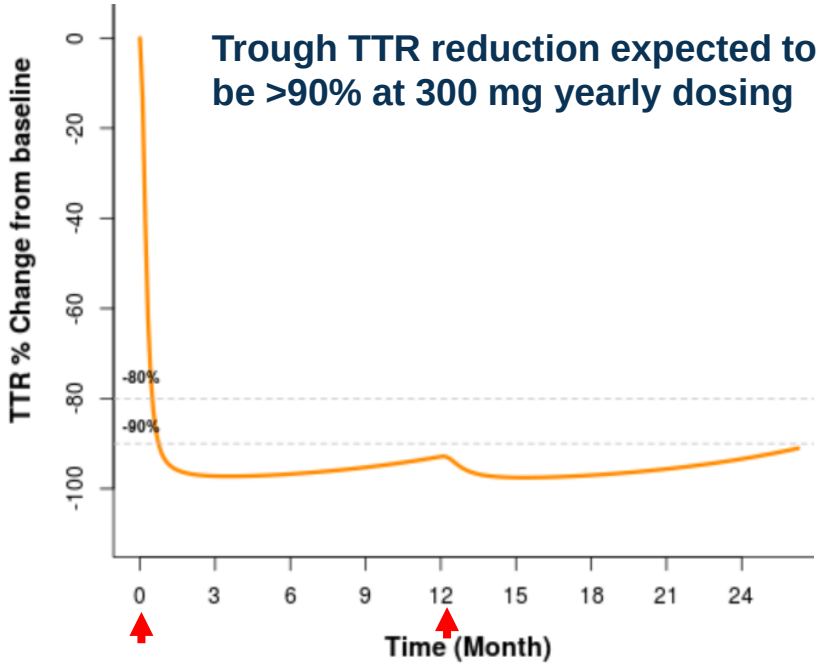
RNAseq analysis

High potency in NHP

0.5 mg/kg single sc dose



Human dose projection



Modeling predicts potential for once-a-year dosing in humans with greater than 90% TTR reduction

Different Dimensions of Unmet Need in the Cardiovascular Space

Non-adherence and Multiple Co-morbidities leading to Adverse Cardiac Outcomes

"Two problems with existing adherence interventions are clear.

1. *Even the most effective interventions did not lead to large improvements in adherence and treatment outcomes. As reported in a recent meta-analysis of adherence interventions, adherence was improved only by approximately 4 to 11% by most interventions*

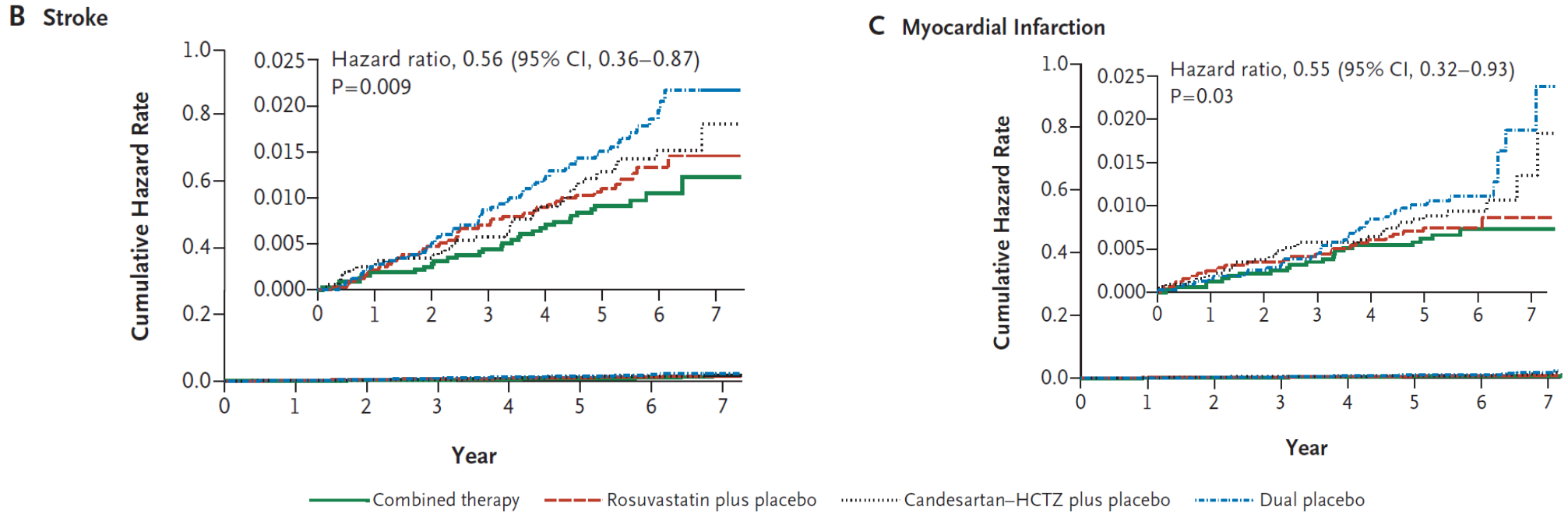
2. *Most interventional trials are focused on a single medication or a particular disease area. In reality, the majority of patients take multiple medications for multiple medical problems."*

Bosworth et al, Am Heart J, (2011)

Clinical Trials Confirm the Benefits of Concomitant Treatment in Primary Prevention of Cardiovascular Disease

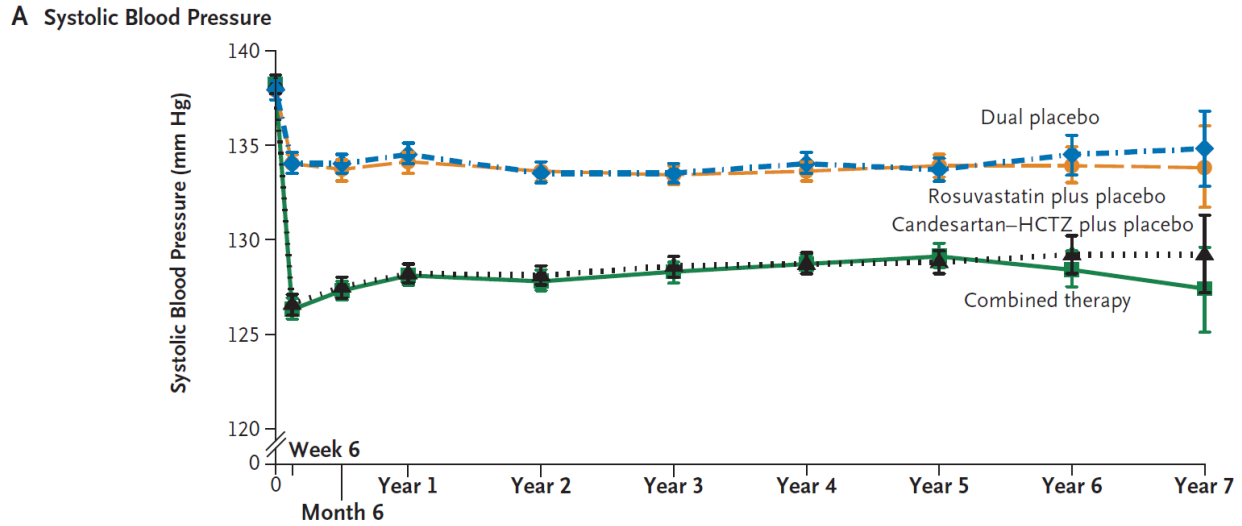
Head-to-Head Comparison of Treatments for High LDL-cholesterol and BP vs. LDL only vs. BP only

- 12705 intermediate CV risk individuals >55 yrs, randomized to rosuvastatin vs. candesartan-HCTZ vs rosuvastatin AND candesartan-HCTZ vs placebo

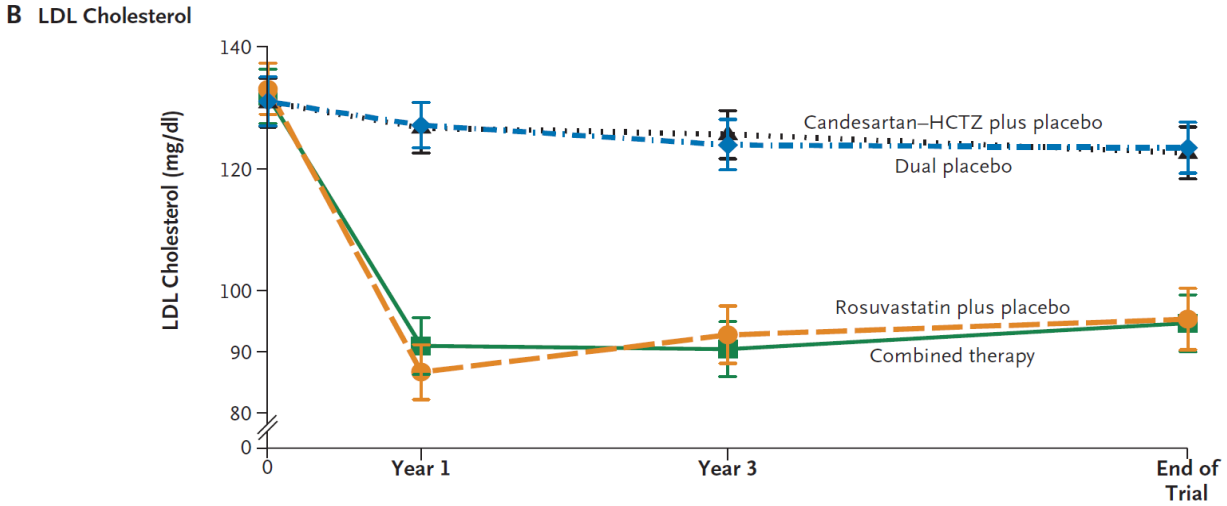


Yusuf et al., NEJM (2016)

Blood Pressure and LDL-cholesterol Reductions in Yusuf et al (2016) Study



Over course of trial mean systolic BP reduction of 6.2 mmHg



Mean LDL reduction of 33.2 mg/dL

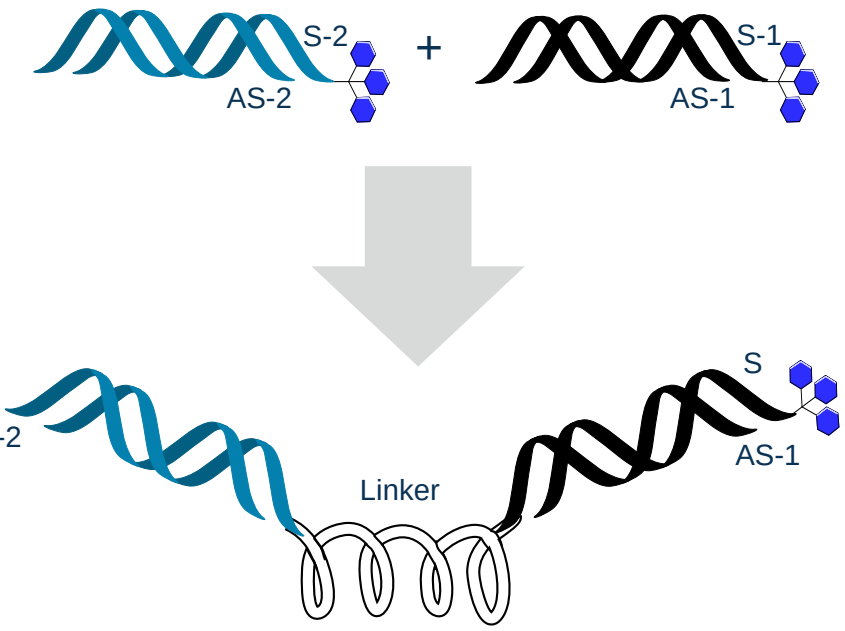
Combined therapy — Rosuvastatin plus placebo — Candesartan–HCTZ plus placebo — Dual placebo

Advances with the Potential to Potently, Durably, Safely and Conveniently Suppress LDL-cholesterol *and* BP

GEMINI Platform

Objective

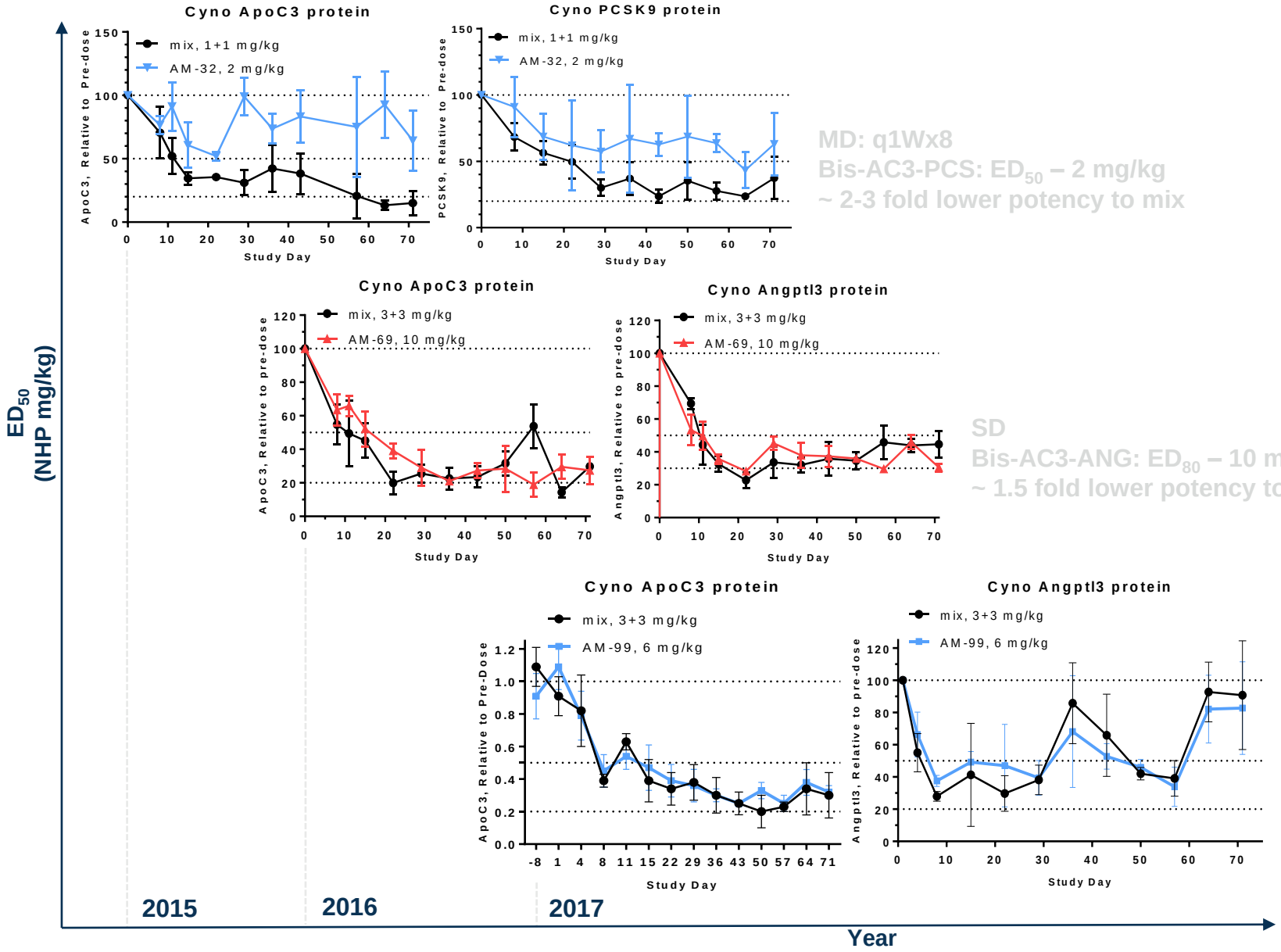
- Effectively combine conjugate siRNAs for the simultaneous silencing of two transcripts using single chemical entity



Rationale

- Potentially simplified development path compared to two entities or combination
- Ensures uptake of both siRNAs in same cell
- Controlled, parallel reductions in two targets
- Potential applications in cardiometabolic, CNS, oncologic and viral disease

Evolution of the GEMINI Platform

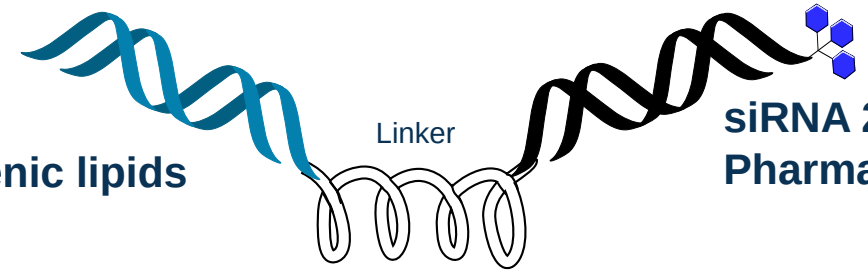


Reimagining the Treatment of Cardiovascular Disease

GEMINI-CVR Program

Potential Design

siRNA 1 targets Angptl3
Genetically-validated: reduces atherogenic lipids



siRNA 2 targets angiotensinogen
Pharmacologically-validated: reduces BP

Potential target product profile

- For the prevention of major adverse cardiac outcomes in high-risk individuals
- q6M/q12M subQ injection in office or pharmacy administration
- ~40% reductions in LDL-cholesterol and triglycerides, and >10mmHg reduction in systolic blood pressure
- Development candidate targeted for 2023

Agenda

Products

Platform

P^{5}x25 and Beyond

Genetically Validated Targets More Likely to Succeed

Medicines are 2x more likely to be approved if target is genetically validated

Progression	*p*(progress|genetics) / *p*(progress|no genetics)
Phase I to Phase II	1.2 (1.1-1.3)
Phase II to Phase III	1.5 (1.3-1.7)
Phase III to Approval	1.1 (1.0-1.2)
Phase I to Phase III	1.8 (1.5-2.1)
Phase I to Approval	2.0 (1.6-2.4)

Nelson et al., Nat Gen. 2015,47:856-60.

Investing in Next Wave of Genetically Validated Targets

Expanding Alnylam Leadership in Genetics

biobank uk

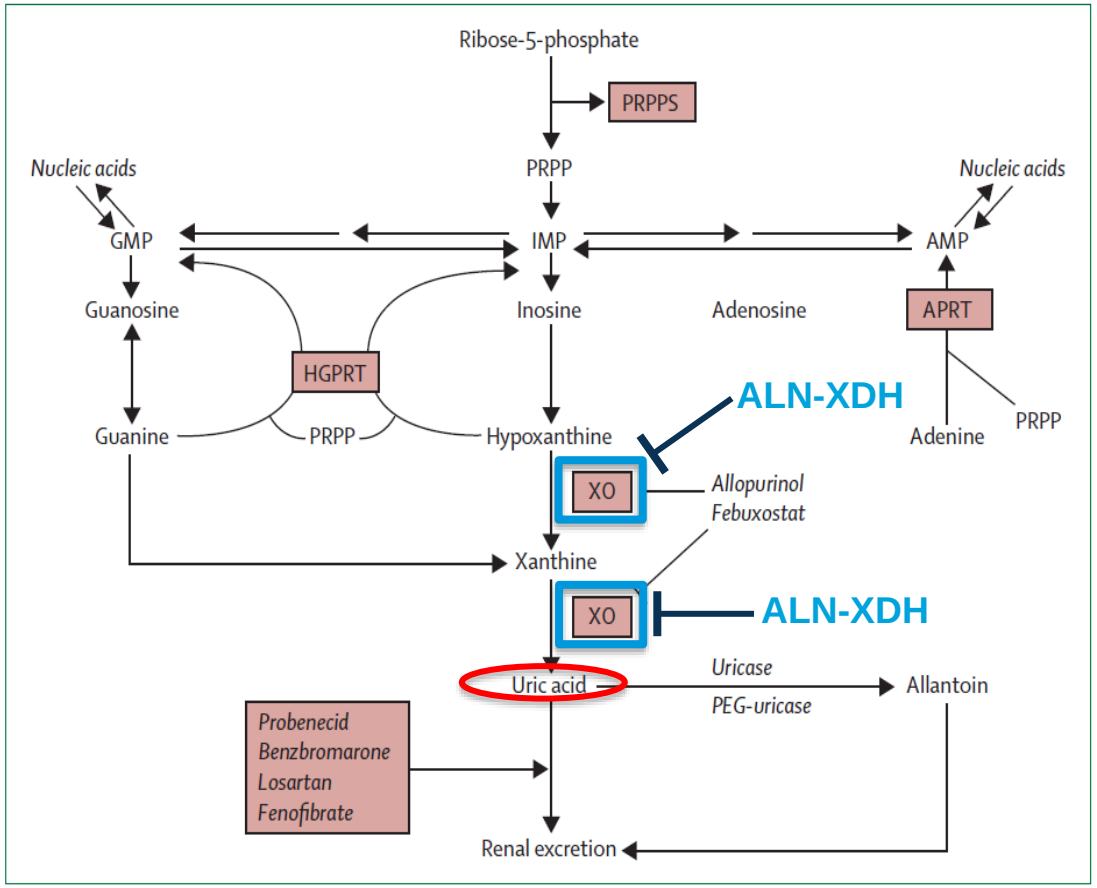
THE UNIVERSITY OF CALIFORNIA
LET THERE BE LIGHT
UCLA

REGENERON

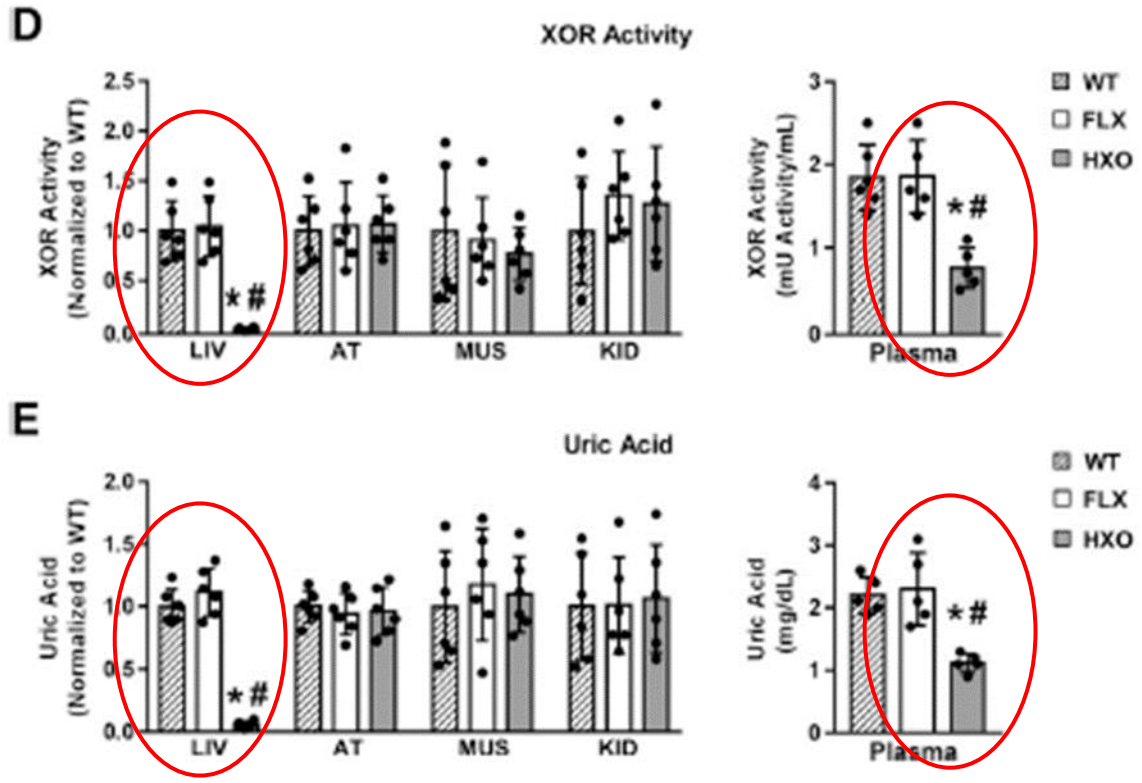
- **Larger, statistically powered datasets**
- **Novel genetically validated targets**
- **Increased ethnic and health diversity**
- **Target safety validation**

Targeting Xanthine Dehydrogenase (XDH)

Enzyme in Purine Metabolism Pathway*



Liver-specific Knockout of XDH in Mice Lowered Circulating Uric Acid*



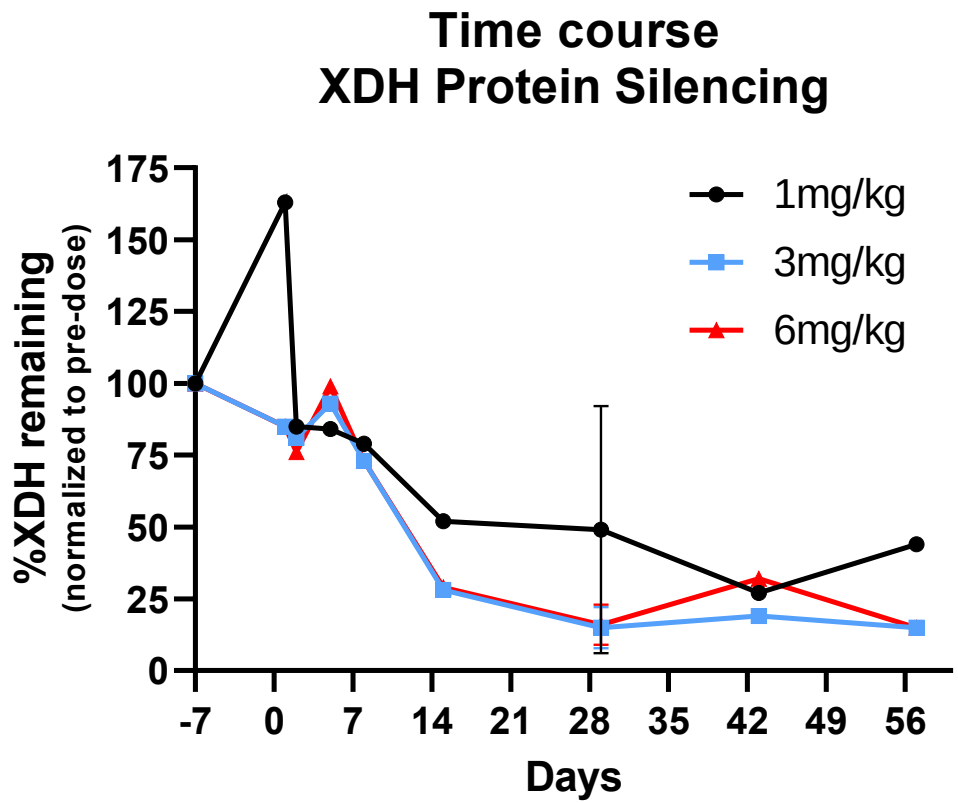
*Xanthine dehydrogenase (XDH) and xanthine oxidase (XO) are enzymatic forms of the protein xanthine oxidoreductase (XOR); the target gene is XDH

Harmon DB, et al Diabetes, 68:1221–1229 (2019); Schumacher HR, et. al, Arth Care Res, 59:1540-48 (2008)

ALN-XDH Achieves Robust Silencing in NHP

Supports Potential for Infrequent Dosing in Humans

- Single dose treatment of cynomolgus monkeys
- Robust and sustained XDH suppression
  - >90% liver XDH protein silencing, with maximum average at ~85% silencing at day 29
  - Suppression maintained up to day 56
- Based on allometric principles, extended XDH suppression (>90 days) expected in humans
  - Nonclinical PD profile supports quarterly and potentially biannual dosing



Sparse biopsy, N=3 on Day 29

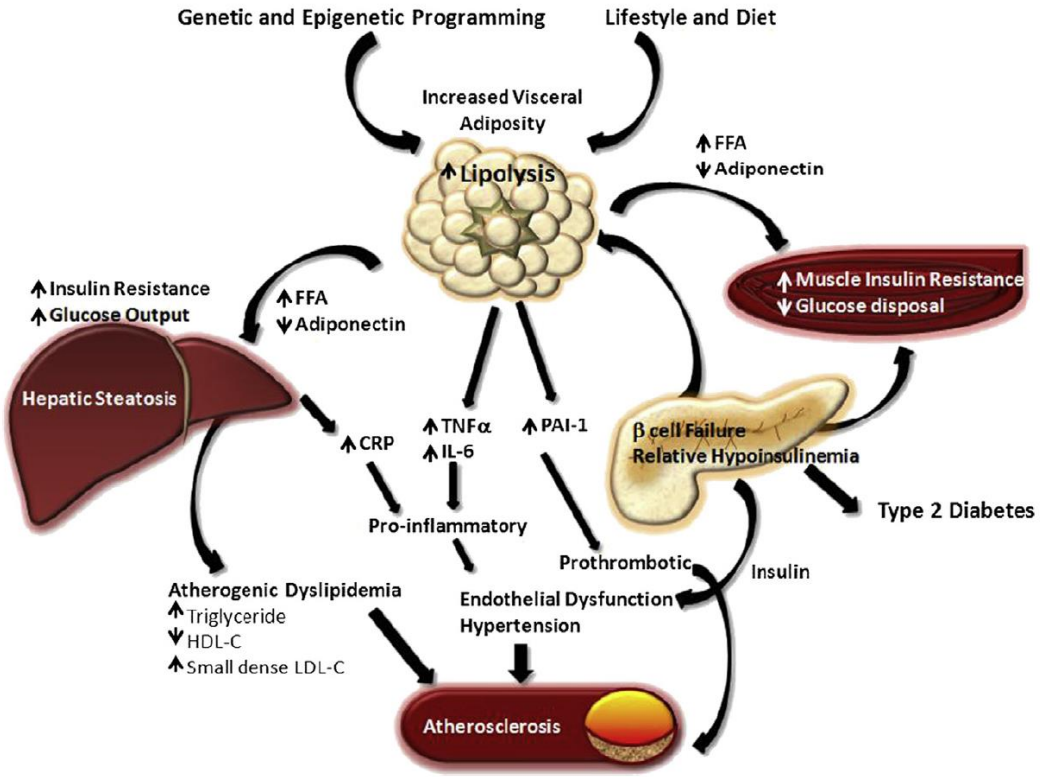
Potential to Improve Gout Control with ALN-XDH

- Current gout therapies have substantial limitations because of partial response, adverse effects, convenience and compliance issues
- As a result, majority of patients are untreated, cannot adhere to prescribed therapy, or do not reach target uric acid levels
- ALN-XDH is an investigational RNAi therapeutic that may address key unmet needs for gout patients – program goals include:
  - Potent urate-lowering effects
  - Infrequent dosing with tonic control between doses
  - Reduction in gout flares
  - Acceptable safety and tolerability

CTA filing planned **late 2021**
Phase 1/2 study start expected **early 2022**

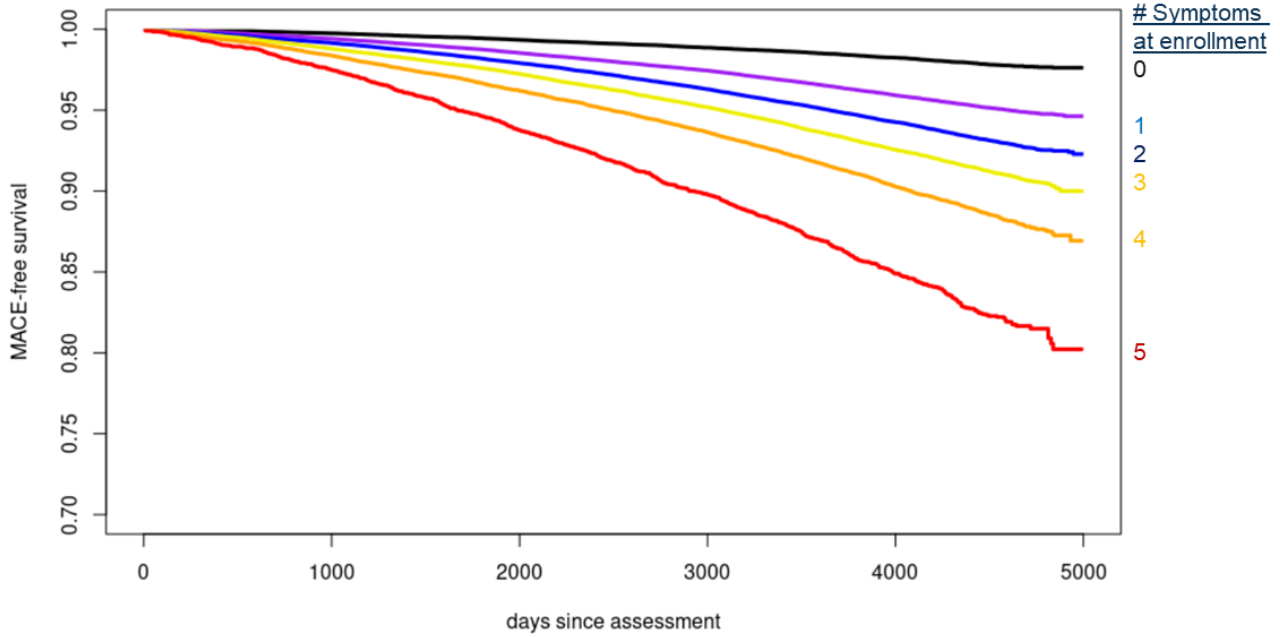
Chen-Xu et al. Arthritis & Rheumatology 71(6): 991-999 (2019); Kim et al. Arthritis Care & Research 65(4): 578-584 (2013); Reinders et al. Ann Rhuem Dis 68: 51-56 (2009); UpToDate July 2020 US KOL & PCP Market Research

Metabolic Syndrome: Major Cause of CV Disease



- Metabolic syndrome (MetS) is diagnosed when 3 or more of following are present:
  - Visceral obesity, high triglycerides, low HDL, insulin resistance and hypertension
- **Affects >20% of adults globally**

Prospective study in UK Biobank (UKBB) Shows MetS Score causally associated with major adverse cardiac events (MACE)



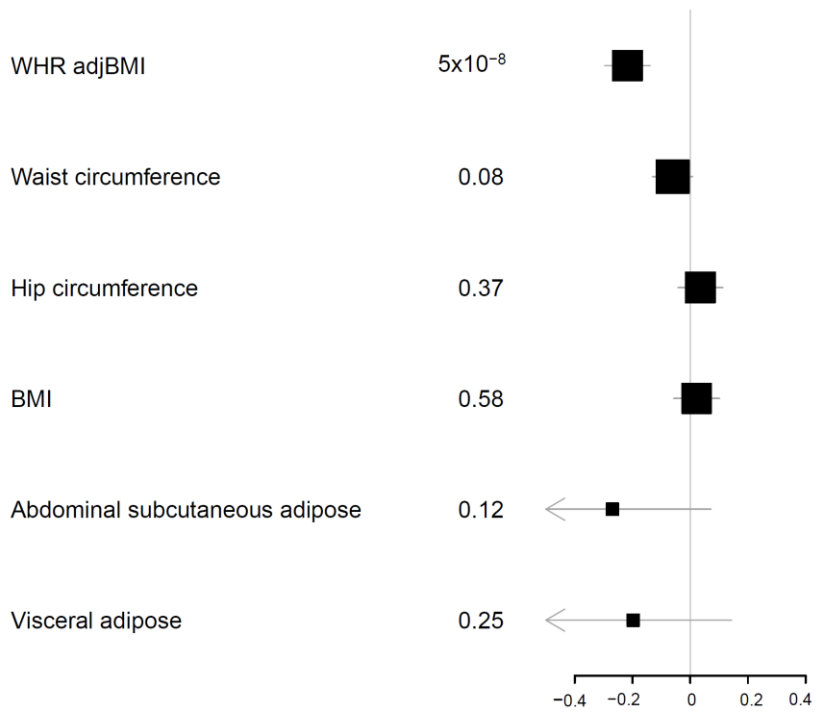
Each additional MetS symptom:
MACE Hazard Ratio = 1.32

Samson and Garber, Endocrinol Metab Clin N Am 43 (2014) 1–23

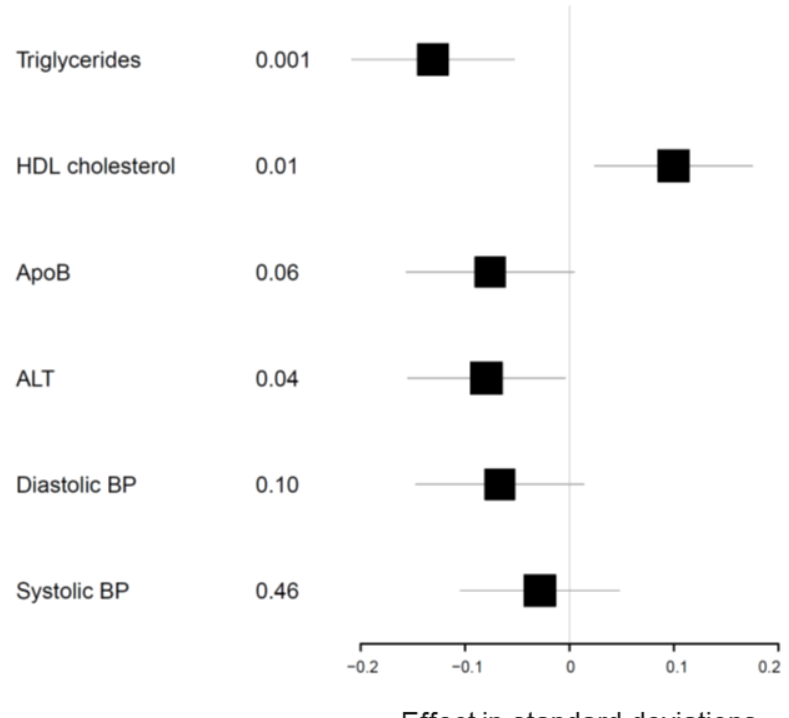
Reimagining the Treatment of Metabolic Syndrome (MetS) by Gene X

Gene X Loss-of-function in UKBB Associated with Major Impact on MetS Phenotype

Lower Waist to Hip Ratio



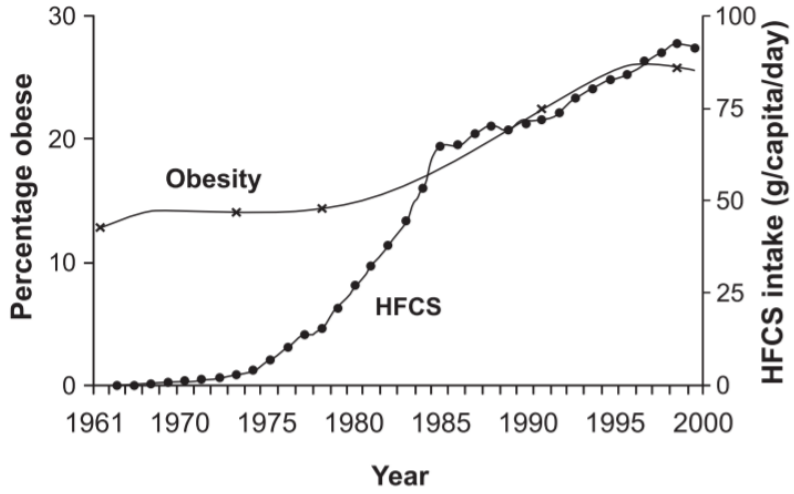
Improved Lipid and BP profile

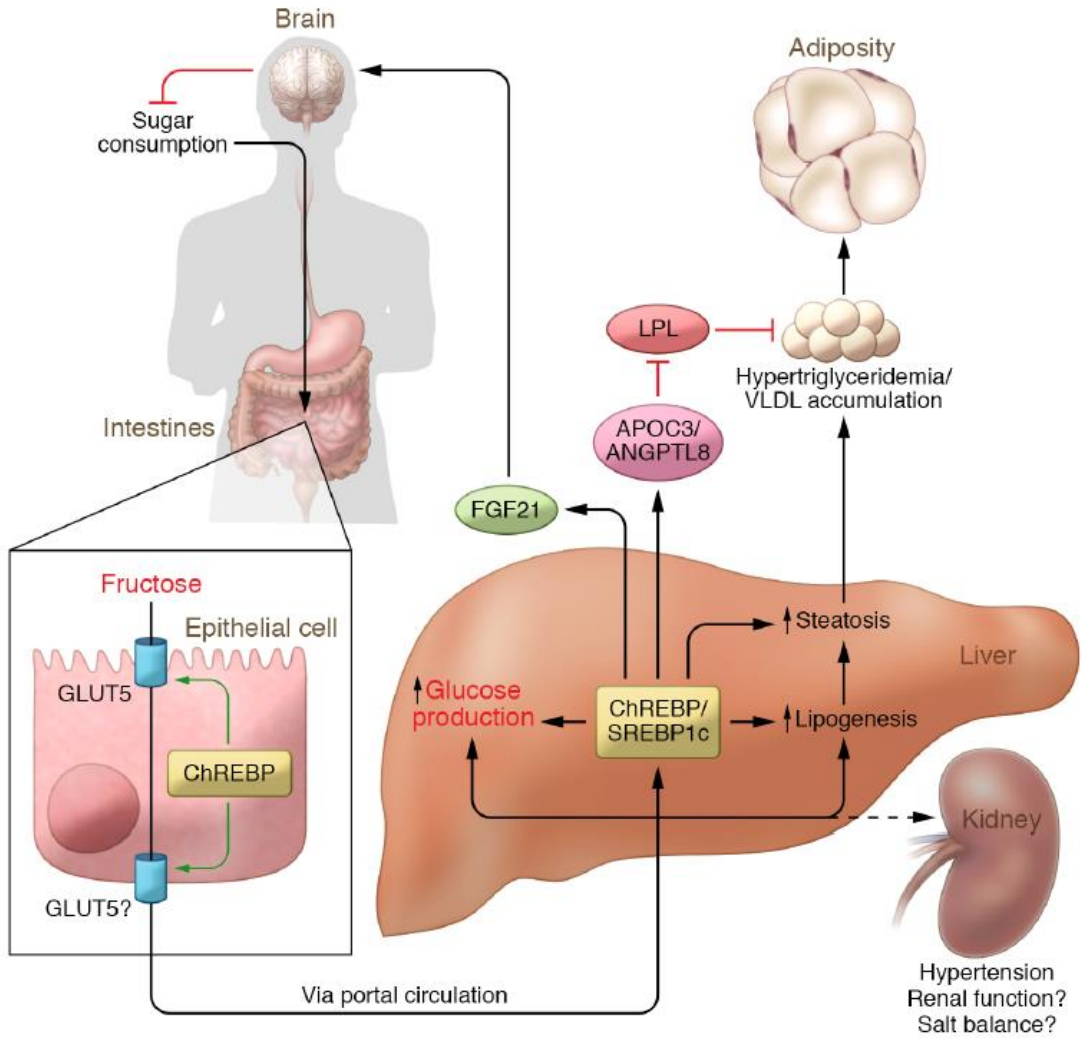


- Gene X is a liver expressed protein
- ~90% Knockdown of Gene X predicted to have broad beneficial effects on all facets of metabolic syndrome with potential reductions in risk of Type 2 diabetes and coronary artery disease
- Development candidate work ongoing for Q 6-monthy or annual subQ investigational RNAi therapeutic targeting Gene X in MetS

Fructose Metabolism Contributes to Metabolic Syndrome

- Sucrose (glucose-fructose disaccharide) and high-fructose corn syrup (HFCS) are added to numerous manufactured foods and beverages
- The average fructose consumption in the US accounts for ~9% of total energy





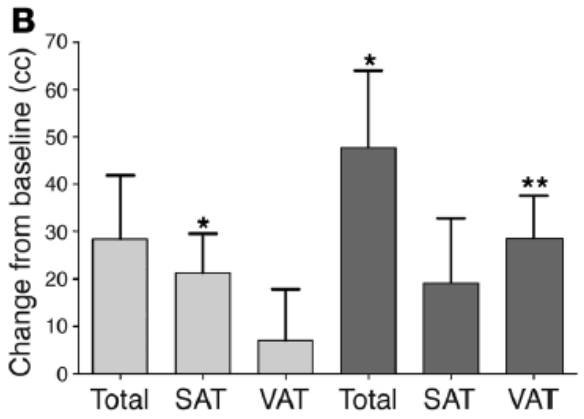
Adapted from Bray et al, Am J Clin Nutr, 2004 | Sun et al, Food and Chem Tox, 2011 | Hannou et al. JCI review, 2018

Fructose Consumption Contributes to Metabolic Syndrome

- Overweight or obese subjects consumed glucose- or fructose-sweetened beverages for 10 weeks
- Fructose specifically increased visceral obseity, dyslipidemia, and insulin resistance

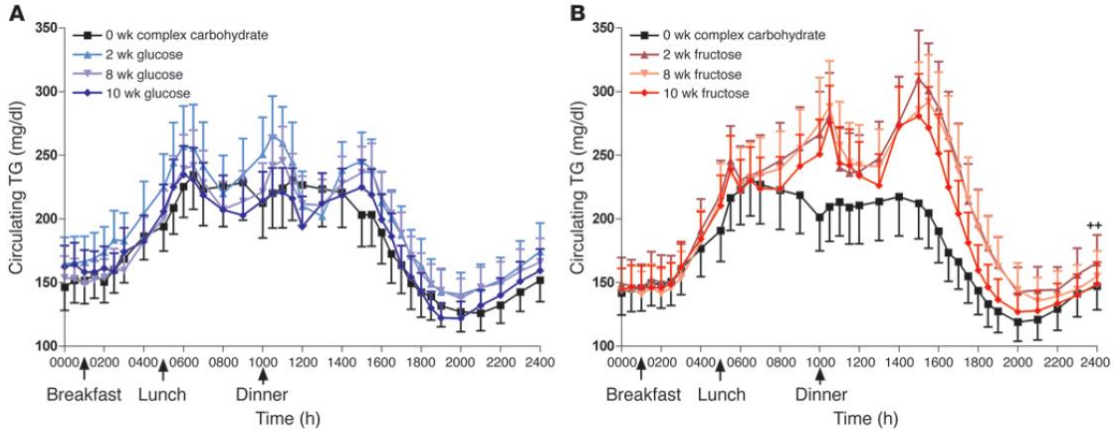
Total, visceral, and subcutaneous adipose

Glucose Fructose



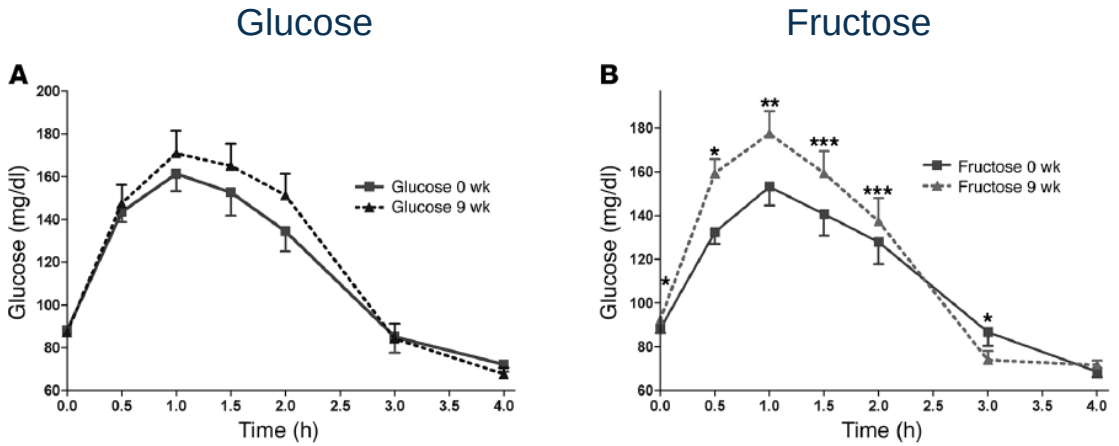
Circulating triglycerides

Glucose Fructose



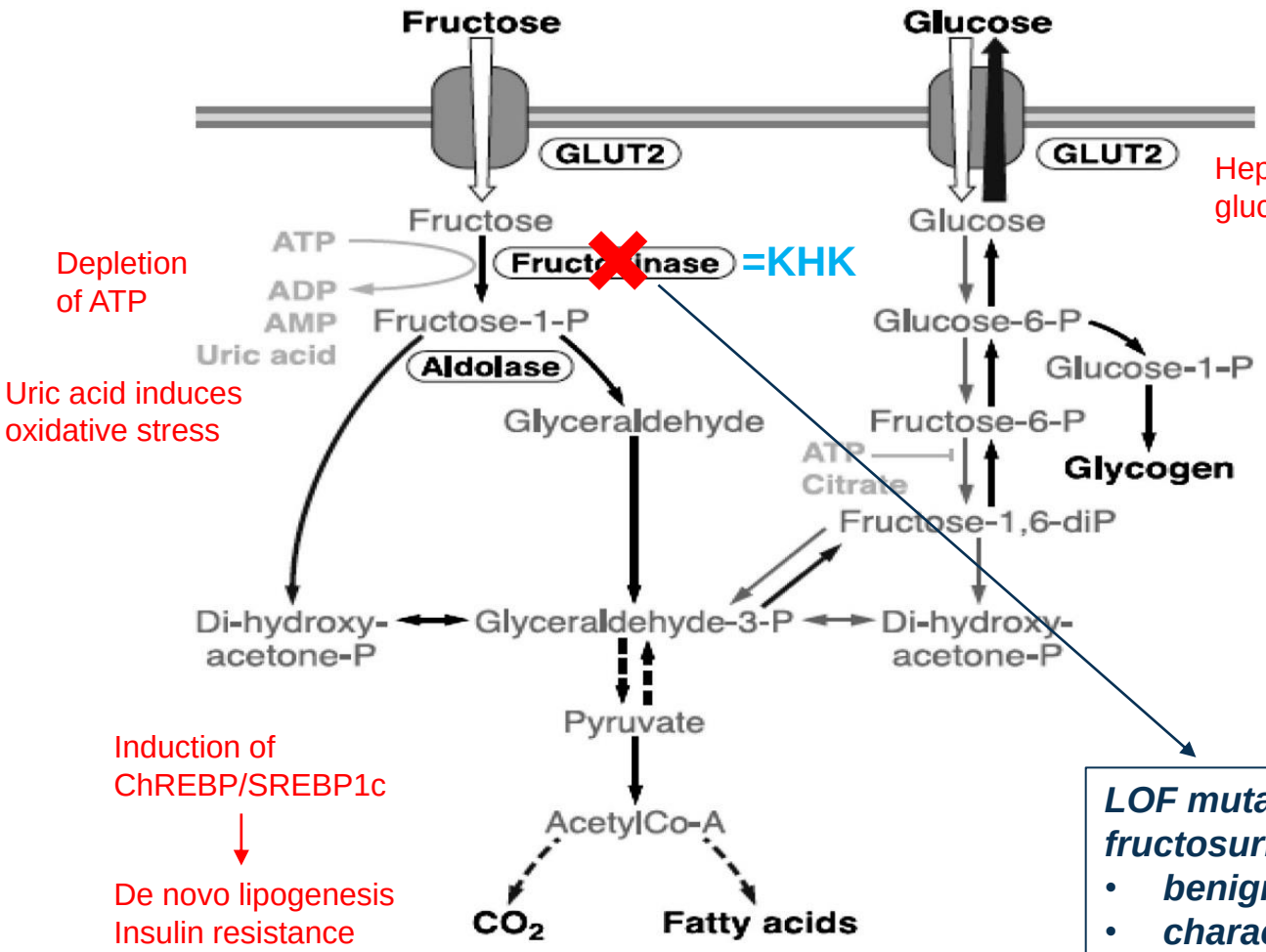
Oral glucose tolerance test

Glucose Fructose



Stanhope et al, 2009, JCI

Ketohexokinase (KHK) is First Enzyme in Fructose Metabolism



LOF mutations in humans cause essential fructosuria

- ***benign, asymptomatic defect***
- ***characterized by increased urinary fructose***

Rippe et al 2013, Adv Nut

Pharmacological Validation of KHK in Humans

Pfizer's KHK Inhibitor (PF-06835919) Improved Markers of Metabolic Syndrome in Adults with NAFLD[1]

PF-06835919 Has Been Evaluated in Two DB, R, PC Studies in Patients with BMI ≥ 28 kg/m2 ; Type 2 diabetes and/or metabolic syndrome

Study 1, 6 Weeks Duration

% change from baseline	Placebo	PF-06835919 (75 mg)	PF-06385919 (300 mg)
Liver fat	-7.8	3.7	-26.5 *
Hs-CRP	8.3	-16.4	-31.0 *
Uric acid	6.5	4.4	-11.5
Adiponectin	-14.3	18.3	38.6 *
Il-6	8.5	-0.7	-7.1

* p<0.05 vs placebo

Study 2, 16 Weeks Duration

- Dose-dependent changes with up to 19% reduction in liver fat at 300mg (5% placebo) and improvements in HbA1C
- 12% of patients discontinued during study
- Program currently not active

- KHK is liver, small intestine and kidney expressed
- RNAi-mediated hepatic knockdown in rodents improves triglyceride levels, hepatic steatosis, hyperinsulinemia, insulin signaling and glucose profile
- Development candidate work ongoing for Q 6-monthy or annual s.c. investigational RNAi therapeutic targeting KHK in patients with Type 2 diabetes and NASH

[1] Pfizer, Inc., NCT03969719, A Double-blind Study to Assess 2 Doses of an Investigational Product for 16 Weeks in Participants With Non-alcoholic Fatty Liver Disease and Type 2 Diabetes Mellitus. A Phase 2a, Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel Group Study to Evaluate Safety, Tolerability and Pharmacodynamics of PF-06835919 Administered Daily for 16 Weeks in Adults With Non-Alcoholic Fatty Liver Disease and Type 2 Diabetes Mellitus on Metformin

Over 25 Preclinical Programs in Four Tissues Feeding Sustainable Innovation

Alnylam
- ALN-XDH
- ALN-KHK
- ALN-LEC
- ALN-CC3
- ALN-F12
- ALN-X
- Many others

Alnylam/Regeneron
- ALN-PNP
- ALN-REGN-L2
- ALN-REGN-L4
- ALN-REGN-L5
- ALN-REGN-L7

Alnylam/Regeneron
- ALN-APP
- ALN-HTT
- ALN-REGN-C3
- ALN-REGN-C4
- ALN-REGN-C5
- ALN-REGN-C6
- ALN-REGN-C7
- ALN-REGN-C8
- ALN-REGN-C9

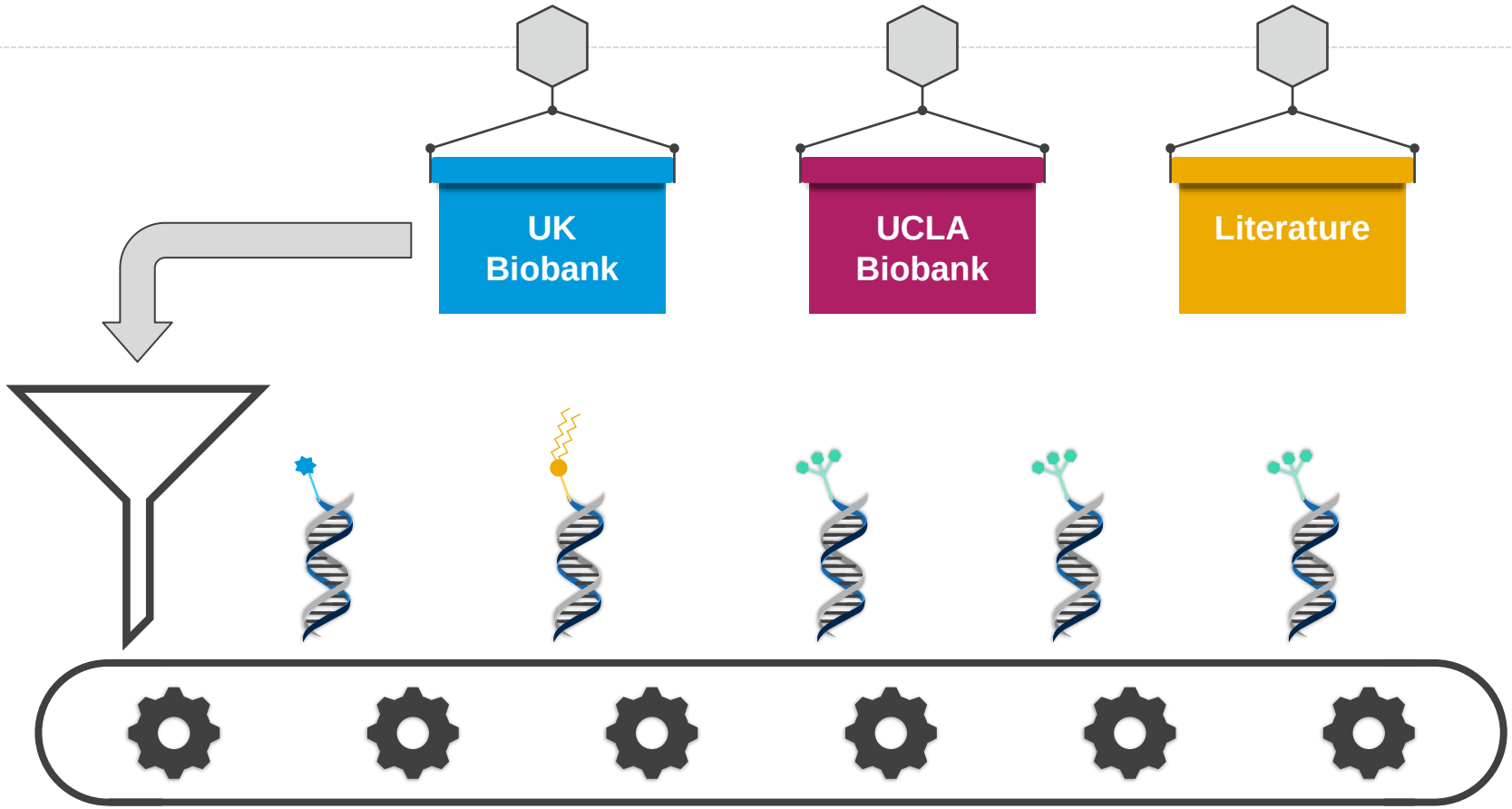
Alnylam
- ALN-TTRoc

Alnylam/Regeneron
- ALN-REGN-E1
- ALN-REGN-E2
- ALN-REGN-E3
- ALN-REGN-E4
- ALN-REGN-E5

Alnylam/Vir
- ALN-COV
  - *discontinued*
- ALN-VIR2 (ACE2)
- ALN-VIR3 (TMPRSS2)

2-4 *INDs planned per year from organic product engine (4+ planned by end-'25)*

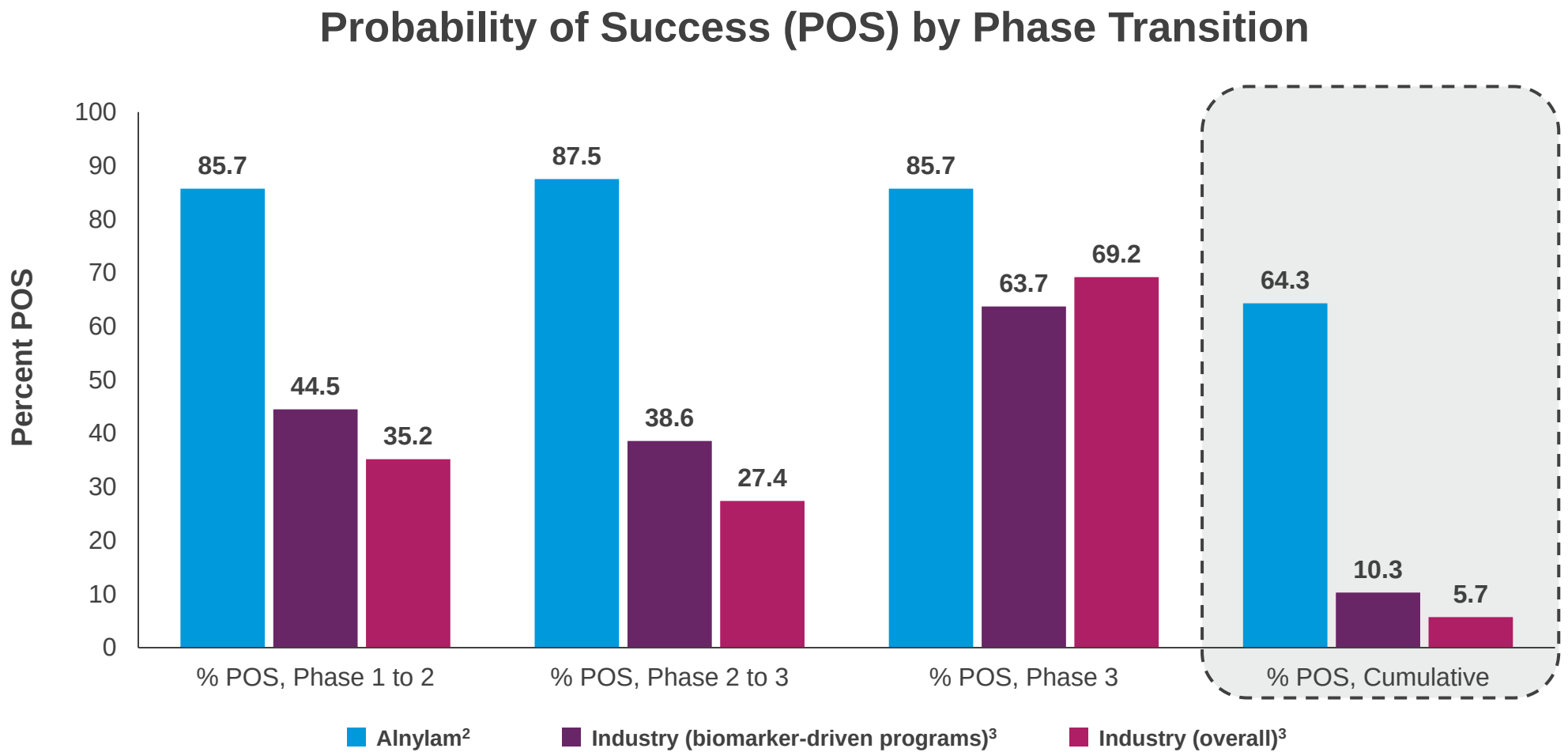
Delivering Sustainable Innovation with RNAi Therapeutics



TRANSFORMATIVE MEDICINES

High-Yield Productivity of Alnylam RNAi Therapeutics Platform

Comparison of Historical Industry Metrics to Alnylam Portfolio[1]



[1] Analysis as of November 2021; Past rates of Alnylam and industry respectively may not be predictive of the future

[2] Alnylam programs biomarker-driven at all stages of development (100%); figures include ALNY-originated molecules now being developed by partners

[3] Wong et al., Biostatistics (2019) 20, 2, pp. 273–286

Expanding Alnylam's TTR Franchise

John Vest, M.D.
Vice President, Clinical Research

Alnylam PHARMACEUTICALS

Agenda

1. Alnylam ATTR Amyloidosis Franchise Overview

2. Vutrisiran HELIOS-A Phase 3 Topline 18-Month Results

3. Potential Expansion into ATTR Amyloidosis with Cardiomyopathy

4. Advancing Innovation with ALN-TTRsc04

5. Stargardt Disease: Promising New Opportunity for Vutrisiran

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Cece
Diagnosed with hATTR amyloidosis (USA)

ATTR Amyloidosis

Rare, Progressively Debilitating, and Fatal Disease

Description

Caused by misfolded TTR protein that accumulates as amyloid deposits in multiple tissues including heart, nerves, and GI tract[1]

Hereditary ATTR (hATTR) Amyloidosis

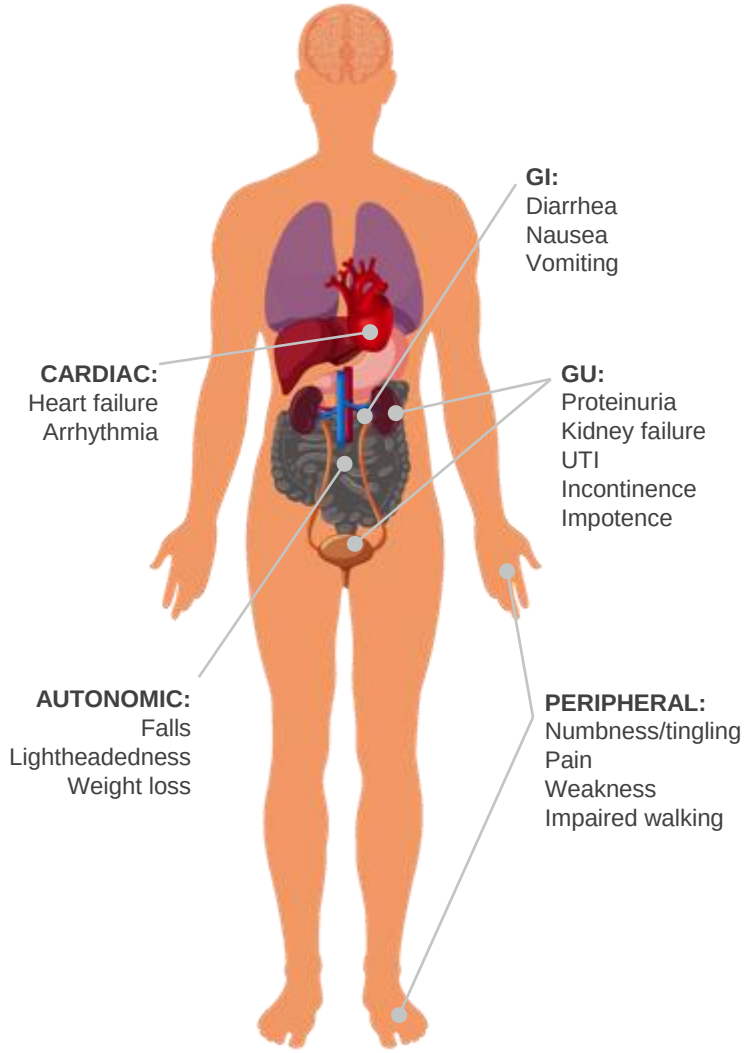
~50,000

patients worldwide*

Wild-Type ATTR (wtATTR) Amyloidosis

~200,000 – 300,000

patients worldwide



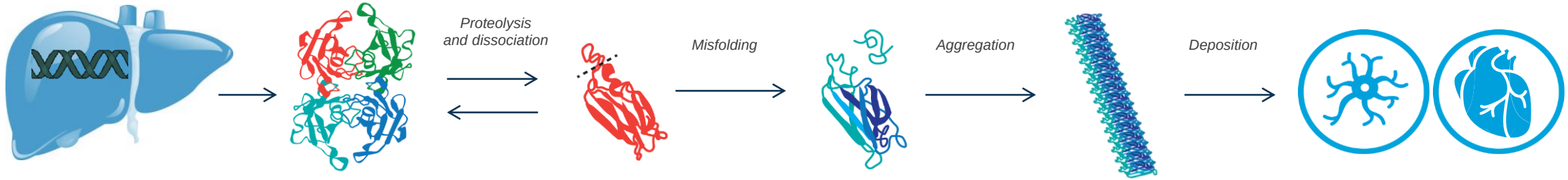
[1] Coelho T, et al. N Engl J Med. 2013;369(9):819-829

* Ando, et al. Orphanet J Rare Dis, 2013; Ruberg, et al. Circulation, 2012 (includes hATTR amyloidosis patients with polyneuropathy and cardiomyopathy)

Current or Potential Therapy Options for ATTR Amyloidosis

RNAi Therapeutics Work by Silencing the Source of Disease

ATTR Amyloidosis Disease Cascade and Current/Potential Therapies



Eliminate production of mutant TTR:
- Orthotopic liver transplant

Suppression of TTR synthesis (gene silencing):
- **RNAi (patisiran, vutrisiran)**
- Antisense oligonucleotides
- Gene editing

Prevent dissociation of TTR tetramer:
- TTR stabilizers

Remove existing amyloid:
- Monoclonal antibodies

Alnylam's ATTR Amyloidosis Franchise

Approved Treatment Option, Investigational Clinical Programs, and a Preclinical Development Program

onpattro (patisiran) lipid complex injection 10 mg/5 mL

An Approved RNAi Therapeutic for Treatment of Polyneuropathy of hATTR Amyloidosis*

About ONPATTRO

- Favorable efficacy and safety profile in APOLLO
- APOLLO-B ongoing to evaluate patisiran in ATTR-CM ‡
- IV administration, once every 3 weeks

Vutrisiran

An Investigational RNAi Therapeutic for Potential Treatment of ATTR Amyloidosis†

About Vutrisiran

- Positive efficacy results and acceptable safety profile in HELIOS-A in hATTR-PN
- HELIOS-B ongoing in ATTR-CM
- Subcutaneous administration, once quarterly, potential for biannual dosing

ALN-TTRsc04

A Preclinical RNAi Therapeutic for Potential Treatment of ATTR Amyloidosis

About ALN-TTRsc04

- IKARIA platform
- IND expected in 2022
- Potential for annual dosing and >90% serum TTR reduction
- No third-party royalties; exclusivity expected beyond 2040

* ONPATTRO is approved in the U.S. and Canada for the polyneuropathy of hATTR amyloidosis in adults, in the EU, Switzerland and Brazil for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy; see Full Prescribing Information ‡ Patisiran has not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in this population;
† Vutrisiran is an investigational agent and has not been approved by the FDA, EMA, or any other regulatory agency and no conclusions can or should be drawn regarding its safety or effectiveness

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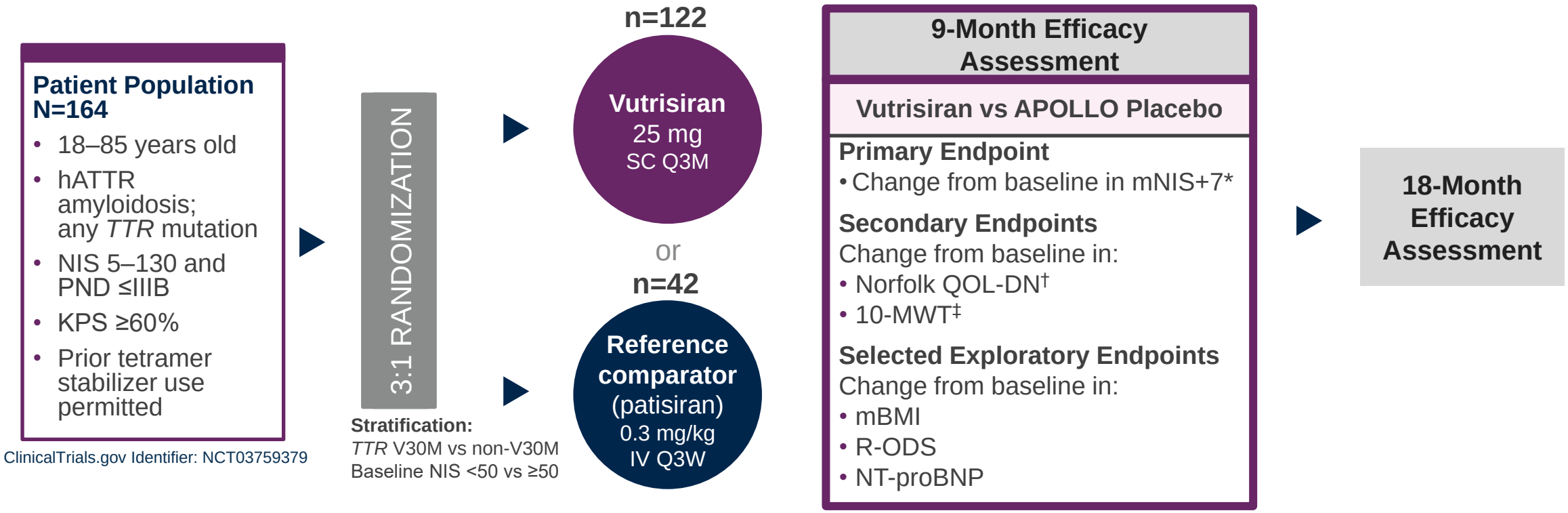
Vutrisiran Phase 3 HELIOS·A Study

Randomized, Open-Label Study in Patients with Hereditary ATTR Amyloidosis with Polyneuropathy



*Higher scores of mNIS+7 indicate more neuropathy impairment (range, 0 to 304). †Higher scores of Norfolk QOL-DN indicate worse quality of life (range, −4 to 136). ‡10-MWT speed (m/s) = 10 meters/mean time (seconds) taken to complete two assessments at each visit, imputed as 0 for patients unable to perform the walk; lower speeds indicate worse ambulatory function.

10-MWT, 10-meter walk test; IV, intravenous; KPS, Karnofsky performance status; mBMI, modified body mass index; mNIS+7, modified Neuropathy Impairment Score +7; NIS, Neuropathy Impairment Score; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP, N-terminal pro-brain natriuretic peptide; PND, polyneuropathy disability; Q3M, every 3 months; Q3W, every 3 weeks; R-ODS, Rasch-built Overall Disability Scale; SC, subcutaneous; TTR, transthyretin.

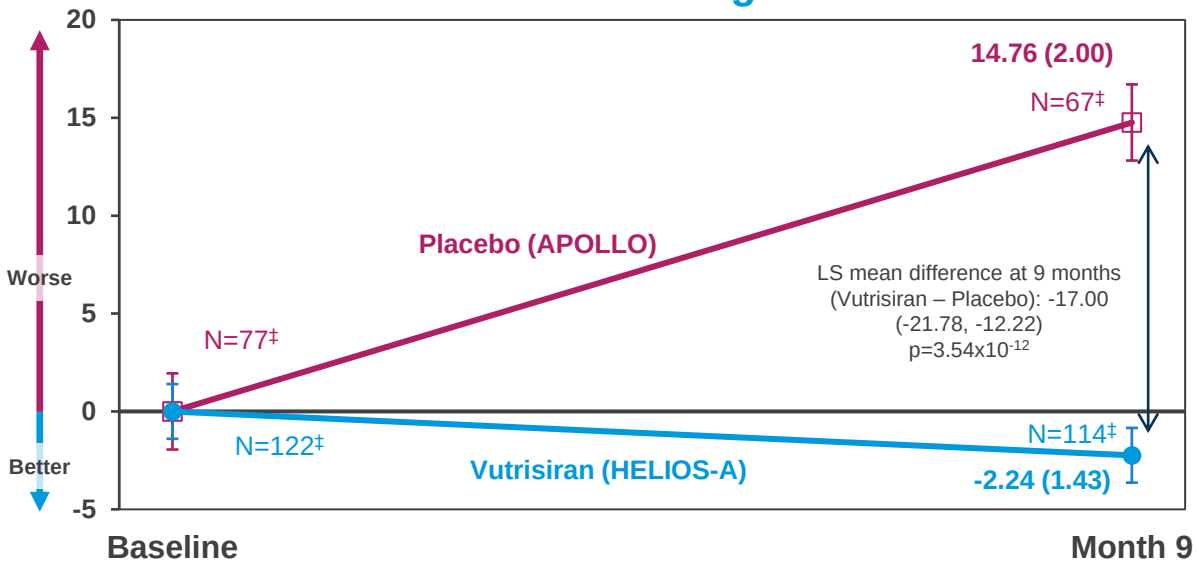
Adams et al., AAN, April 2021

APOLLO refers to the randomized, placebo-controlled Phase 3 study of ONPATTRO (patisiran) in hATTR patients with polyneuropathy (Adams et al., NEJM, 2018). HELIOS-A compares vutrisiran-treated hATTR patients with polyneuropathy to the prespecified external placebo group from APOLLO

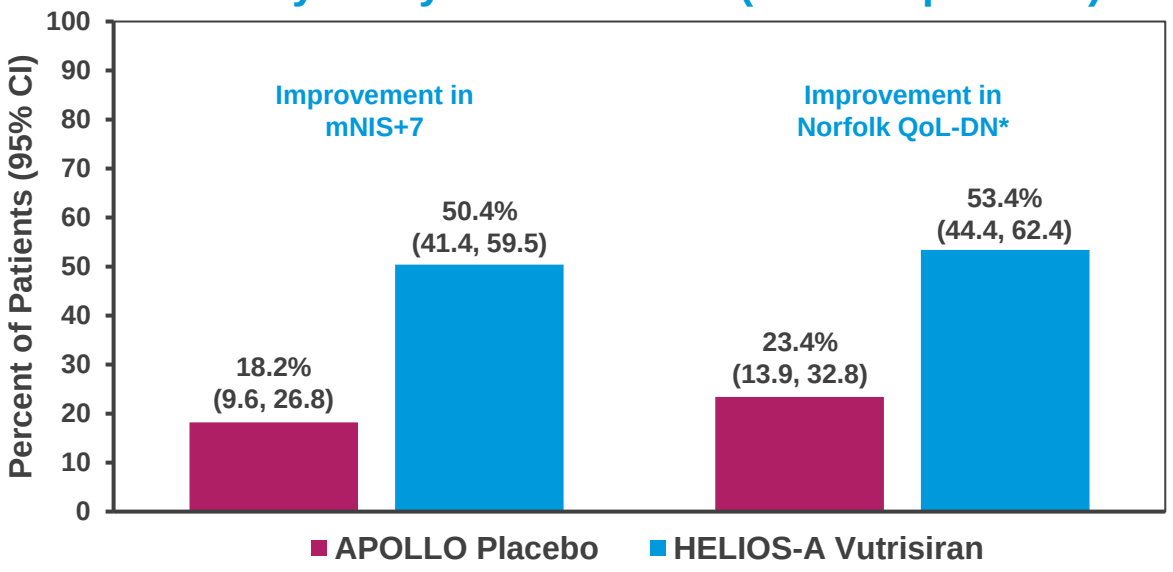
HELIOS-A 9-Month Results

Randomized, Open-Label Study in Patients with Hereditary ATTR Amyloidosis with Polyneuropathy (N=164)

mNIS+7 LS Mean Change from Baseline



Binary Analysis at Month 9 (mITT Population)



Both secondary endpoints met

- Improvement demonstrated in quality of life and 10-meter walk test

Positive exploratory cardiac endpoint result

- Improvement in NT-proBNP biomarker in cardiac subpopulation, relative to placebo (p=0.0016)

Encouraging safety and tolerability profile

- No drug-related discontinuations or deaths; two SAEs deemed drug-related: dyslipidemia, urinary tract infection
- Treatment emergent AEs in ≥10% of vutrisiran patients all common in disease natural history and occurred at similar or lower rates than placebo comparator group
  - Include diarrhea, pain in extremity, fall and urinary tract infections
- Low incidence of injection site reactions (ISRs), all mild and transient
- No safety signals regarding liver function tests, hematology or renal function related to vutrisiran

Adams et al., *AAN*, April 2021 as to primary endpoint and safety/tolerability at Month 9; additional data presented by Alnylam in conference call held April 19, 2021

APOLLO refers to the randomized, placebo-controlled Phase 3 study of ONPATTRO (patisiran) in hATTR patients with polyneuropathy (Adams et al, NEJM, 2018). HELIOS-A compares vutrisiran treated hATTR patients with polyneuropathy to the prespecified external placebo group from APOLLO

HELIOS-A 18-Month Topline Results: Efficacy

Sustained Treatment Benefit with Vutrisiran Through 18 Months

Positive results for all Month 18 secondary efficacy endpoints, relative to external placebo group

Month 18 Secondary Endpoint	P-value
mNIS+7	6.5E-20
Norfolk QoL-DN total score	1.8E-10
10-MWT	1.2E-07
mBMI	4.2E-15
R-ODS	3.5E-15

Vutrisiran results in HELIOS-A generally comparable to patisiran results from APOLLO*, across primary and all secondary endpoints

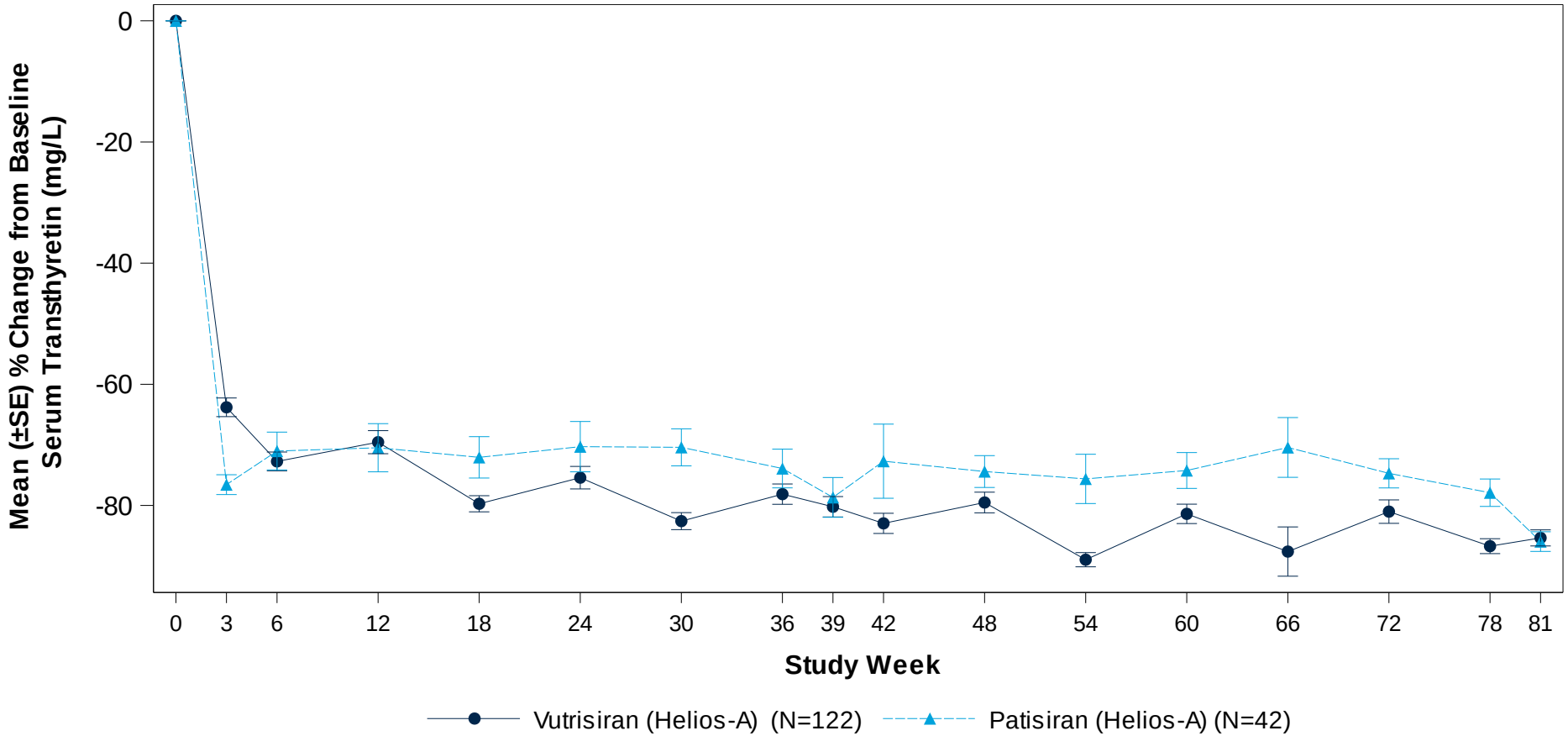
Encouraging results on exploratory cardiac endpoints at 18 months

- Favorable changes in NT-proBNP and certain echocardiographic parameters, relative to external placebo group
- Favorable change in cardiac technetium uptake relative to baseline in majority of cohort patients, suggesting potential evidence for reduced cardiac amyloid burden

* Within limitations of cross-study comparisons

Serum TTR: Percent Change from Baseline

Confirmed Non-inferiority of Vutrisiran Relative to Within-Study Patisiran at Month 18, as Expected



N evaluable																	
Vutrisiran (Helios-A) (N=122)	122	114	109	119	105	117	92	118	115	56	116	42	118	15	118	100	114
Patisiran (Helios-A) (N=42)	42	42	41	41	37	38	39	34	39	23	40	23	36	9	37	36	38

Month 9 and Month18 non-trough TTR assessments presented at Week 39 and 81, respectively.

HELIOS-A 18-Month Topline Results: Safety

Continued signs of encouraging safety and tolerability profile during 18-month treatment period

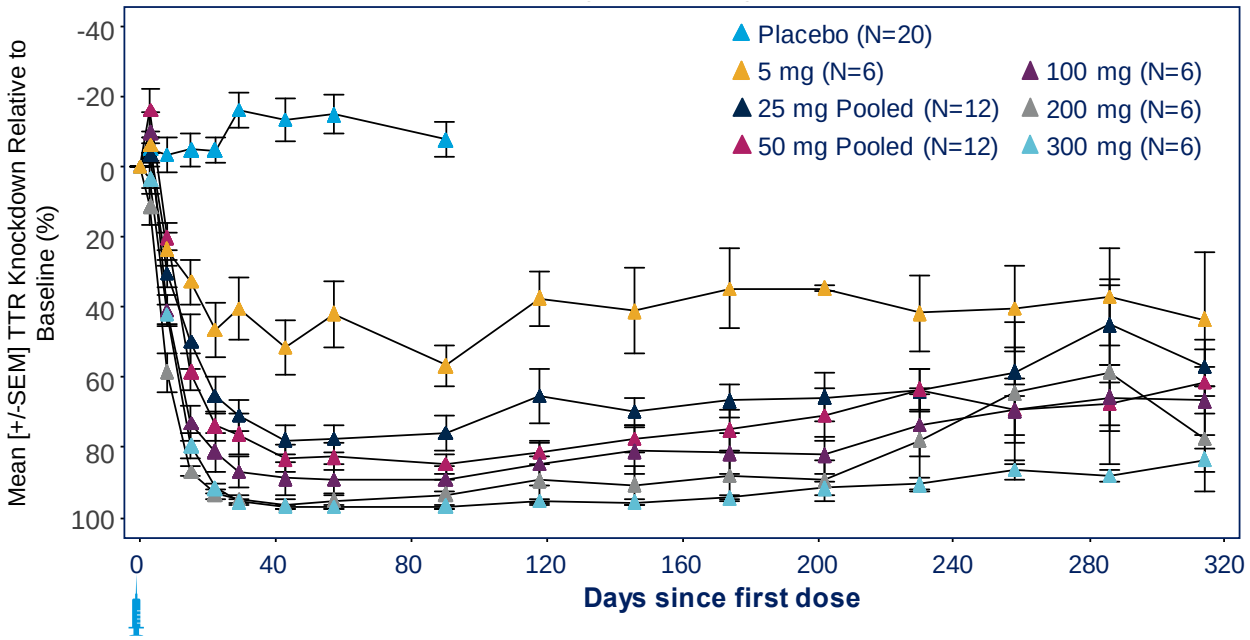
- No drug-related discontinuations or deaths
- Three discontinuations due to adverse events in vutrisiran arm during 18-month treatment period (none considered related to study drug)
  - Two fatal events (previously reported at month 9); one due to COVID-19, one due to iliac artery occlusion during hospitalization for pneumonia in patient with CHF
  - Single event of cardiac failure leading to discontinuation
- Two SAEs deemed drug-related: dyslipidemia, urinary tract infection
- Treatment emergent adverse events occurring in ≥10% of patients receiving vutrisiran included fall, pain in extremity, diarrhea, peripheral edema, urinary tract infection, arthralgia, and dizziness
  - With exception of pain in extremity and arthralgia, each event occurred at similar or lower rate as compared with external placebo
- Injection site reactions (ISRs) reported in five patients (4.1%); all mild and transient
- No hepatic safety concerns

Opportunity for Biannual Vutrisiran Dosing Regimen

Modeling Supports Potential Biannual 50mg Dosing Regimen in Addition to Quarterly 25mg Dosing Regimen

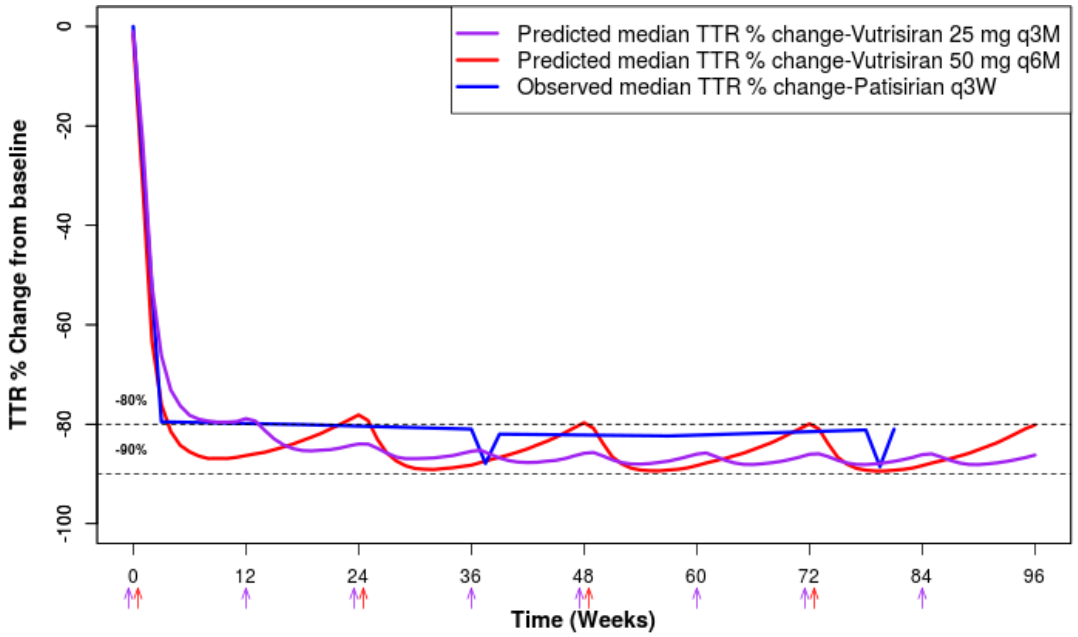
Phase 1 Study – Healthy Volunteers

- Mean max TTR reduction of >80% after single dose of either 25mg or 50mg†



Pharmacodynamic Modeling

- After repeat dosing, ~90% peak TTR reduction predicted with both 25mg q3M and 50mg q6M vutrisiran regimens
- 50mg q6M vutrisiran dosing predicted to have similar TTR reduction as 0.3mg/kg q3W patisiran
- Comparable median TTR reduction at steady state predicted for both 25mg and 50mg repeat dosing

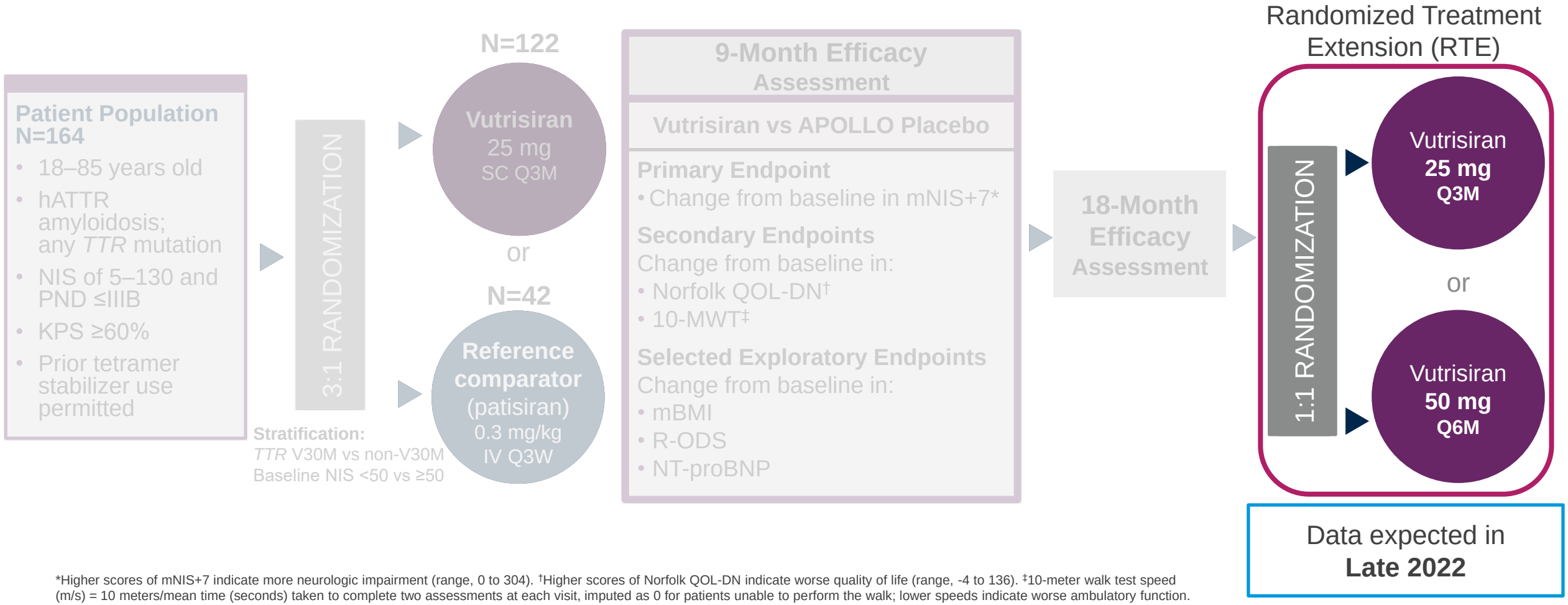


† Taubel J, et al. Phase 1 Study of ALN-TTRsc02, a Subcutaneously Administered Investigational RNAi Therapeutic for the Treatment of Transthyretin-Mediated Amyloidosis. ISA 2018: XVIIth International Symposium of Amyloidosis; Kumamoto, Japan; March 2018 (poster)

q3M – dosing every three months
q6M – dosing every six months

Vutrisiran HELIOS·A Phase 3 Study

Randomized, Open-Label Study in Patients with Hereditary ATTR Amyloidosis with Polyneuropathy



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10-MWT, 10-meter walk test;; IV, intravenous; KPS, Karnofsky performance status; mBMI, modified body mass index; mNIS+7, modified Neuropathy Impairment Score +7; NIS, Neuropathy Impairment Score; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP, N-terminal pro–brain natriuretic peptide; PND, polyneuropathy disability; Q3M, every 3 months; Q3W, every 3 weeks; R-ODS, Rasch-built overall disability scale; SC, subcutaneous; TTR, transthyretin.

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4. Advancing Innovation with ALN-TTRsc04
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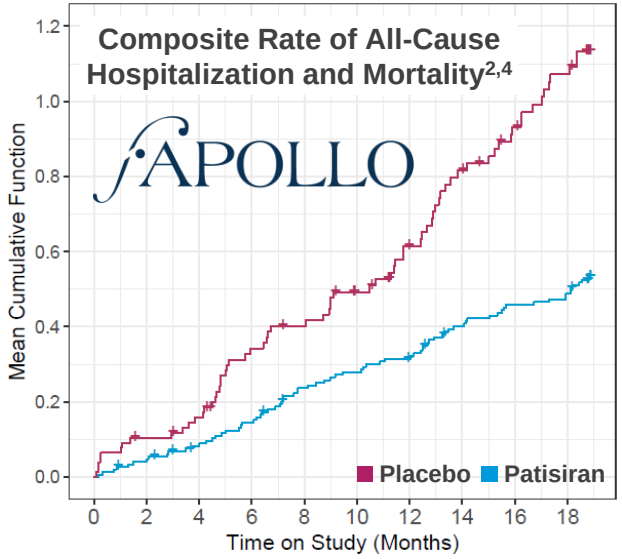
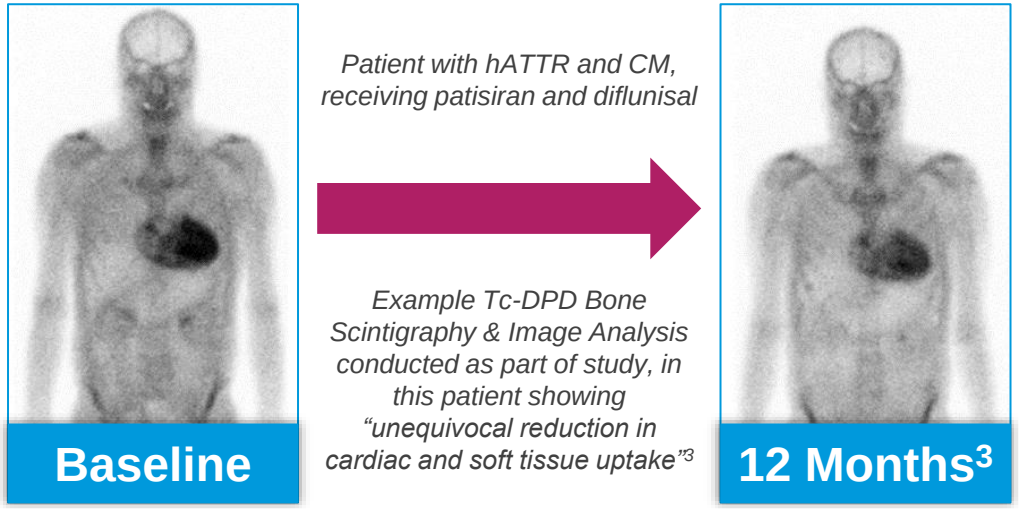
Evidence for Investigational RNAi Therapeutics in ATTR Cardiomyopathy[1]

Exploratory & Post-hoc Data from APOLLO[2]



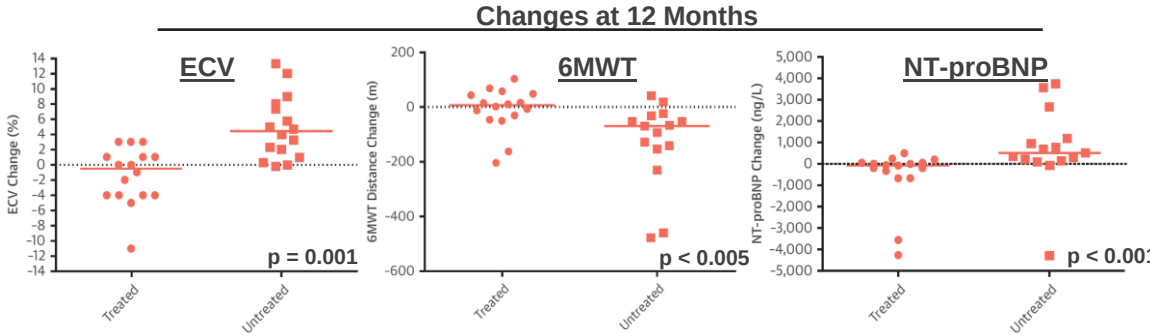
- **55%** Relative reduction in **NT-proBNP** vs. placebo[2,†]
- **0.9mm** Mean reduction in **LV wall thickness** vs. placebo[2,‡]
- **-1.4%** Improvement in **global longitudinal strain** vs. placebo[2,‡]
- **0.35m/s** Improvement in **10-MWT** vs. placebo[2,†]

Investigator-Sponsored Study from National Amyloidosis Centre, UK[3]



Cardiac Safety Data in Entire APOLLO Study Population:

	Placebo[5] (n=77)	Patisiran[5] (n=148)
Rates of Death/Hospitalization, per 100 py (95% CI)		
Death	6.2 (2.5 – 12.7)	3.2 (1.4 – 6.2)
All-cause hospitalization	69.7 (54.3 – 87.7)	32.9 (25.9 – 41.1)
Cardiac hospitalization	15.6 (9.0 – 24.9)	8.2 (5.0 – 12.6)
Hospitalization and/or death	71.8 (56.1 – 90.1)	34.7 (27.5 – 43.1)
Cardiac hospitalization and/or death	18.7 (11.4 – 28.8)	10.1 (6.4 – 14.9)



[1] Patisiran has not been approved by the FDA, EMA, or any other regulatory agency for treatment of cardiac amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in treating CM in this population; [2] Solomon S, et al. Circulation 2018;

[3] Fontana, et al. J Am Coll Cardiol Cardiovasc Imaging. Oct 28, 2020. Epublished DOI:10.1016/j.jcmg.2020.07.043; [4] Analysis of hospitalization/death data was conducted post-hoc based on data collected from AE CRFs; hospitalization/death events caused by SAEs within 28 days of last dose of study drug were included; hospitalization events caused by SAEs within SOC of cardiac disorder were classified as cardiac hospitalization; [5] For any hospitalization/death analysis: negative binomial regression rate ratio (RR) 0.49 [0.30, 0.79]; Anderson-Gill hazard ratio (HR) 0.48 [0.34, 0.69]; † nominal p<0.01; ‡ nominal p<0.05

ATTR Amyloidosis Franchise Phase 3 Program

Randomized, Double-Blind, Placebo-Controlled Studies in ATTR Amyloidosis Patients with Cardiomyopathy

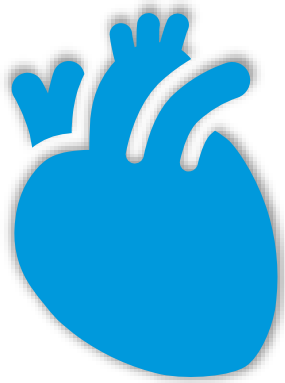
APOLLO-B

patisiran

N ~ 300
hereditary & wild-type
6-minute walk test
12 months

Enrollment **complete**

Topline results expected **mid-2022**



HELIOS-B

vutrisiran

N ~ 600
hereditary & wild-type
mortality & cardiovascular events
30 months

Enrollment **complete**

Topline results on 30-month endpoint expected **early 2024**

Study includes optional interim analysis

Patisiran APOLLO-B Phase 3 Study

Randomized, Double-Blind, Placebo-Controlled Study in ATTR Amyloidosis Patients with Cardiomyopathy

N ~ 300
Patient Population

- ATTR amyloidosis; wild-type or any TTR mutation
  - TTR stabilizer naïve and/or TTR stabilizer progressor
- Confirmed cardiomyopathy and medical history of symptomatic heart failure
- NYHA ≤III; minimum walk and NT-proBNP limits at baseline

1:1 RANDOMIZATION

Patisiran
IV q3w†
0.3 mg/kg

or

Placebo
IV q3w†

Primary Endpoint

- Change in 6-MWT at 12 months

Key Secondary Endpoints

- Cardiomyopathy symptoms and health status
- Death and hospitalization outcomes
- Cardiac biomarkers

12-Month Treatment Extension

ClinicalTrials.gov Identifier: NCT03997383

APOLLO-B

Enrollment complete

Topline results expected **mid-2022**

Concomitant use of local standard of care allowed during study, including TTR stabilizer
† To reduce likelihood of infusion-related reactions, patients receive following premedication or equivalent at least 60 min. before each study drug infusion: 10 mg (low dose) dexamethasone; oral acetaminophen; H1 and H2 blockers
NYHA: New York Heart Association; NT-proBNP: N-terminal pro b-type natriuretic peptide; 6-MWT: 6-Minute Walk Test

Vutrisiran HELIOS·B Phase 3 Study

Randomized, Double-Blind Outcomes Study in ATTR Amyloidosis Patients with Cardiomyopathy

N ~ 600
Patient Population

- ATTR amyloidosis; wild-type or any TTR mutation
- Confirmed cardiomyopathy and medical history of symptomatic heart failure
- NYHA ≤ III; minimum walk and NT-proBNP limits at baseline

ClinicalTrials.gov Identifier: NCT04153149

1:1 RANDOMIZATION

Vutrisiran
SC q3M
25 mg

or

Placebo
SC q3M

Primary Endpoint

- Composite outcome of all-cause mortality and recurrent CV events (when last patient reaches Month 30)

Select Secondary Endpoints

- 6-MWT distance
- Kansas City Cardiomyopathy Questionnaire (KCCQ OS) score
- Echocardiographic parameters
- All-cause mortality and recurrent all-cause hospitalizations and HF events
- All-cause mortality
- Recurrent CV events
- NT-proBNP

HELIOS·B

Enrollment complete

Topline results on 30-month endpoint expected **early 2024**

Study includes optional interim analysis

Optional HELIOS-B Interim Analysis

Evaluating Options for Potential Readout Before Last Patient Reaches Month 30

- Optional interim analysis included in protocol
  - Details not specified
- Engagement with regulatory authorities to align on a potential approach
- Staging after APOLLO-B data readout in mid ’22
  - Inform finalization of strategy
  - Ensure optimal balance between speed and desired label expansion for vutrisiran in ATTR amyloidosis with cardiomyopathy

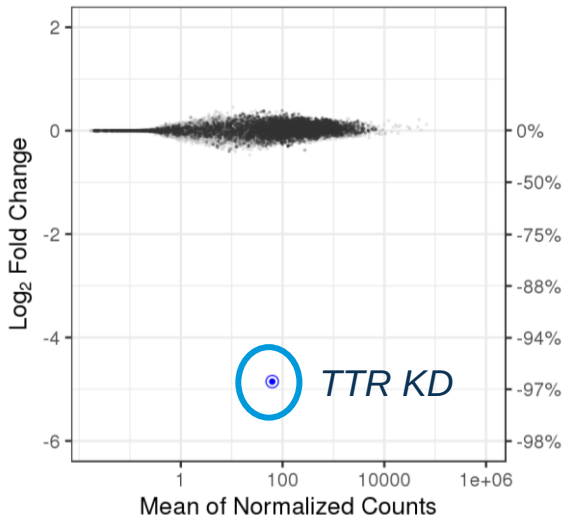
Agenda

1. Alnylam ATTR Amyloidosis Franchise Overview
2. Vutrisiran HELIOS-A Phase 3 Topline 18-Month Results
3. Potential Expansion into ATTR Amyloidosis with Cardiomyopathy
4. **Advancing Innovation with ALN-TTRsc04**
5. Stargardt Disease: Promising New Opportunity for Vutrisiran

IKARIA™ Platform: Proprietary siRNA Design with Novel Chemistry

Super-specific siRNAs May Enable Higher Doses to Achieve Annual Dosing

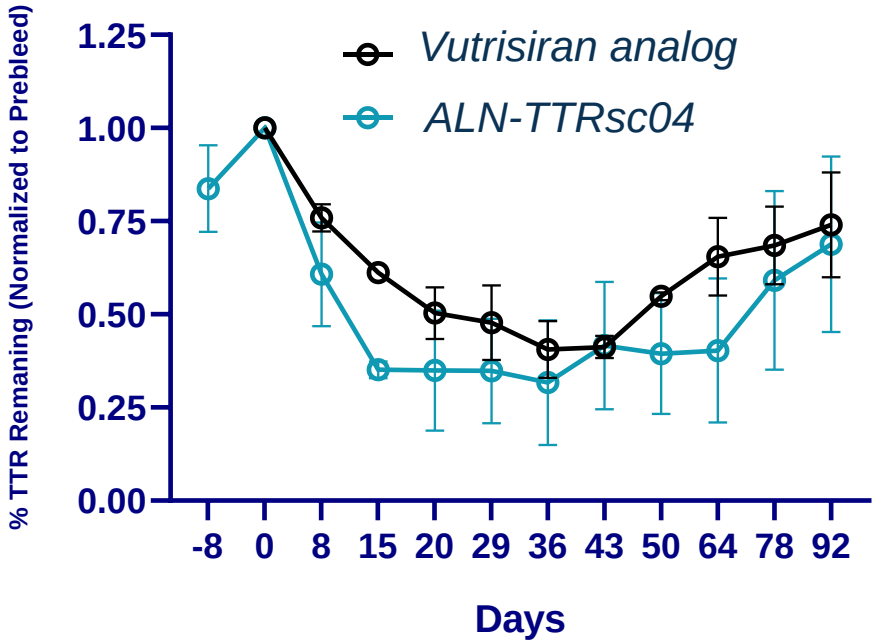
Exquisite specificity



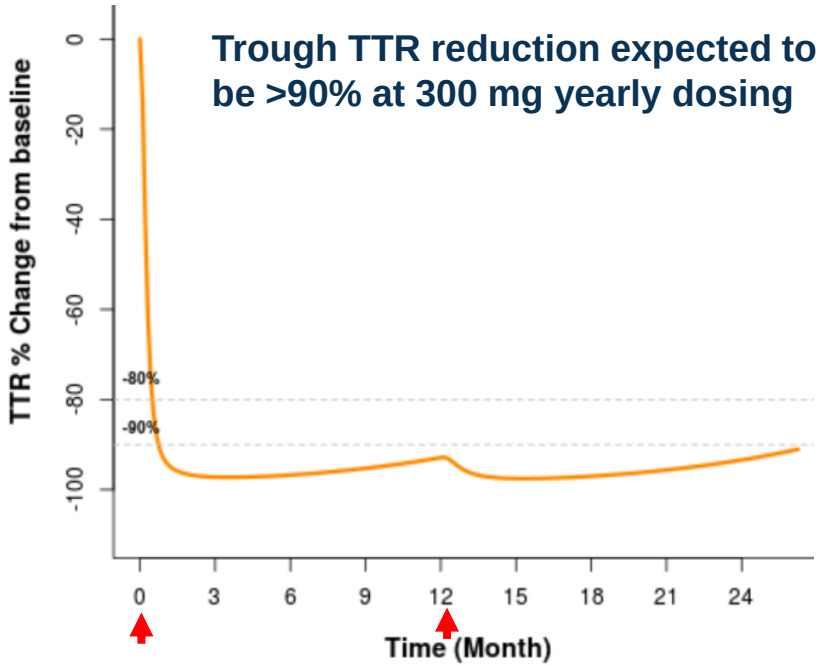
RNAseq analysis

High potency in NHP

0.5 mg/kg single sc dose



Human dose projection



Trough TTR reduction expected to be >90% at 300 mg yearly dosing

Modeling predicts potential for once-a-year dosing in humans with greater than 90% TTR reduction

ALN-TTRsc04 Key Features and Upcoming Milestone

- Potential for annual subcutaneous dosing regimen with potent and reversible effects
- No third-party royalty obligations
- Loss of exclusivity expected to extend beyond 2040
- Alnylam demonstrated track record for rapidly advancing innovation in ATTR amyloidosis
  - E.g., ~3 years from vutrisiran first-in-human readout to positive Phase 3 data in HELIOS-A

IND application filing expected
late 2022

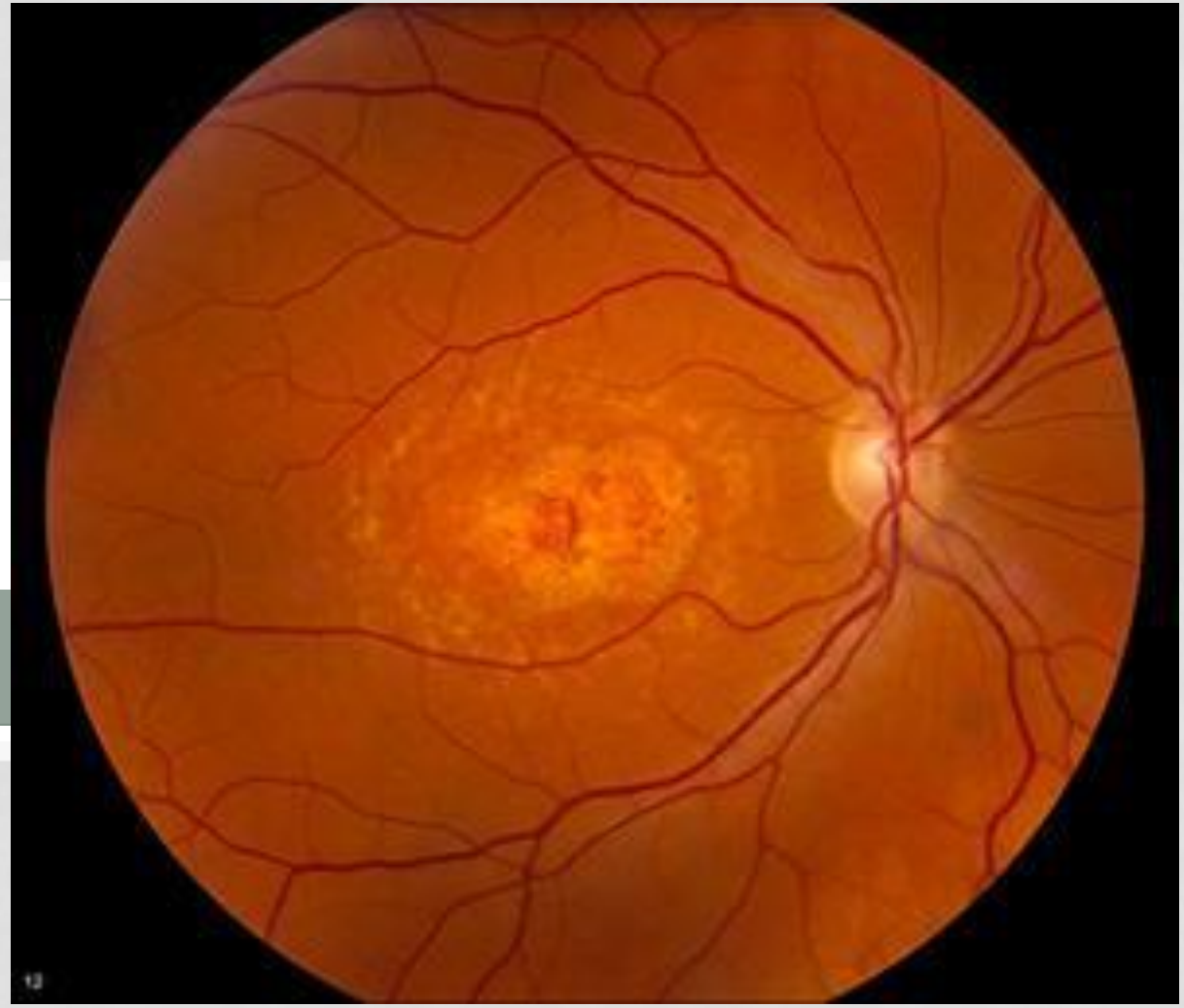
Agenda

1. Alnylam ATTR Amyloidosis Franchise Overview
2. Vutrisiran HELIOS-A Phase 3 Topline 18-Month Results
3. Potential Expansion into ATTR Amyloidosis with Cardiomyopathy
4. Advancing Innovation with ALN-TTRsc04
5. Stargardt Disease: Promising New Opportunity for Vutrisiran

OVERVIEW OF STARGARDT DISEASE

SriniVas Sadda, MD

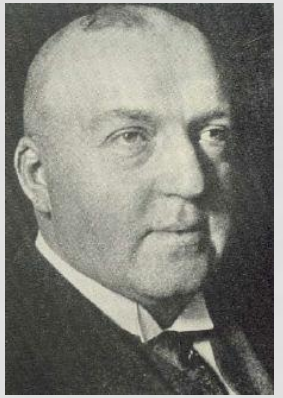
Professor of Ophthalmology
Doheny Eye Institute
David Geffen School of Medicine, UCLA
Los Angeles, California, USA



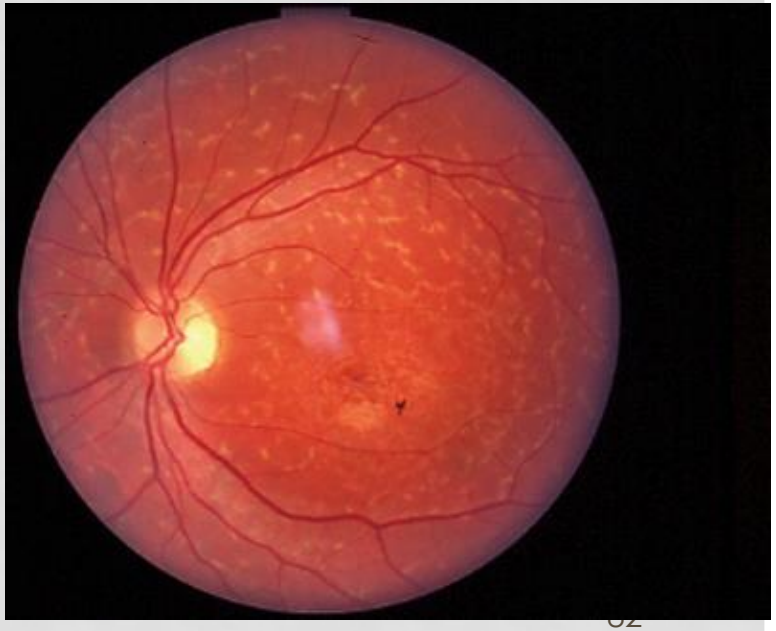
Stargardt Disease

BACKGROUND

- Original description in 1909 by Karl Stargardt (Berlin)
- Prevalence: 1 in 8-10,000 individuals in the US
  - No racial or gender predilection
  - Found worldwide



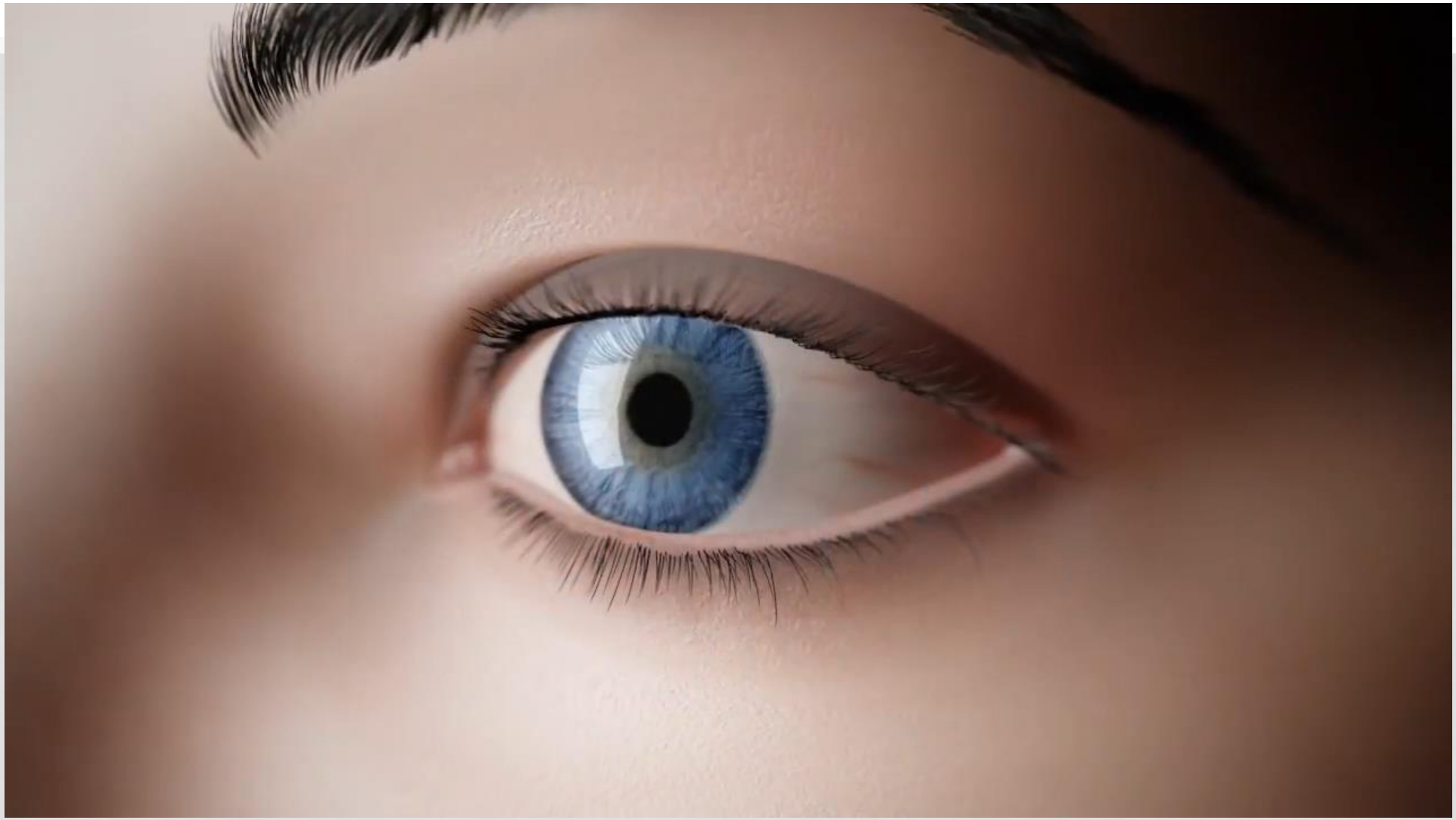
- Most common cause of juvenile macular dystrophy in the US and important cause of vision loss in younger individuals



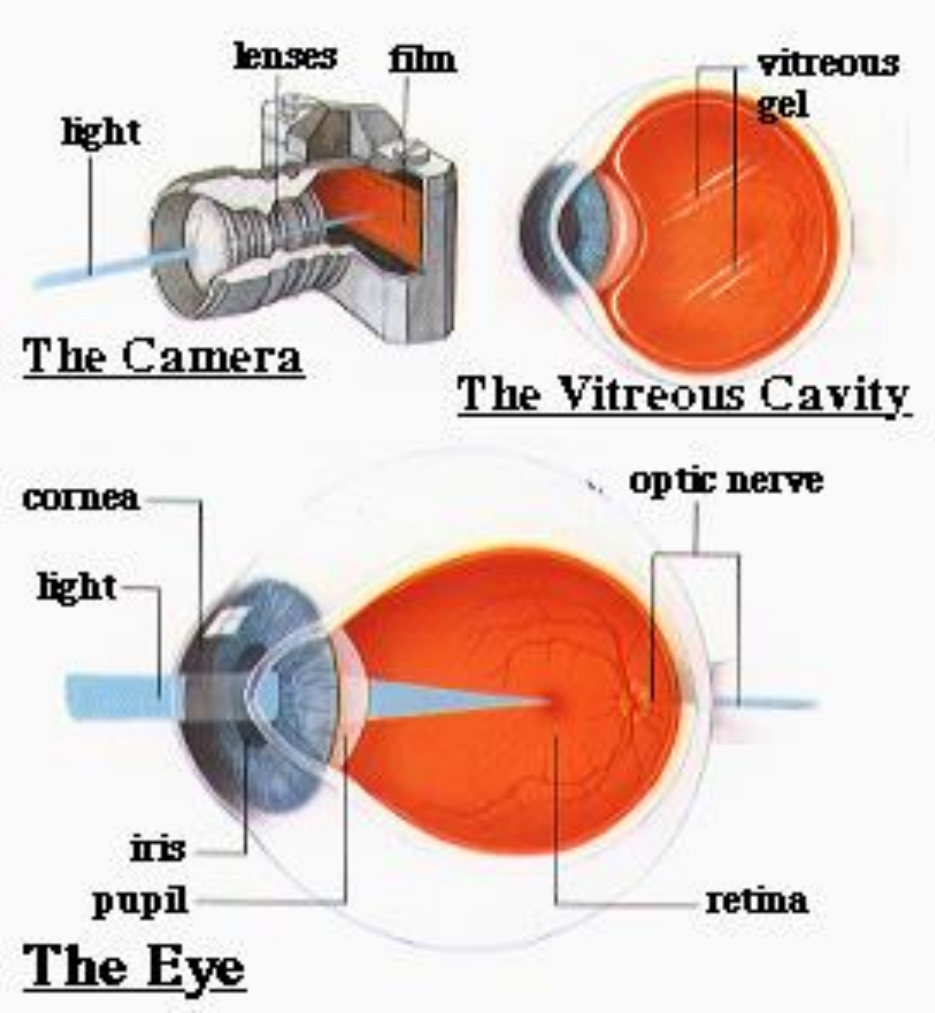
WHAT IS THE MACULA?

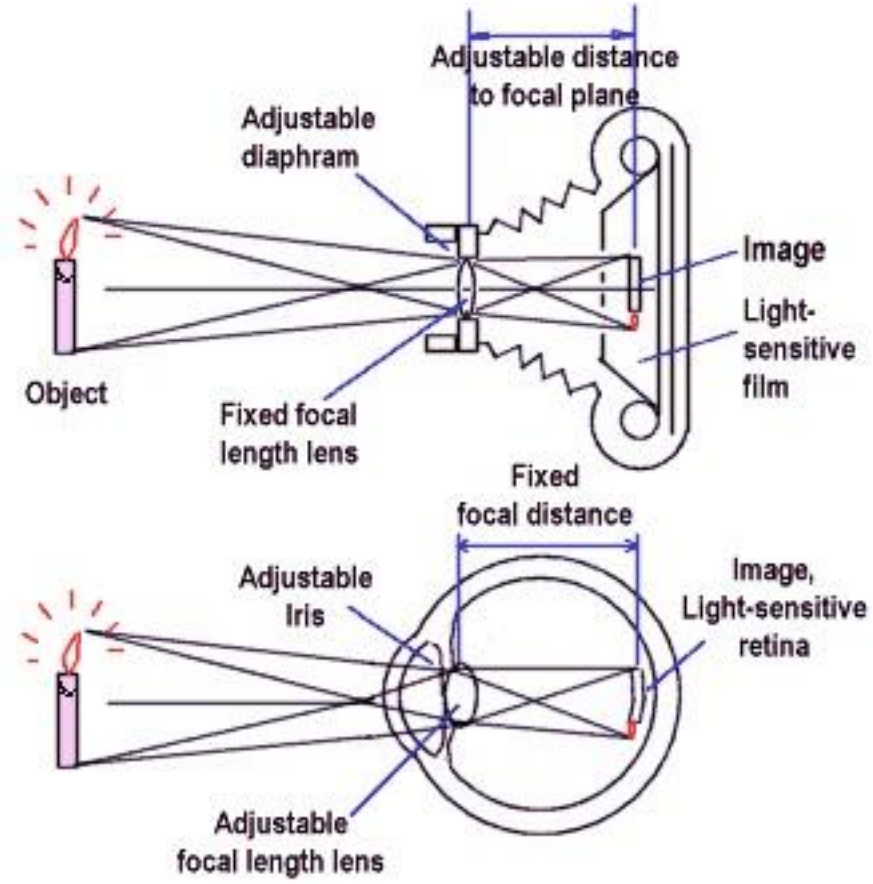
AND WHY IS IT IMPORTANT?

INTRODUCTION TO THE EYE

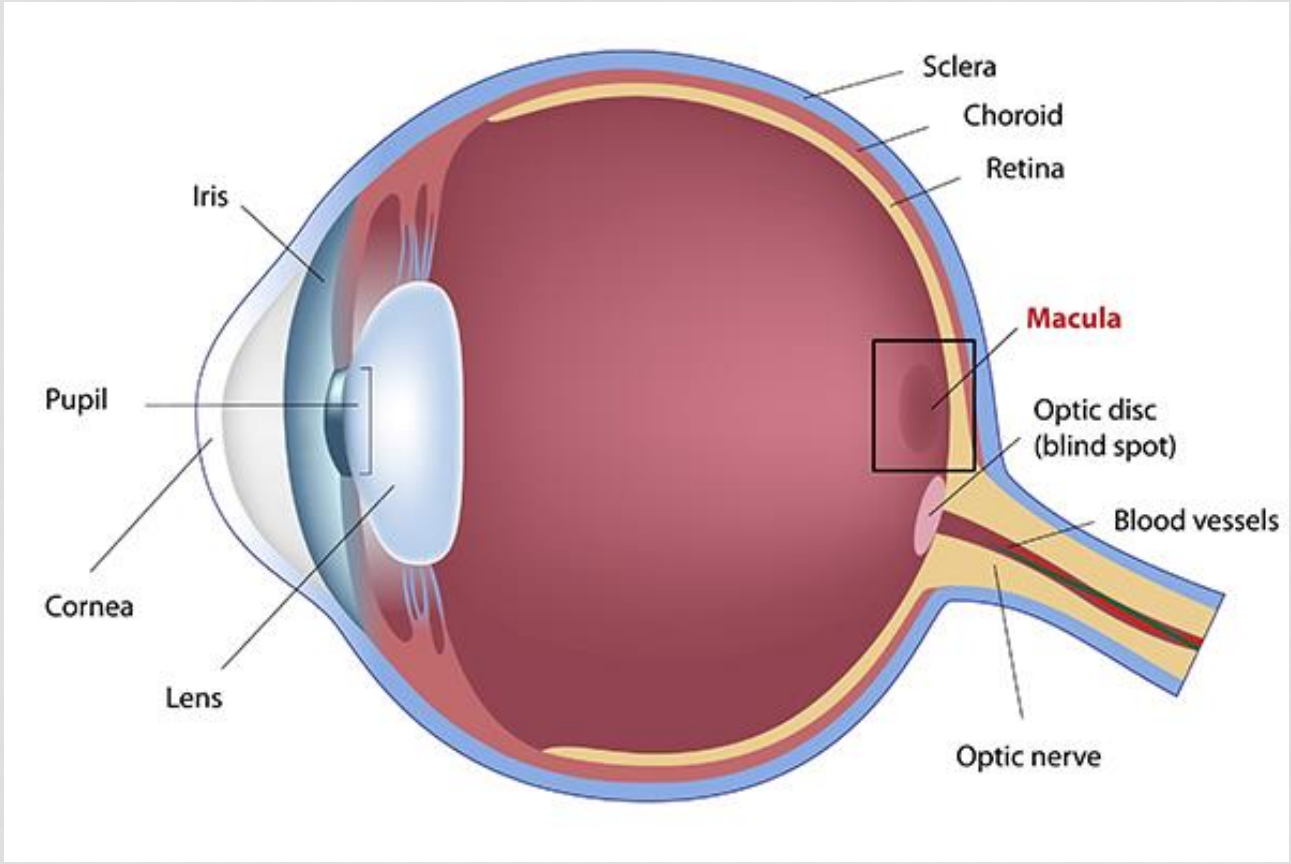


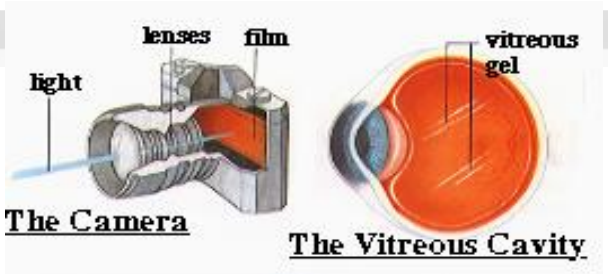
THE EYE - CAMERA ANALOGY

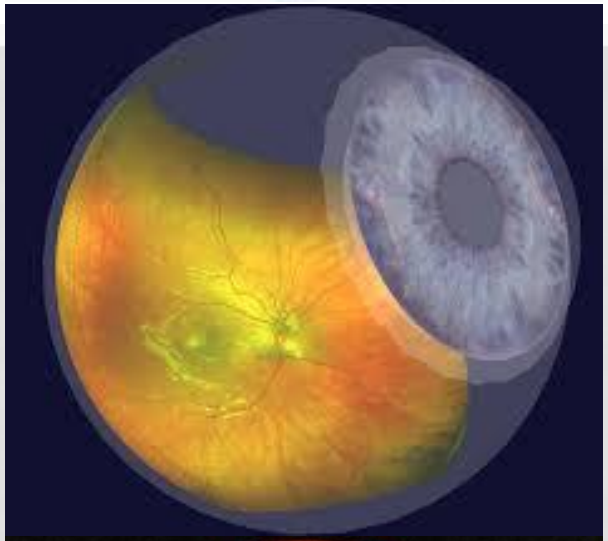


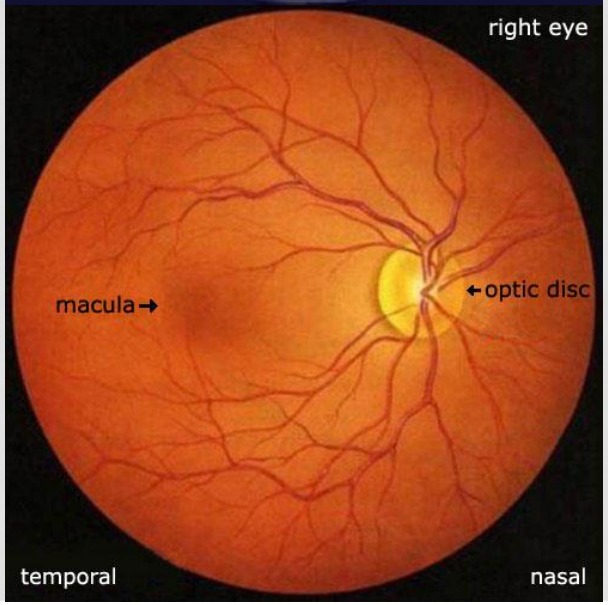


RETINAL ANATOMY









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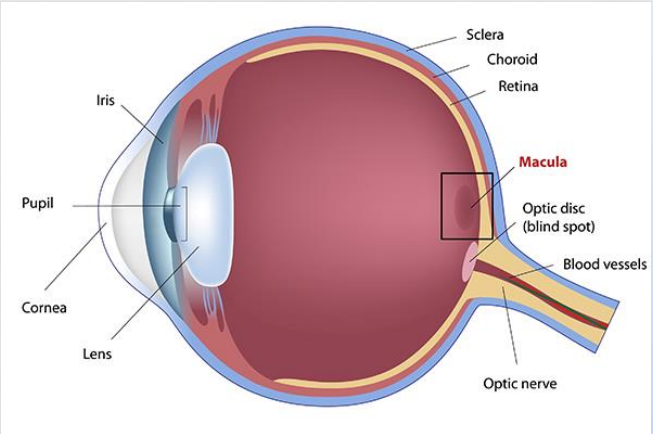
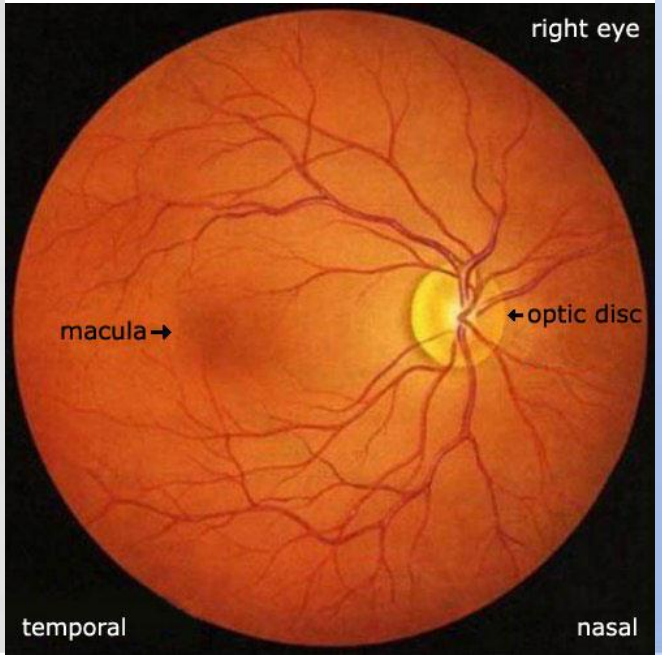
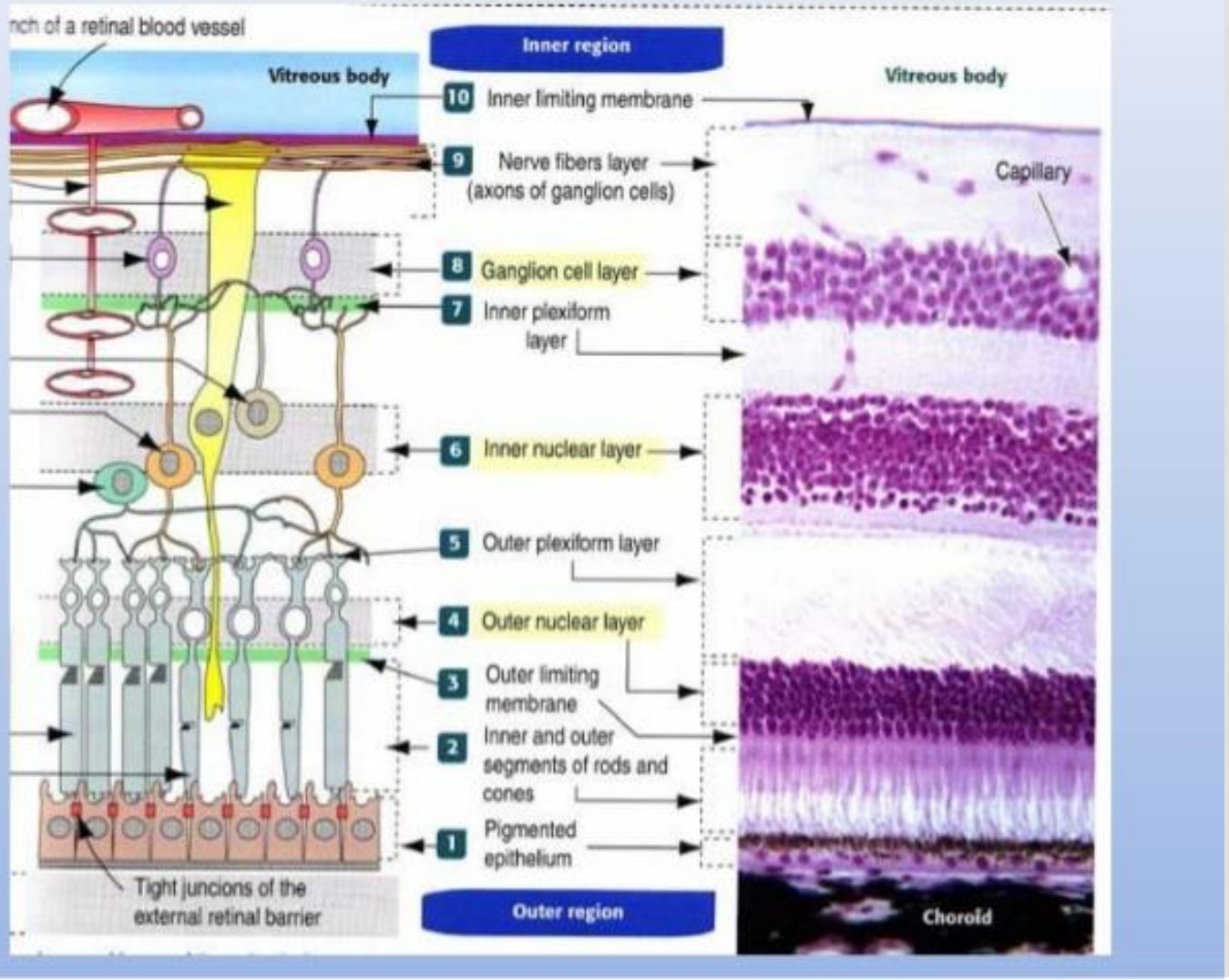
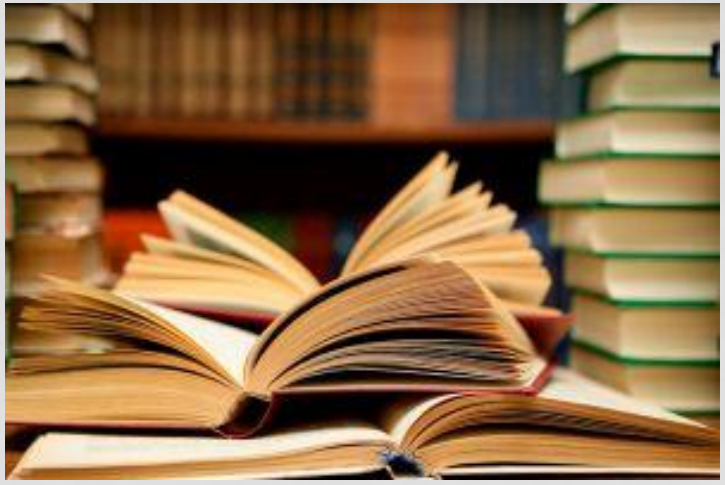






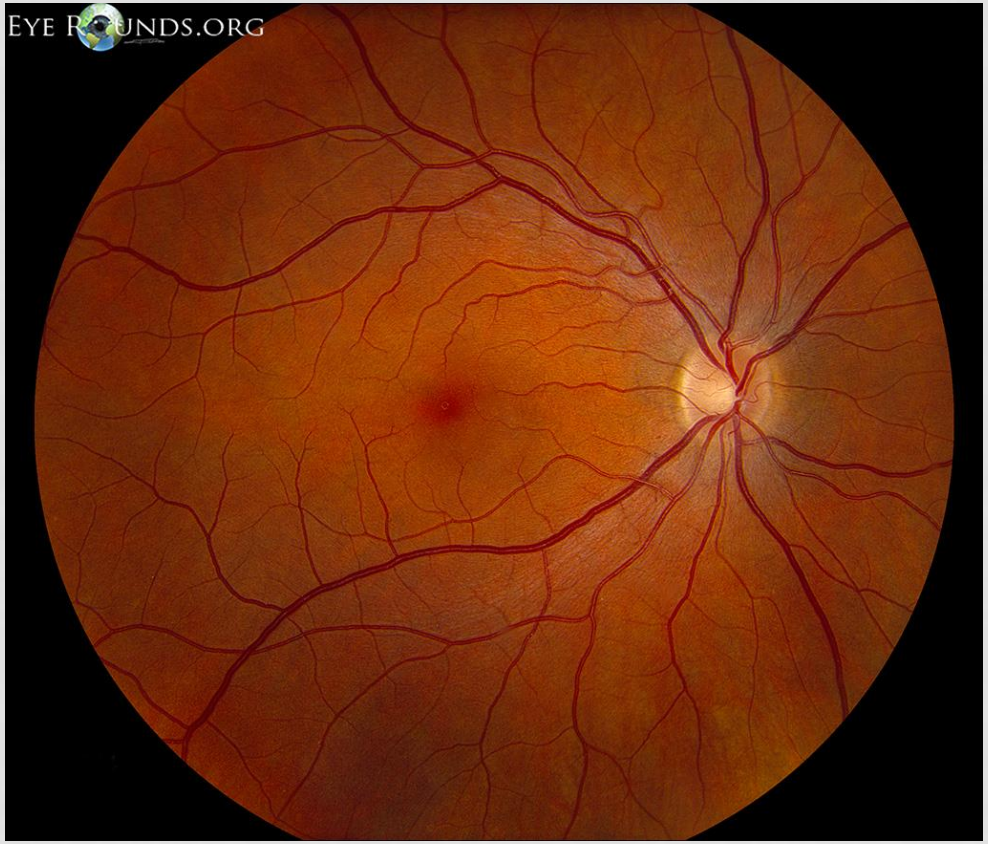
VISUAL IMPACT OF MACULAR DISEASES

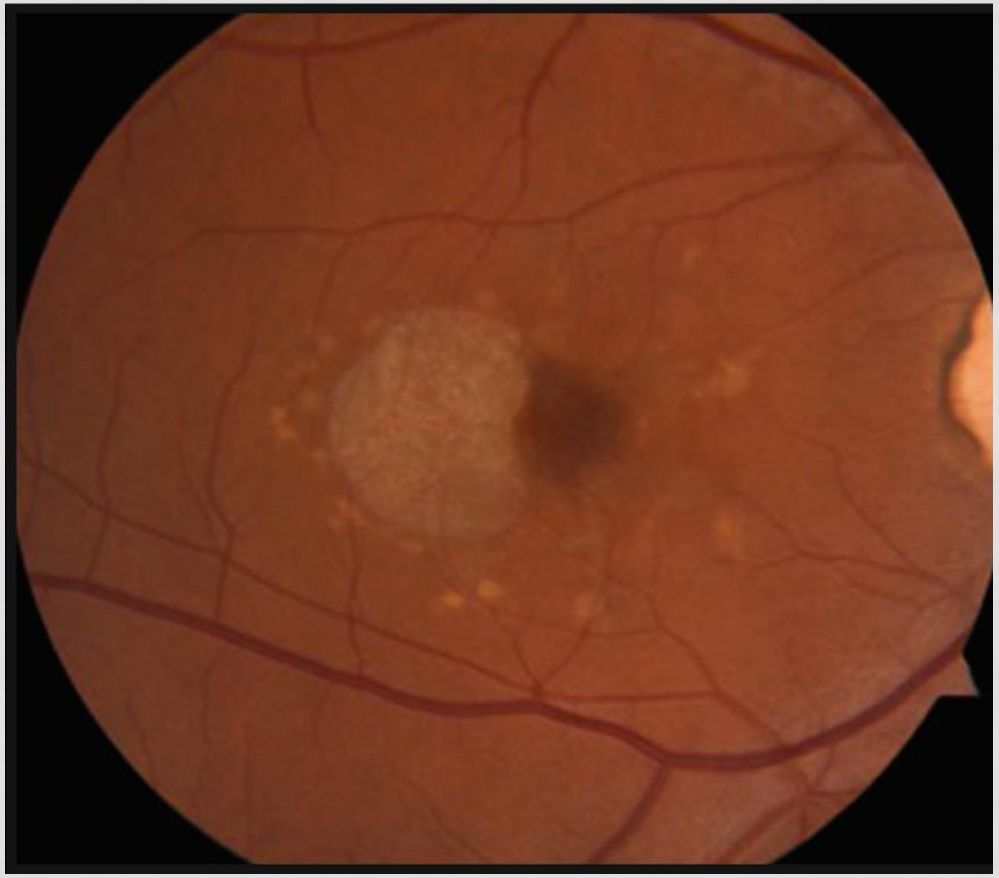
- Central vision is most severely impacted
  - Cones – sharpest vision, color vision
  - Reading, driving, watching television



"Legally Blind": 20/200 or worse in the better eye

STARGARDT'S AND THE MACULA





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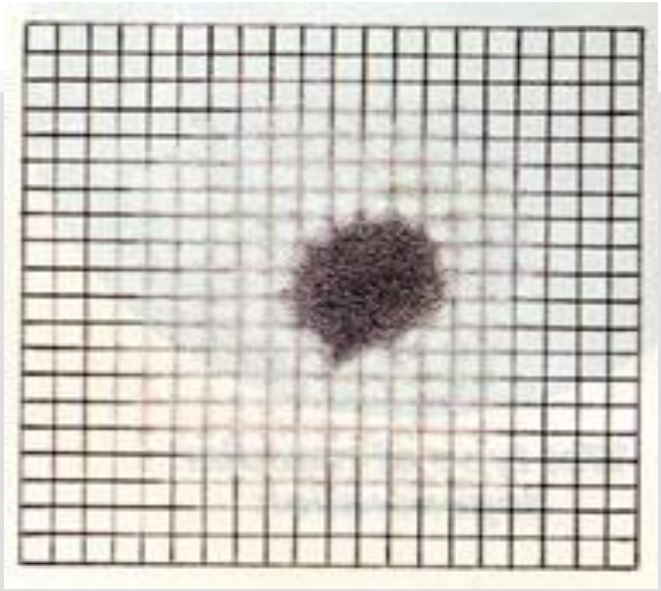
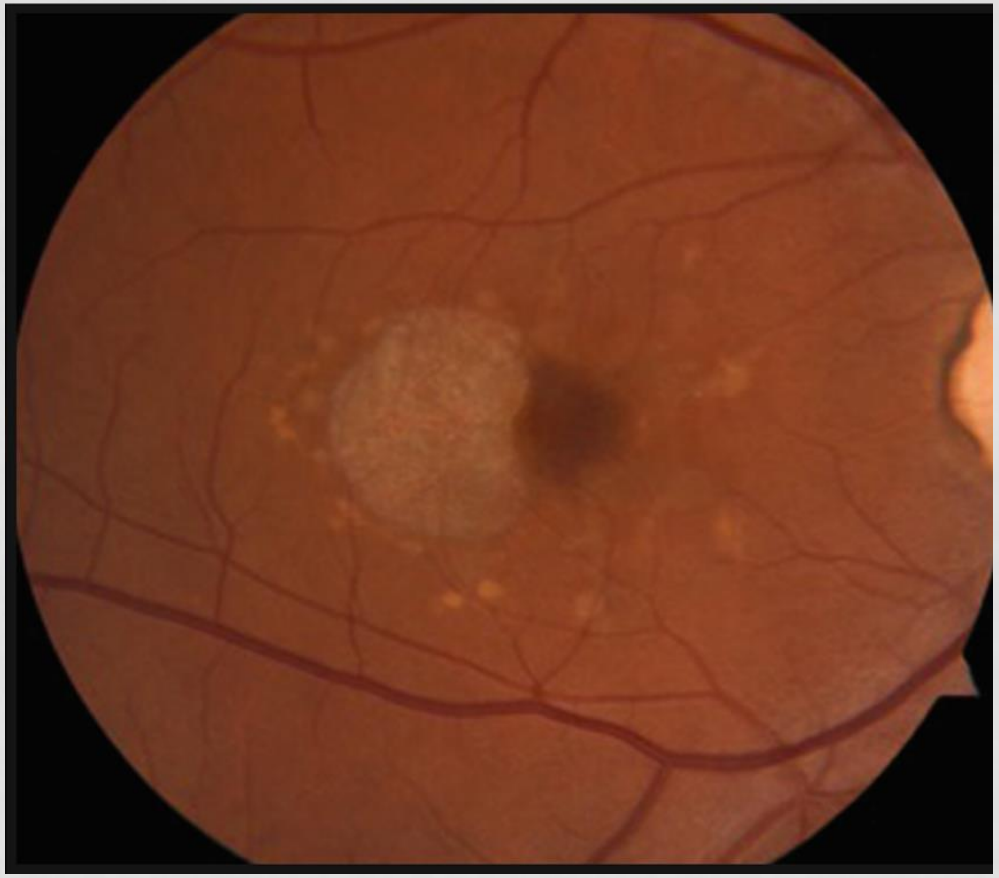
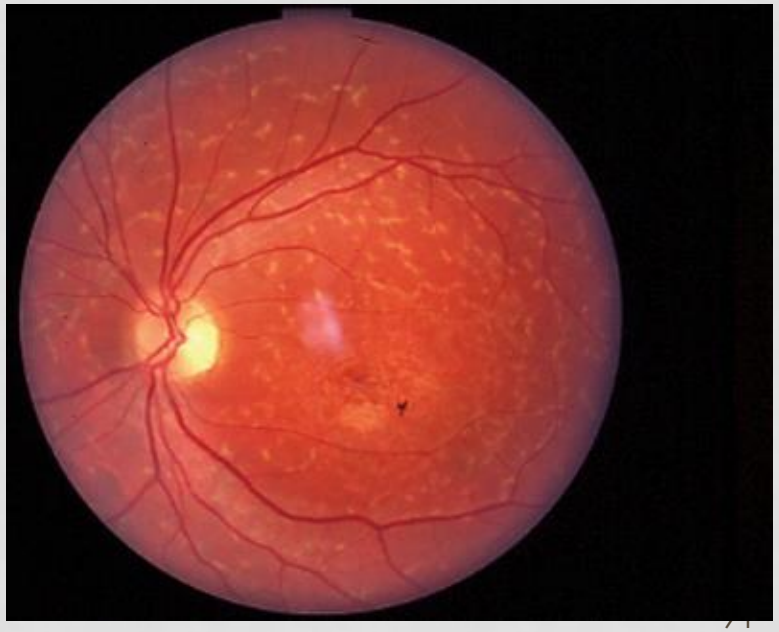




Stargardt Disease
GENETICS

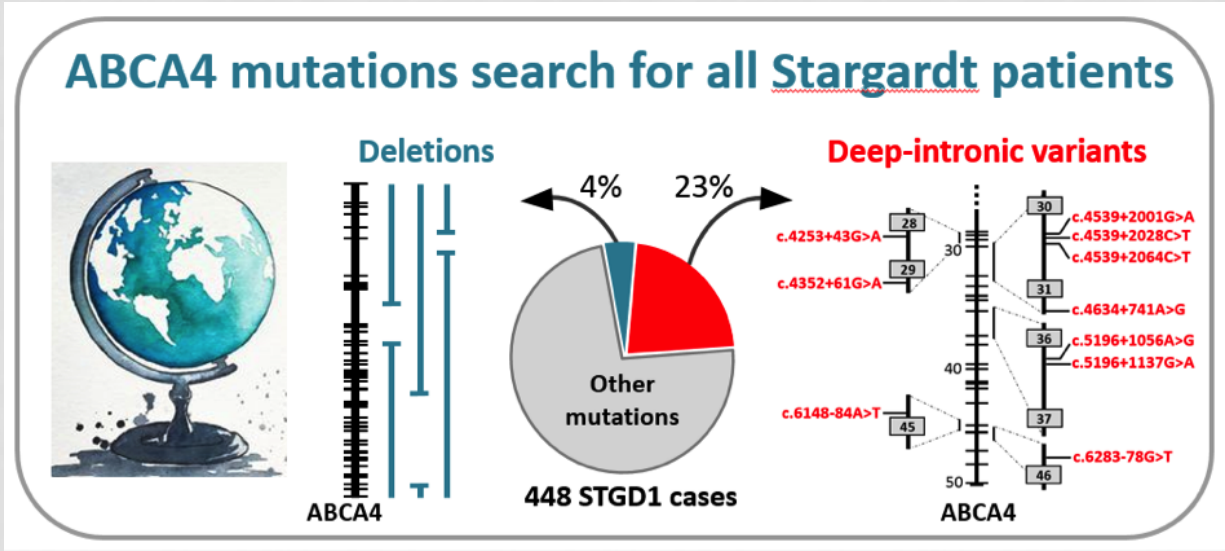
- Stargardt disease -- most common inherited macular dystrophy

- Genetics
  - Autosomal Recessive
    - STGD1 (ABCA4) – 90% of cases
      - Compound heterozygotes are common
  - Autosomal Dominant
    - STGD2 (ELOVL4)
    - STGD4 (PROM-1)



WHAT IS ABCA4?

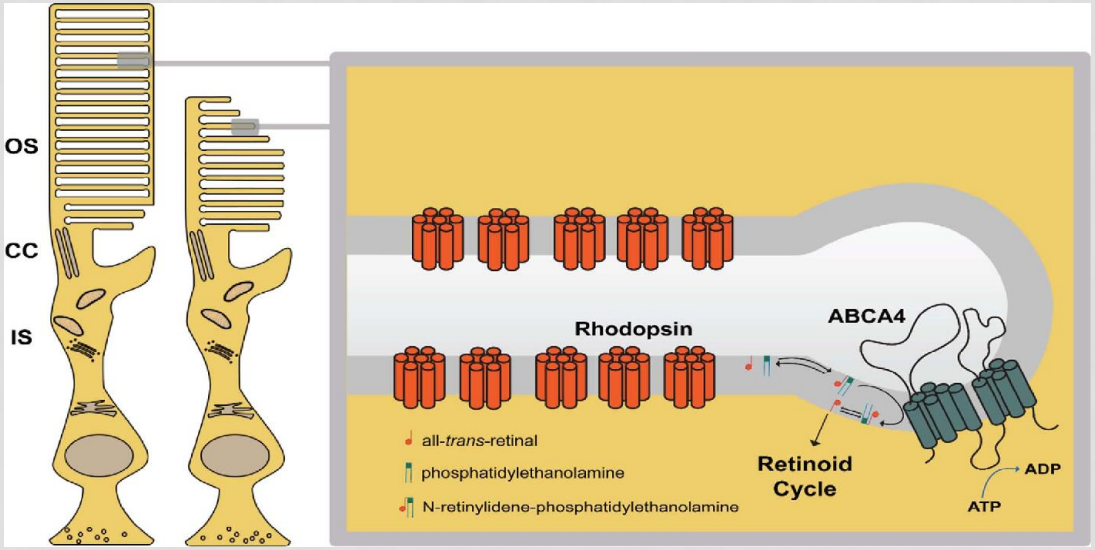
- Short arm of Chromosome 1 (1p22.1)
- Large Gene
  - 150kb/50 exons –2273 amino acid protein
- Very large allelic heterogeneity
- >490 disease-causing mutations



WHAT IS ABCA4?

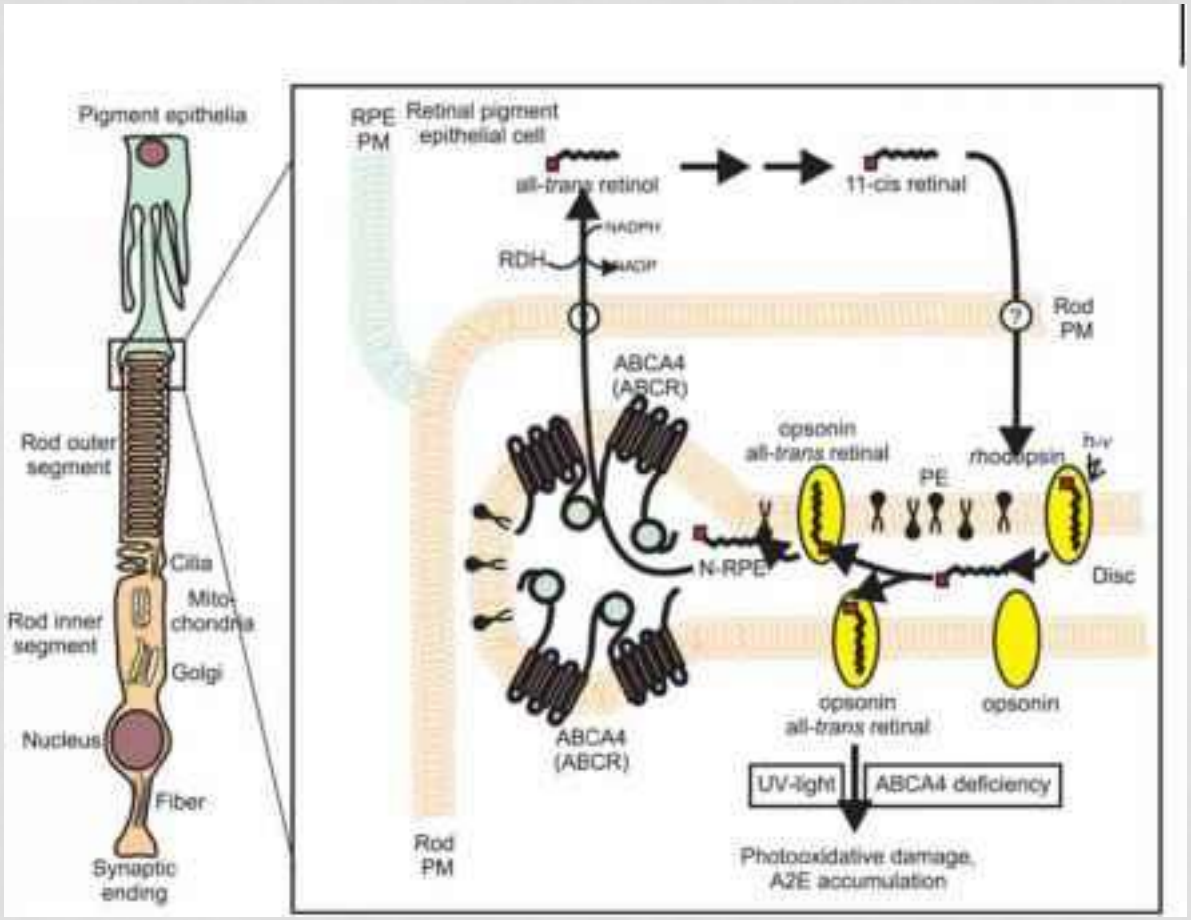
- ABCA4 belongs to a larger family of ATP-binding cassette (ABC) family proteins that are important for transporting various molecules

- ABCA4 is specifically localized/expressed in the retina



WHAT IS ABCA4?

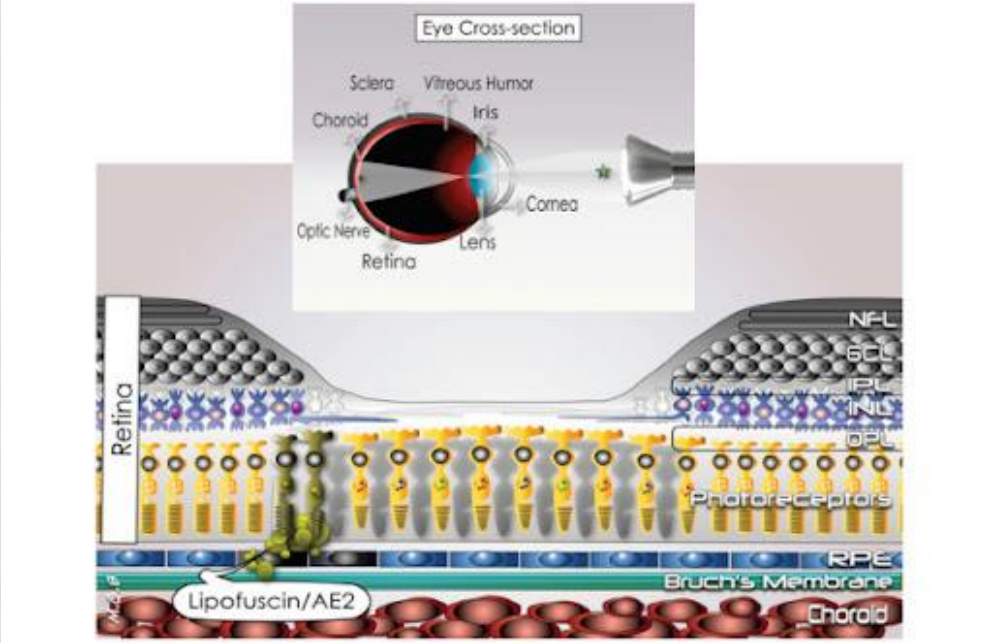
- ABCA4 is responsible for transport of all-trans-retinal across the disk membranes of retinal photoreceptors (cones/rods)
- all-trans-retinal is a Vitamin A metabolite important for vision



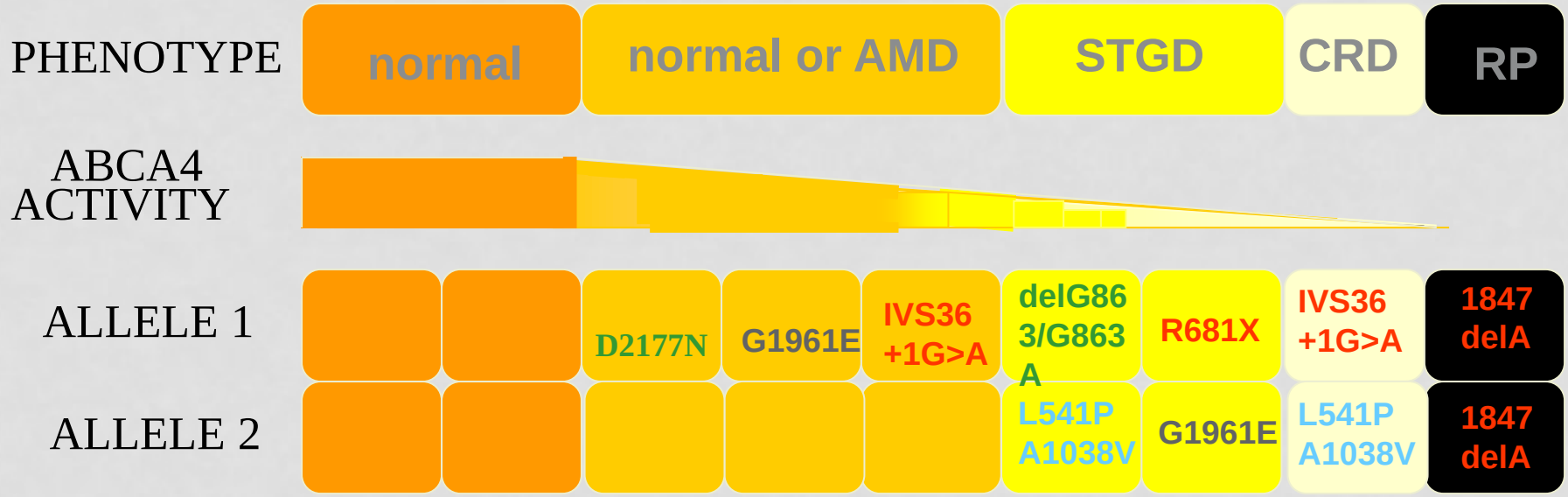
WHAT IS ABCA4?

- Without proper ABCA4 function toxic Vitamin A metabolites (A2E) accumulate as lipofuscin deposits in the retinal pigment epithelial (RPE) cells

- Dysfunctional RPE can lead to photoreceptor cell loss and loss of vision



GENOTYPE/PHENOTYPE MODEL FOR ABCA4



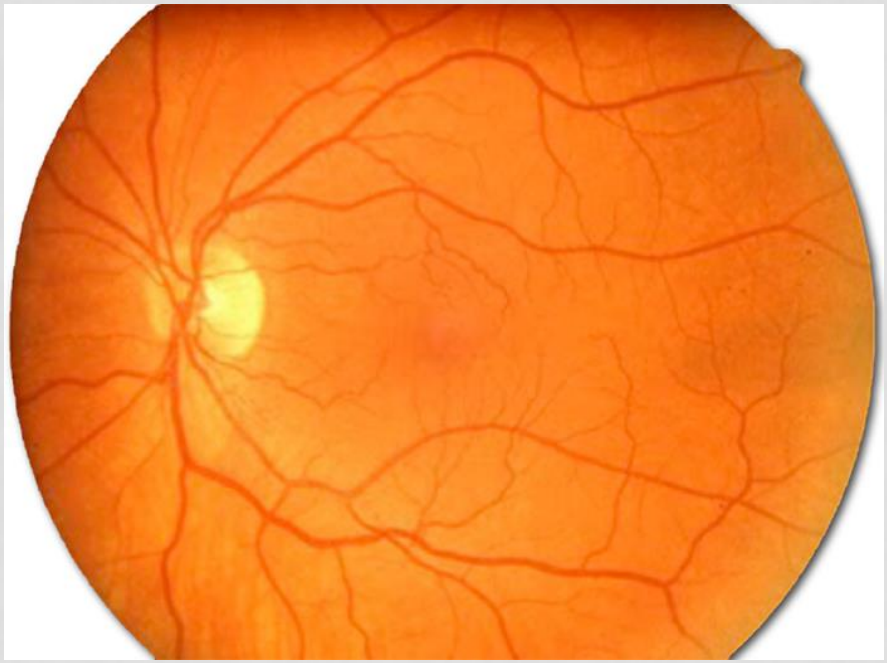
MILD - MODERATE - SEVERE ABCA4 MUTATIONS

Amount of residual ABCA4 activity predicts the disease phenotype

Stargardt Disease

CLINICAL PRESENTATION

- Presenting symptom: progressive bilateral vision loss
- Initial presenting vision: 20/30 to 20/200; color vision impacted
- Onset typically in teens or twenties
  - Earlier onset generally associated with "more severe" mutation
  - Late-onset (sometimes confused with AMD) – milder mutations
  - Faster progression with earlier onset
- Retinal exam findings:
  - Early on may appear grossly normal



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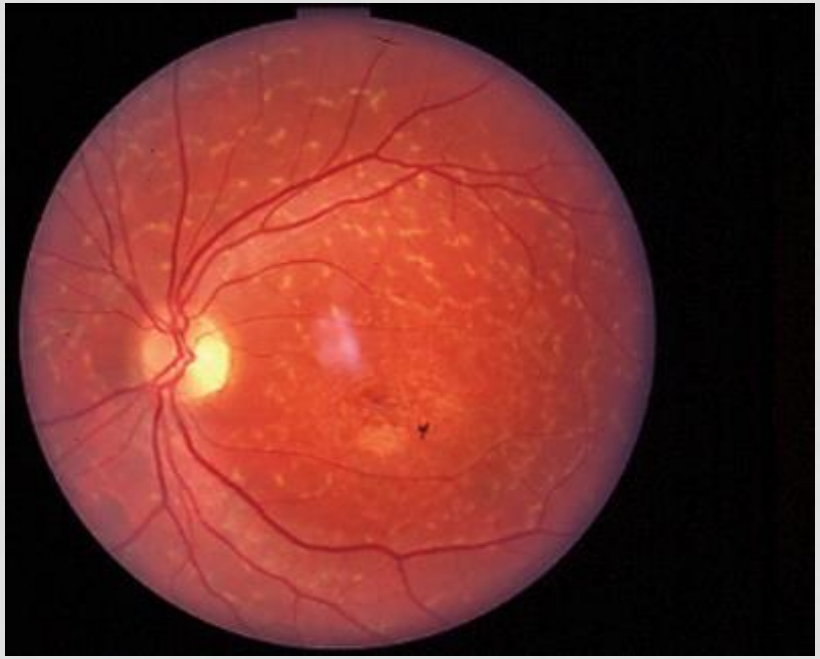
- Retinal exam findings:
  - Early on may appear grossly normal
  - Hallmark feature: pisciform flecks
    - Yellowish-white color, at level of RPE
    - Irregular shape ("fish-like")



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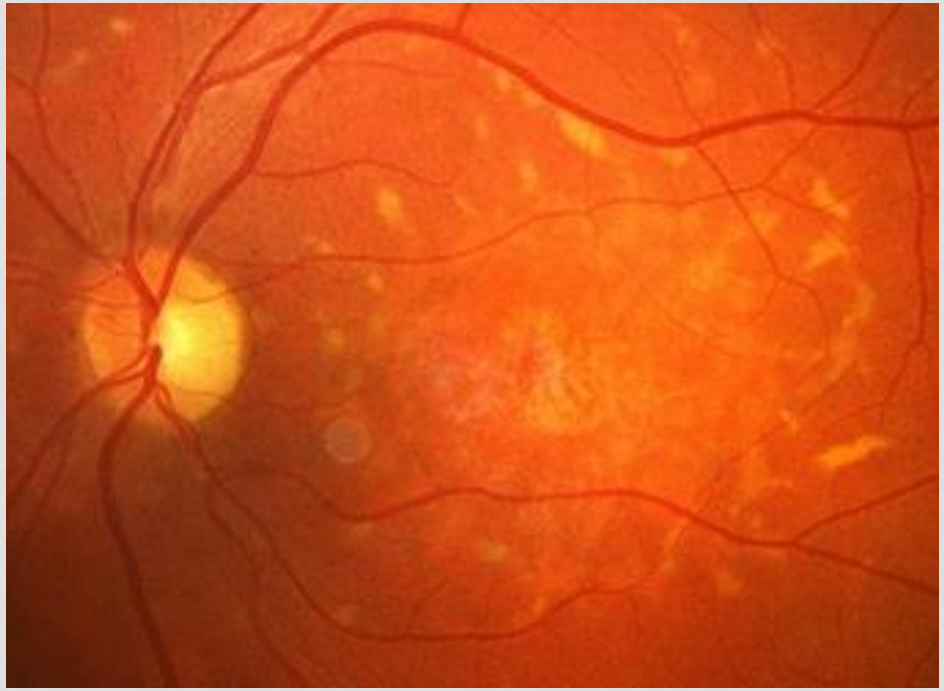
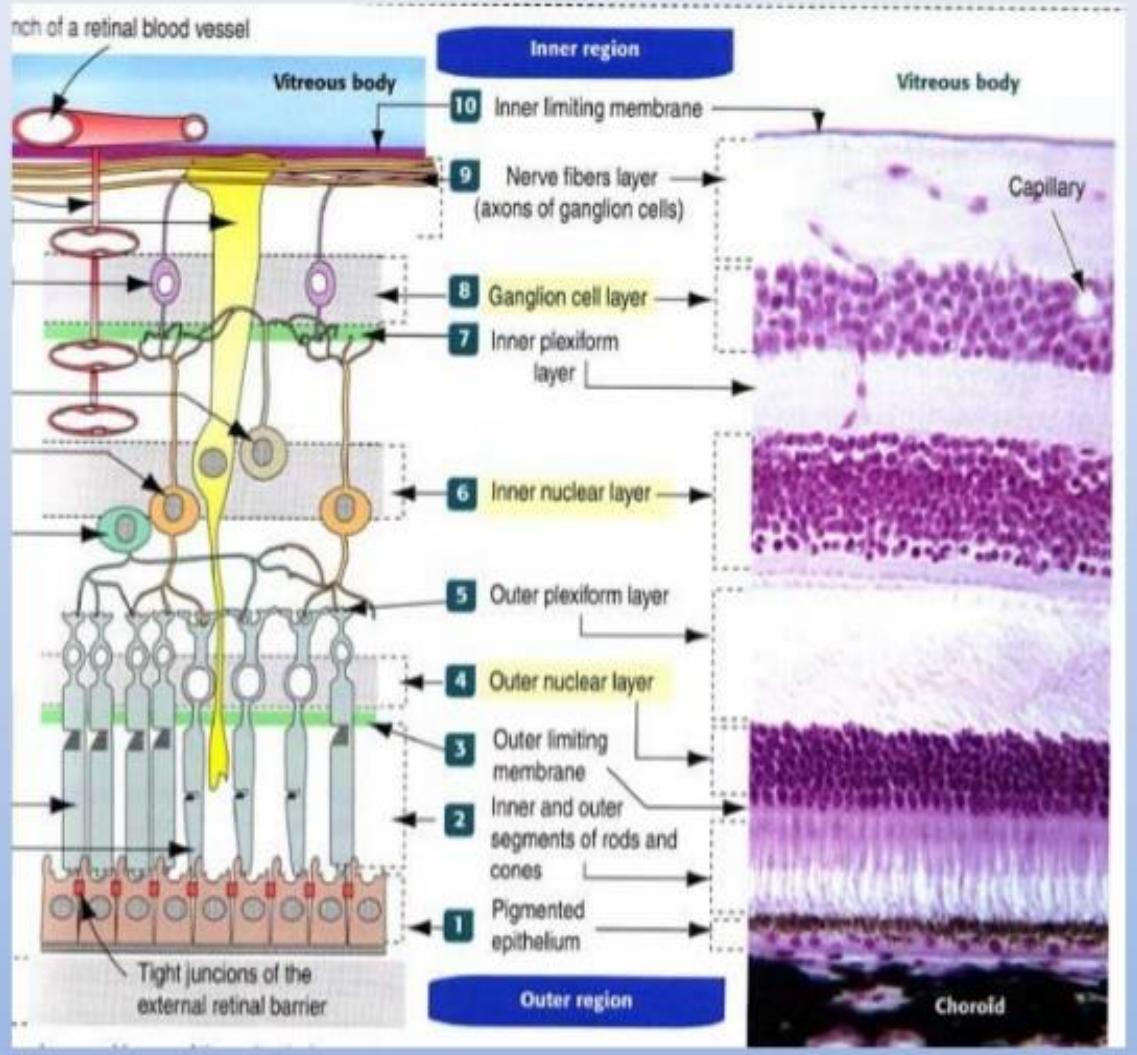
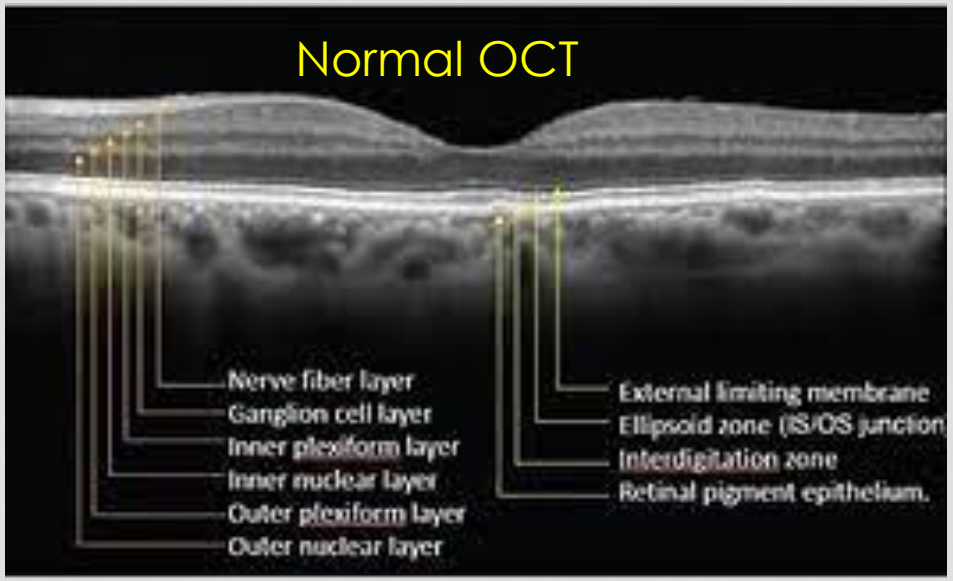
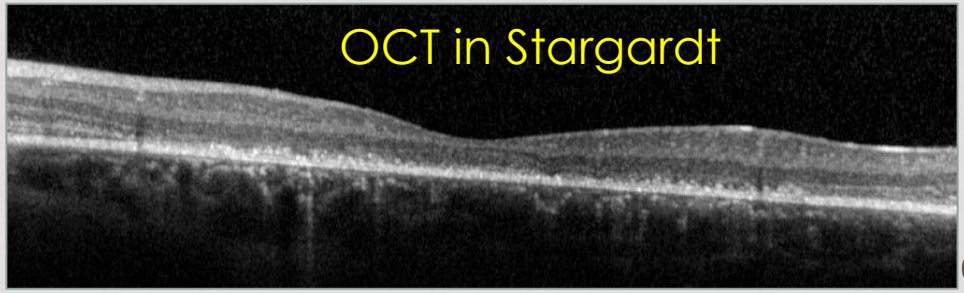
  - Hallmark feature: pisciform flecks
    - Yellowish-white color, at level of RPE
    - Irregular shape ("fish-like")
  - Progressive macular atrophy
    - "beaten bronze"; bull's-eye



LOSS OF THE PHOTORECEPTORS

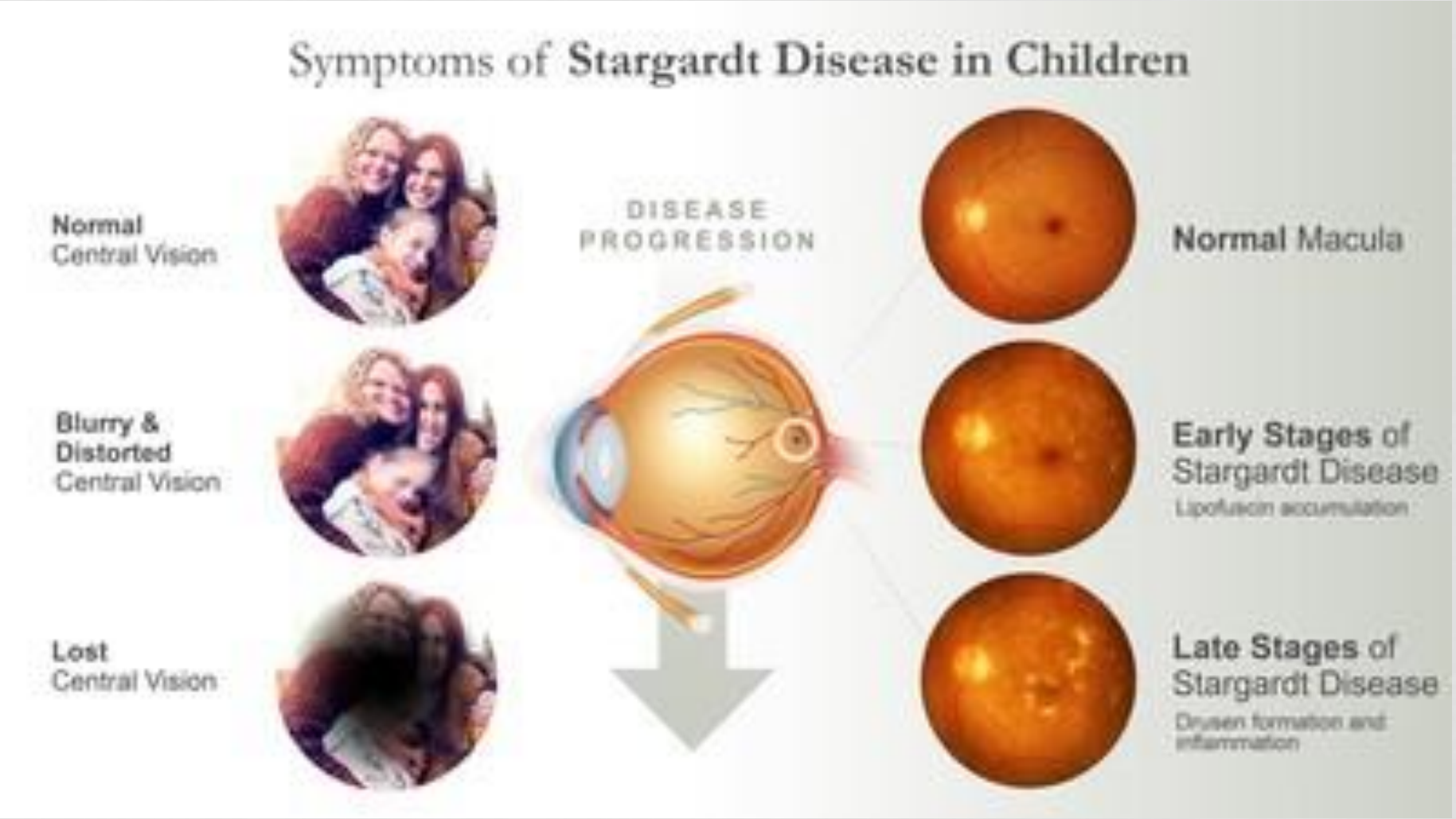






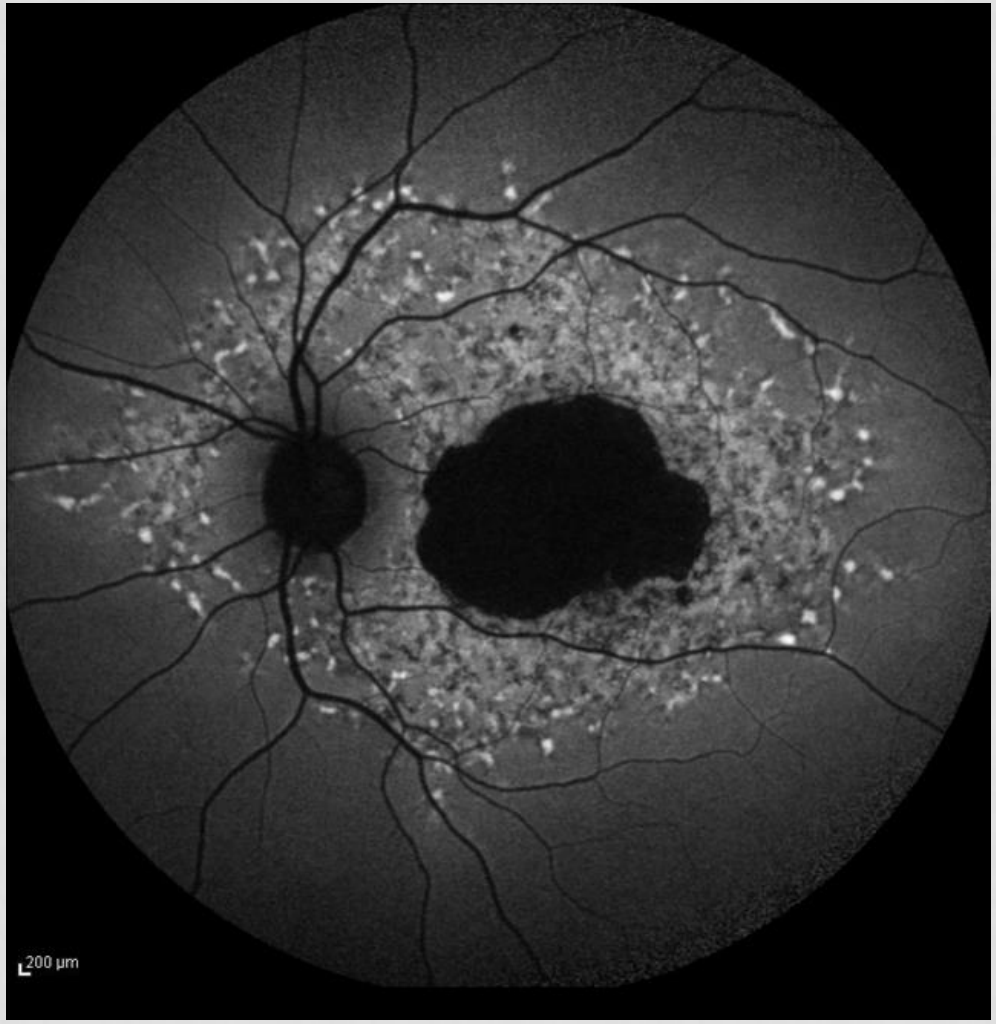
Stargardt Disease

CLINICAL PRESENTATION



Stargardt Disease
DIAGNOSTIC TOOLS

- **Fundus Autofluorescence**
  - Takes advantage of the fact that lipofuscin fluoresces with blue light
  - Flecks
    - Hyperfluorescent or hypofluroescent (older)
  - Atrophy
    - FAF suggested as a potential tool to quantify and monitor progression of atrophy over time in clinical trials



Stargardt Disease

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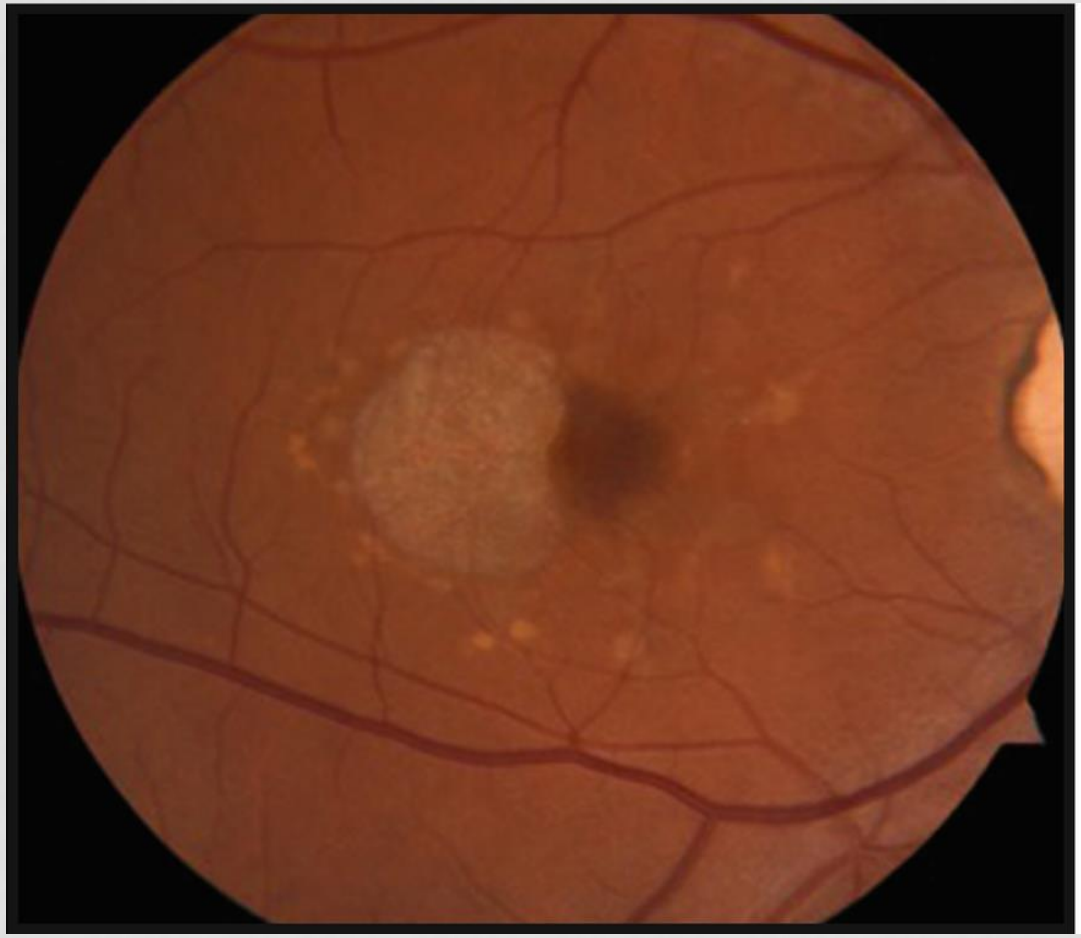
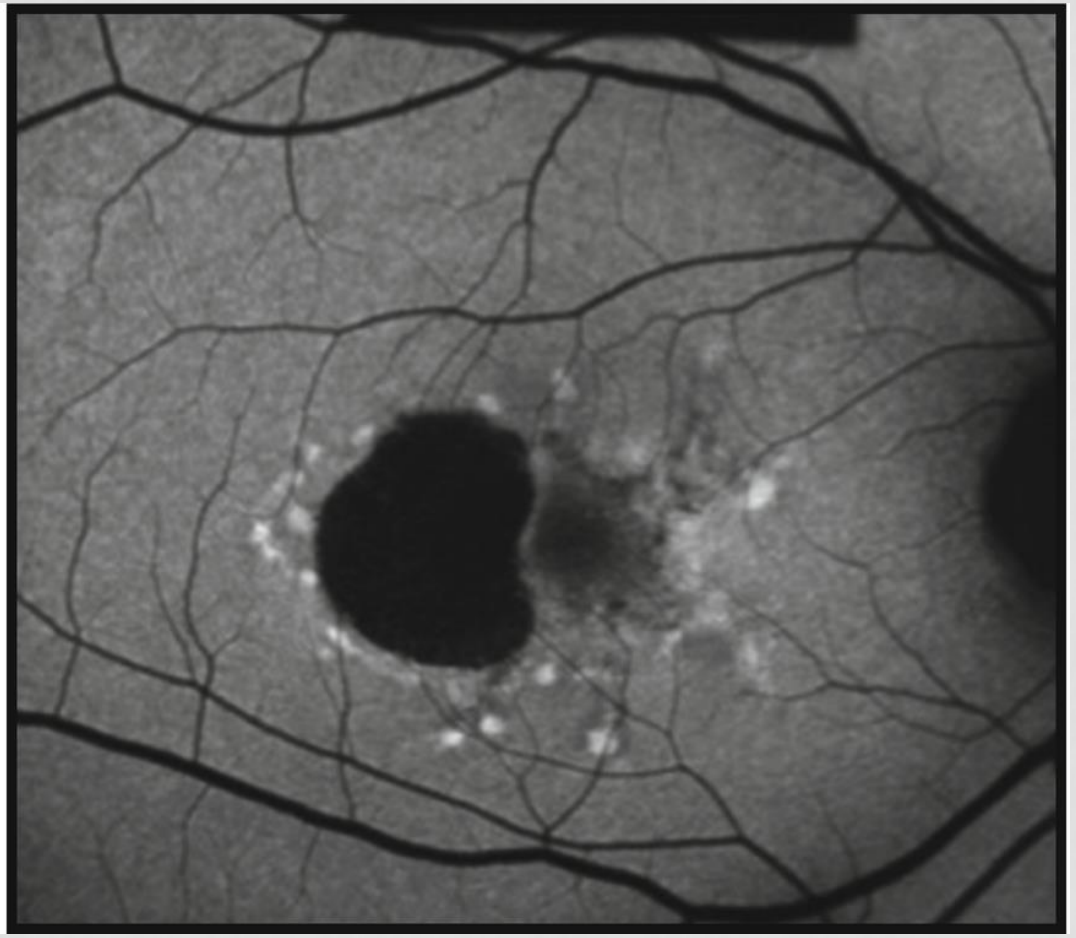
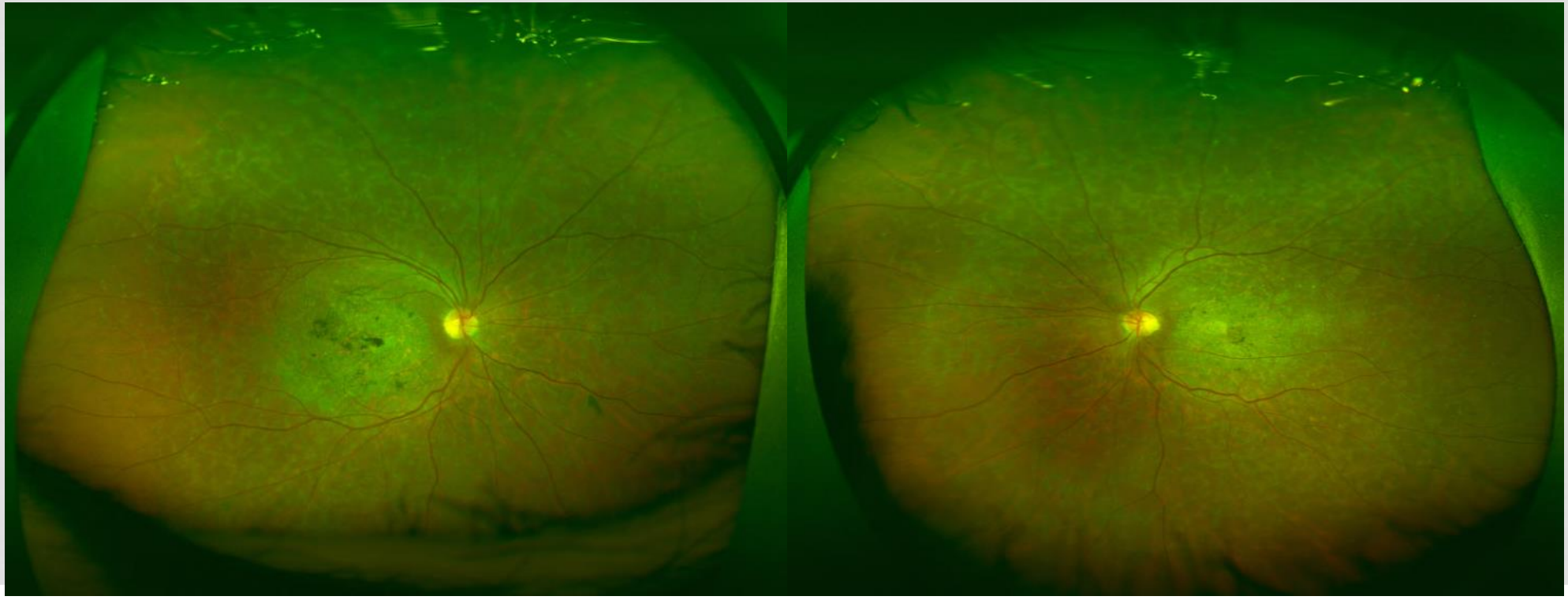




Stargardt Disease

DIAGNOSTIC TOOLS

- **Fundus Autofluorescence**
  - Flecks can be extensive



Stargardt Disease

DIAGNOSTIC TOOLS

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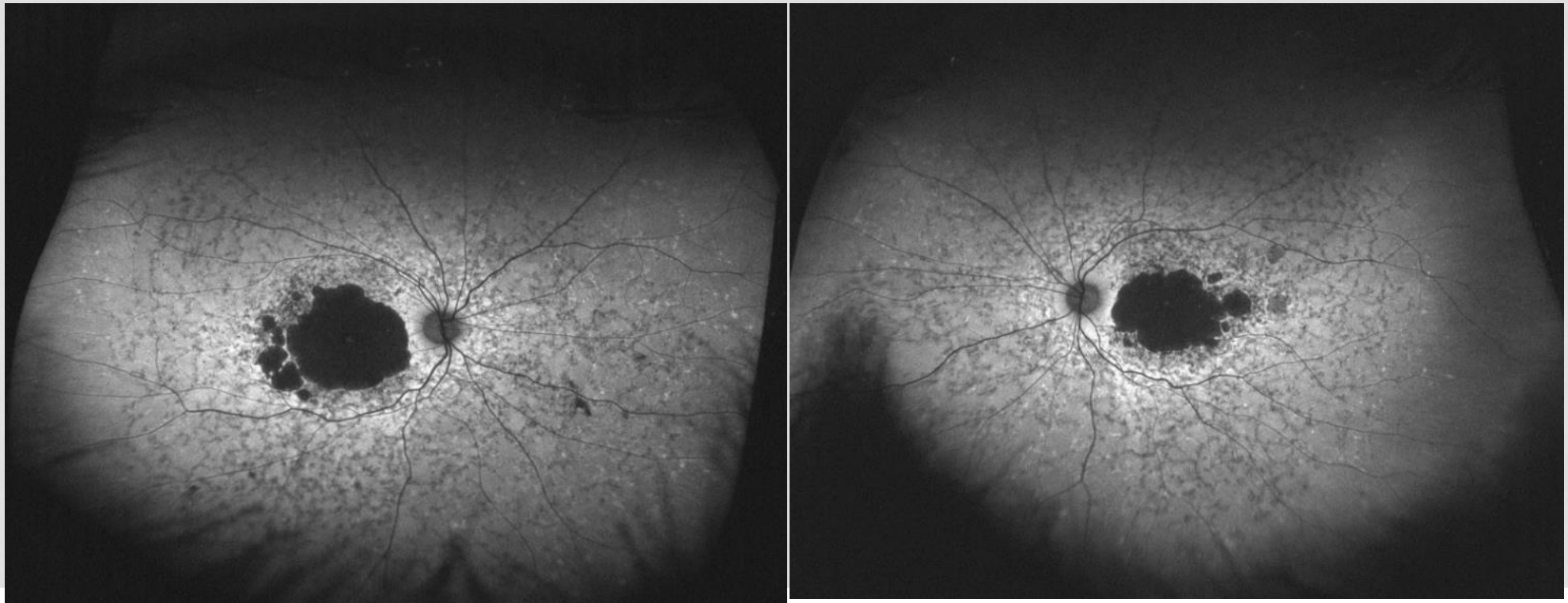
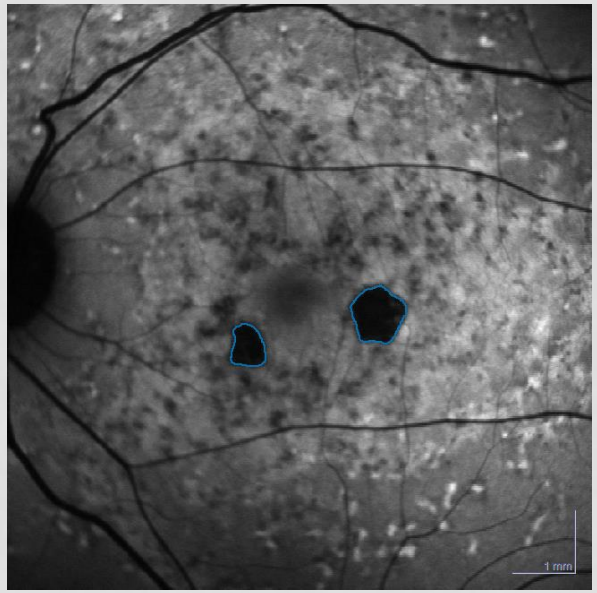
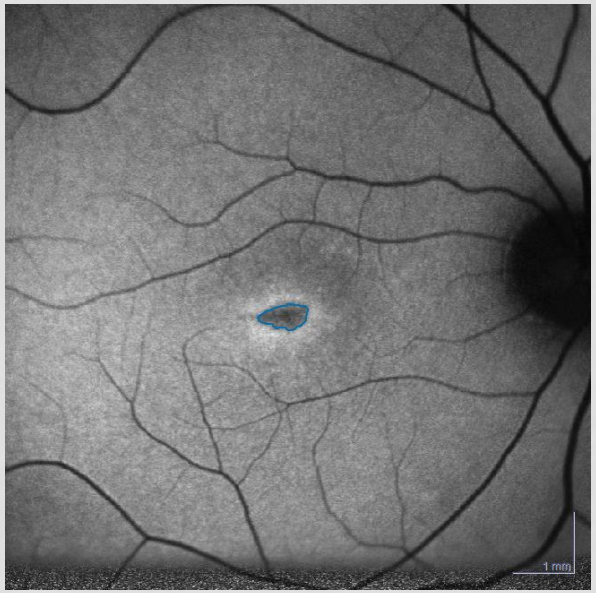


STARGARDT DISEASE

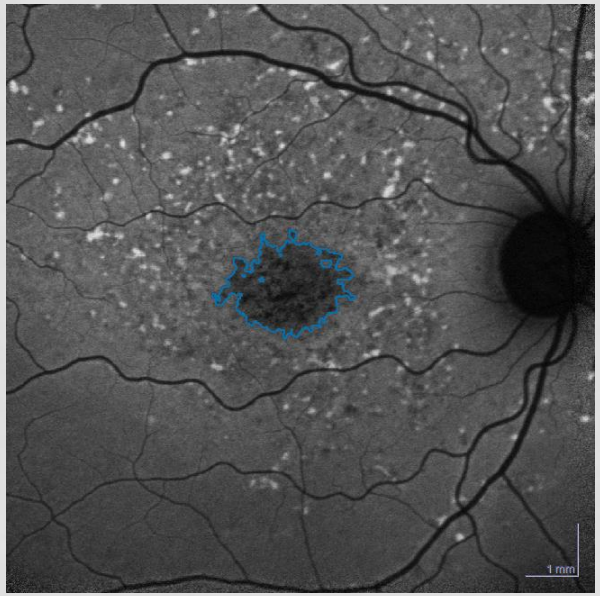
VARIABILITY OF PHENOTYPE



DDAF

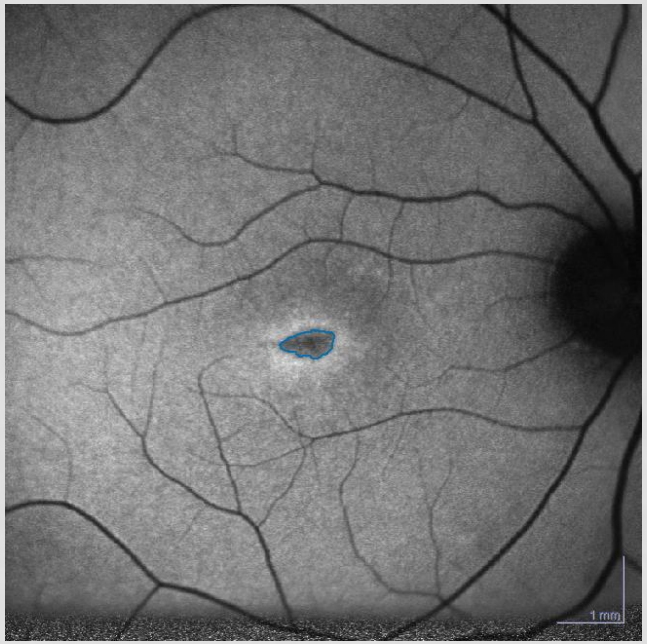


well-demarcated QDAF

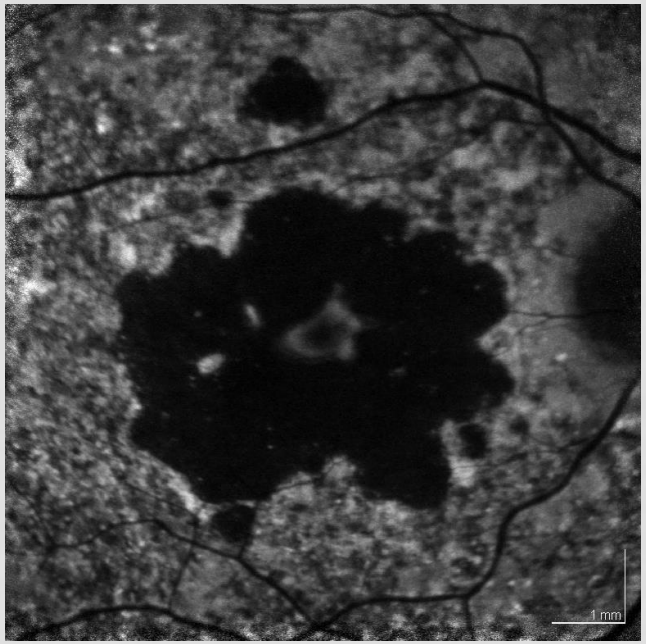


poorly-demarcated QDAF

STARGARDT DISEASE
VARIABILITY OF PHENOTYPE



Homogeneous background



Heterogeneous background

Stargardt Disease

DIAGNOSTIC TOOLS

- Genetic testing now widely available
- Can be obtained free of charge in most cases

- My preferred diagnostic approach: screen for ABCA4 mutations in patient's with the suspected phenotype

TREATMENT FOR STARGARDT DISEASE

- Unfortunately, there is none!
- So what do we do currently?
  - Photoprotection
    - Avoid bright light (esp. blue light) exposure → sunglasses

TREATMENT FOR STARGARDT DISEASE

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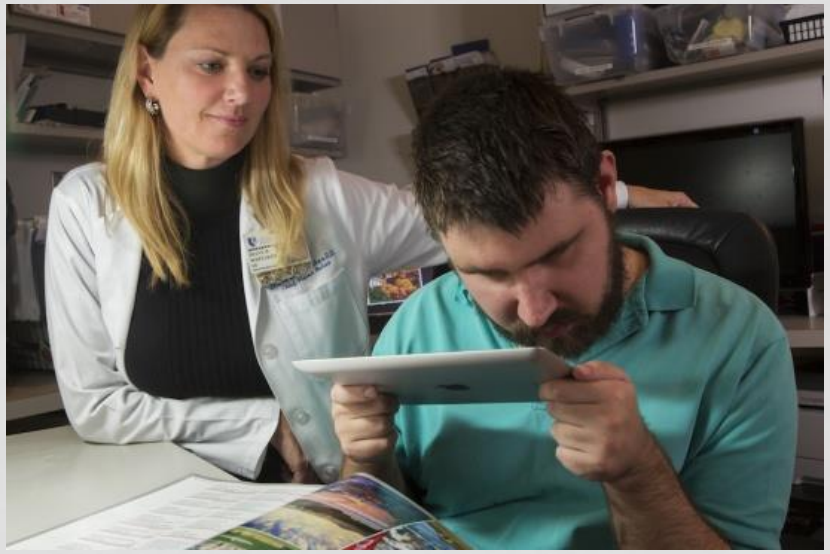
TREATMENT FOR STARGARDT DISEASE

- Unfortunately, there is none!
- So what do we do currently?
  - Photoprotection
    - Avoid bright light (esp. blue light) exposure → sunglasses
  - Avoid Vitamin A supplementation
  - Visual rehabilitation/Visual aids



VISUAL AIDS

UNMET NEED!

TREATMENT APPROACHES UNDER INVESTIGATION

1. Visual Cycle Modulation
   Slow down visual cycle and accumulation of toxic Vitamin A metabolites

2. Complement Inhibition/ Neuroprotection
   Inhibit immune response and mechanisms of cell-death

3. Gene therapy
   Large size of ABCA4 gene poses a challenge
   Lentiviral vectors or other novel delivery strategies

4. Stem Cells/Artificial Vision
   Primarily relevant for late stage after extensive photoreceptor loss

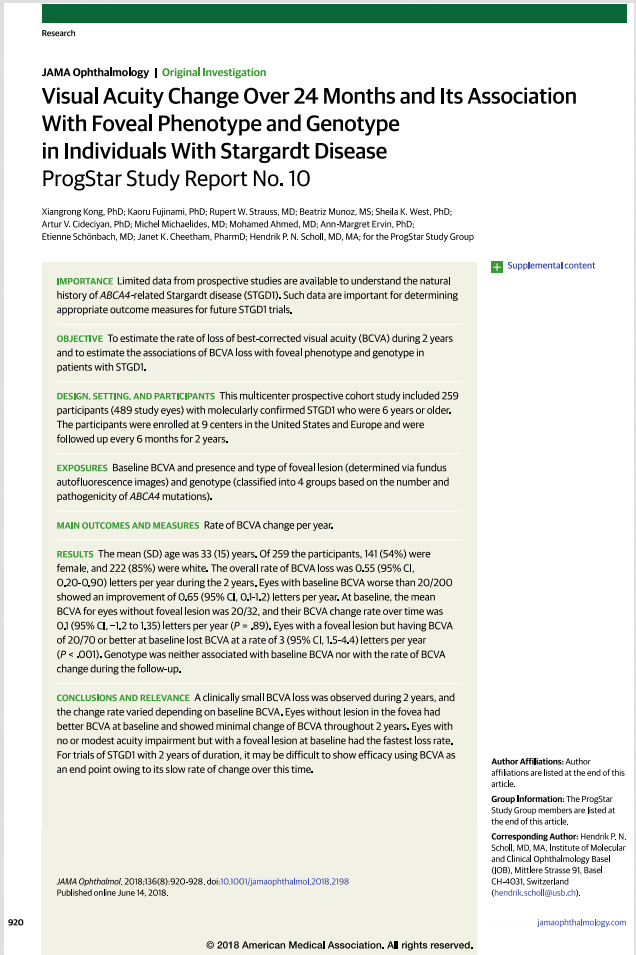
STAGE SET FOR THERAPEUTIC TRIALS

- ProgSTAR program (funded by Foundation Fighting Blindness) has defined natural history of the disease

STAGE SET FOR THERAPEUTIC TRIALS

- ProgSTAR program (funded by Foundation Fighting Blindness) has defined natural history of the disease with respect to:
  - Visual acuity

Characteristic	Mean BCVA Change Rate, logMAR/y, (95% CI)	Univariate Model: Difference in Change Rate Compared With Reference Group (95% CI)
Baseline BCVA		
No VI[c]	0.025 (−0.002 to 0.051)	1 [Reference]
Mild VI	0.038 (0.025 to 0.050)	0.013 (−0.017 to 0.042)
Moderate VI	0.012 (0.004 to 0.019)	−0.013 (−0.041 to 0.015)
SevereVI	−0.013 (−0.023 to −0.002)	−0.037 (−0.066 to 0.008)



Research

JAMA Ophthalmology | Original Investigation

Visual Acuity Change Over 24 Months and Its Association With Foveal Phenotype and Genotype in Individuals With Stargardt Disease

ProgStar Study Report No. 10

Xiangrong Kong, PhD; Kaoru Fujinami, PhD; Rupert W. Strauss, MD; Beatriz Munoz, MS; Sheila K. West, PhD; Artur V. Cideciyan, PhD; Michel Michaelides, MD; Mohamed Ahmed, MD; Ann-Margret Ervin, PhD; Etienne Schönbach, MD; Janet K. Cheetham, PharmD; Hendrik P. N. Scholl, MD, MA; for the ProgStar Study Group

Supplemental content

IMPORTANCE Limited data from prospective studies are available to understand the natural history of *ABCA4*-related Stargardt disease (STGD1). Such data are important for determining appropriate outcome measures for future STGD1 trials.

OBJECTIVE To estimate the rate of loss of best-corrected visual acuity (BCVA) during 2 years and to estimate the associations of BCVA loss with foveal phenotype and genotype in patients with STGD1.

DESIGN, SETTING, AND PARTICIPANTS This multicenter prospective cohort study included 259 participants (489 study eyes) with molecularly confirmed STGD1 who were 6 years or older. The participants were enrolled at 9 centers in the United States and Europe and were followed up every 6 months for 2 years.

EXPOSURES Baseline BCVA and presence and type of foveal lesion (determined via fundus autofluorescence images) and genotype (classified into 4 groups based on the number and pathogenicity of *ABCA4* mutations).

MAIN OUTCOMES AND MEASURES Rate of BCVA change per year.

RESULTS The mean (SD) age was 33 (15) years. Of 259 the participants, 141 (54%) were female, and 222 (85%) were white. The overall rate of BCVA loss was 0.55 (95% CI, 0.20-0.90) letters per year during the 2 years. Eyes with baseline BCVA worse than 20/200 showed an improvement of 0.65 (95% CI, 0.1-1.2) letters per year. At baseline, the mean BCVA for eyes without foveal lesion was 20/32, and their BCVA change rate over time was 0.1 (95% CI, −1.2 to 1.35) letters per year ($P = .89$). Eyes with a foveal lesion but having BCVA of 20/70 or better at baseline lost BCVA at a rate of 3 (95% CI, 1.5-4.4) letters per year ($P < .001$). Genotype was neither associated with baseline BCVA nor with the rate of BCVA change during the follow-up.

CONCLUSIONS AND RELEVANCE A clinically small BCVA loss was observed during 2 years, and the change rate varied depending on baseline BCVA. Eyes without lesion in the fovea had better BCVA at baseline and showed minimal change of BCVA throughout 2 years. Eyes with no or modest acuity impairment but with a foveal lesion at baseline had the fastest loss rate. For trials of STGD1 with 2 years of duration, it may be difficult to show efficacy using BCVA as an end point owing to its slow rate of change over this time.

JAMA Ophthalmol. 2018;136(8):920-928. doi:10.1001/jamaophthalmol.2018.2198
Published online June 14, 2018.

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The ProgStar Study Group members are listed at the end of this article.

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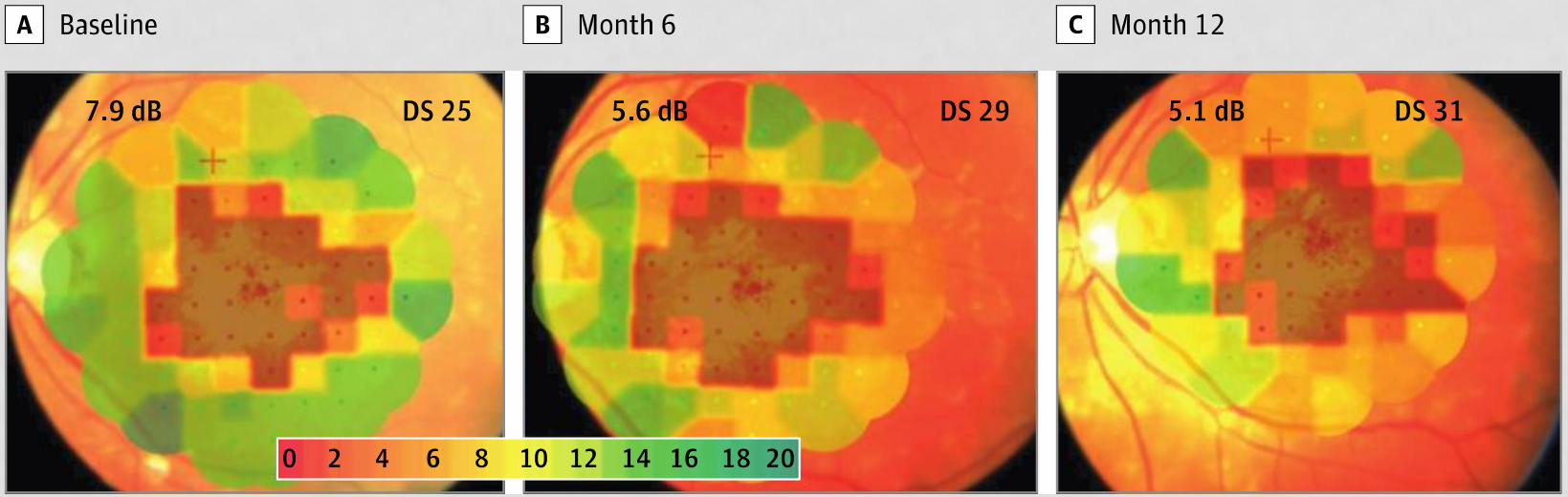
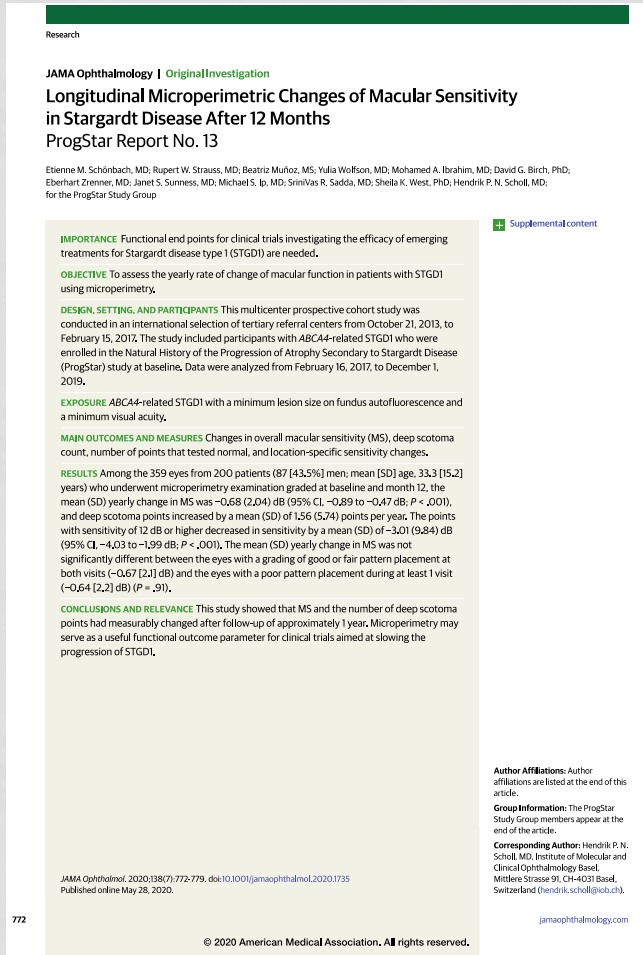
STAGE SET FOR THERAPEUTIC TRIALS

- ProgSTAR program (funded by Foundation Fighting Blindness) has defined natural history of the disease with respect to:
  - Visual acuity
  - Microperimetric (visual field) sensitivity





Research

JAMA Ophthalmology | Original Investigation

Longitudinal Microperimetric Changes of Macular Sensitivity in Stargardt Disease After 12 Months
ProgStar Report No. 13

Etienne M. Schönbach, MD; Rupert W. Strauss, MD; Beatriz Muñoz, MS; Yulia Wolfson, MD; Mohamed A. Ibrahim, MD; David G. Birch, PhD; Eberhart Zrenner, MD; Janet S. Sunness, MD; Michael S. Ip, MD; SriniVas R. Sadda, MD; Sheila K. West, PhD; Hendrik P. N. Scholl, MD; for the ProgStar Study Group

Supplemental content

IMPORTANCE Functional end points for clinical trials investigating the efficacy of emerging treatments for Stargardt disease type 1 (STGD1) are needed.

OBJECTIVE To assess the yearly rate of change of macular function in patients with STGD1 using microperimetry.

DESIGN, SETTING, AND PARTICIPANTS This multicenter prospective cohort study was conducted in an international selection of tertiary referral centers from October 21, 2013, to February 15, 2017. The study included participants with *ABCA4*-related STGD1 who were enrolled in the Natural History of the Progression of Atrophy Secondary to Stargardt Disease (ProgStar) study at baseline. Data were analyzed from February 16, 2017, to December 1, 2019.

EXPOSURE *ABCA4*-related STGD1 with a minimum lesion size on fundus autofluorescence and a minimum visual acuity.

MAIN OUTCOMES AND MEASURES Changes in overall macular sensitivity (MS), deep scotoma count, number of points that tested normal, and location-specific sensitivity changes.

RESULTS Among the 359 eyes from 200 patients (87 [43.5%] men; mean [SD] age, 33.3 [15.2] years) who underwent microperimetry examination graded at baseline and month 12, the mean (SD) yearly change in MS was −0.68 (2.04) dB (95% CI, −0.89 to −0.47 dB; $P < .001$), and deep scotoma points increased by a mean (SD) of 1.56 (5.74) points per year. The points with sensitivity of 12 dB or higher decreased in sensitivity by a mean (SD) of −3.01 (9.84) dB (95% CI, −4.03 to −1.99 dB; $P < .001$). The mean (SD) yearly change in MS was not significantly different between the eyes with a grading of good or fair pattern placement at both visits (−0.67 [2.1] dB) and the eyes with a poor pattern placement during at least 1 visit (−0.64 [2.2] dB) ($P = .91$).

CONCLUSIONS AND RELEVANCE This study showed that MS and the number of deep scotoma points had measurably changed after follow-up of approximately 1 year. Microperimetry may serve as a useful functional outcome parameter for clinical trials aimed at slowing the progression of STGD1.

JAMA Ophthalmol. 2020;138(7):772-779. doi:10.1001/jamaophthalmol.2020.1735
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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The ProgStar Study Group members appear at the end of the article.

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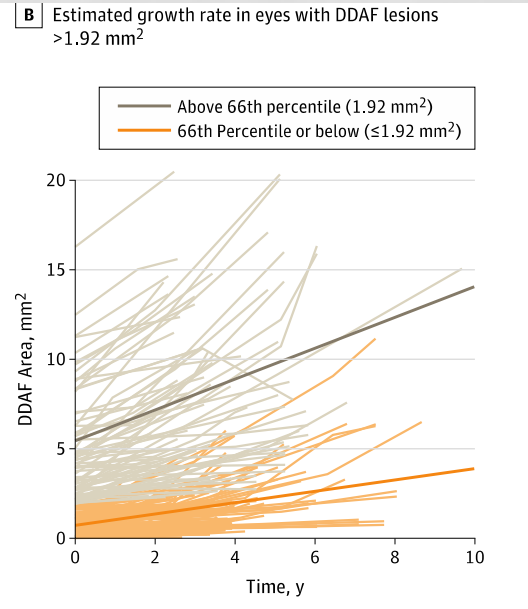
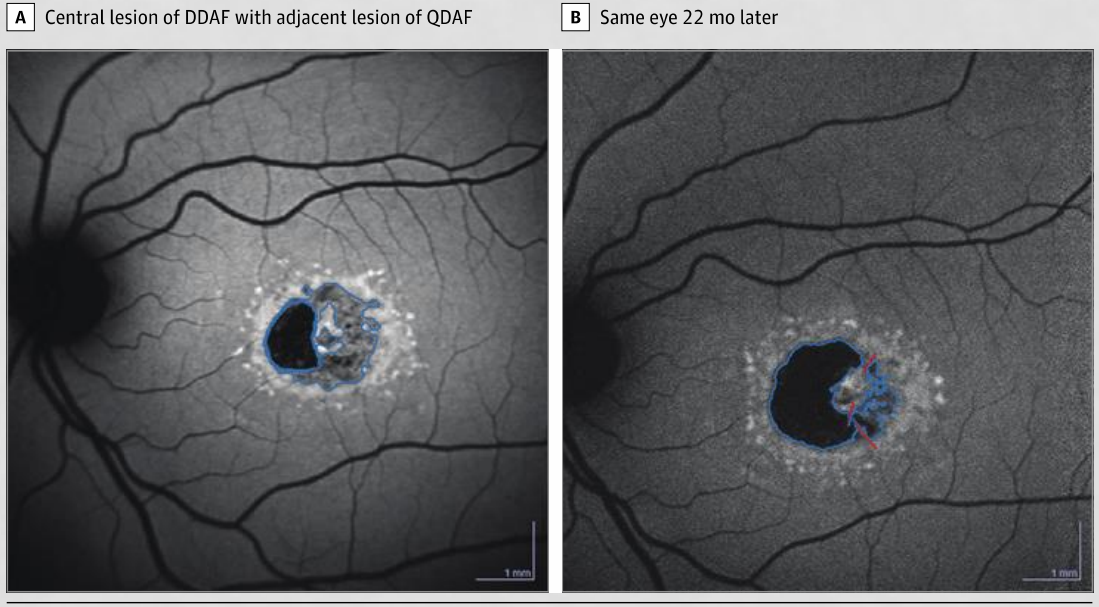
STAGE SET FOR THERAPEUTIC TRIALS

- ProgSTAR program (funded by Foundation Fighting Blindness) has defined natural history of the disease with respect to:
  - Visual acuity
  - Microperimetric (visual field) sensitivity
  - Loss of RPE/autofluorescence on FAF imaging





Research

JAMA Ophthalmology | Original Investigation

Progression of Stargardt Disease as Determined by Fundus Autofluorescence in the Retrospective Progression of Stargardt Disease Study (ProgStar Report No. 9)

Rupert W. Strauss, MD; Beatriz Muñoz, MS; Alexander Ho, BSE; Anamika Jha, MBS; Michel Michaelides, MD; Artur V. Cideciyan, PhD; Isabelle Audo, MD; David G. Birch, PhD; Amir H. Hariri, MD; Muneeswar G. Nittala, PhM Opt; SriniVas Sadda, MD; Sheila West, PhD; Hendrik P. N. Scholl, MD, MA; for the ProgStar Study Group

IMPORTANCE Sensitive outcome measures for disease progression are needed for treatment trials of Stargardt disease.

OBJECTIVE To describe the yearly progression rate of atrophic lesions in the retrospective Progression of Stargardt Disease study.

DESIGN, SETTING, AND PARTICIPANTS A multicenter retrospective cohort study was conducted at tertiary referral centers in the United States and Europe. A total of 251 patients aged 6 years or older at baseline, harboring disease-causing variants in *ABCA4* (OMIM 601691), enrolled in the study from 9 centers between August 2, 2013, and December 12, 2014; of these patients, 215 had at least 2 gradable fundus autofluorescence images with atrophic lesion(s) present in at least 1 eye.

EXPOSURES Areas of definitely decreased autofluorescence (DDAF) and questionably decreased autofluorescence were quantified by a reading center. Progression rates were estimated from linear mixed models with time as the independent variable.

MAIN OUTCOMES AND MEASURES Yearly rate of progression using the growth of atrophic lesions measured by fundus autofluorescence.

RESULTS A total of 251 participants (458 study eyes) were enrolled. Images from 386 eyes of 215 participants (126 females and 89 males; mean [SD] age, 29,9 [14,7] years; mean [SD] age of onset of symptoms, 21,9 [13,3] years) showed atrophic lesions present on at least 2 visits and were graded for 2 (156 eyes), 3 (174 eyes), or 4 (57 eyes) visits. A subset of 224 eyes (123 female participants and 101 male participants; mean [SD] age, 33,0 [15,1] years) had areas of DDAF present on at least 2 visits; these eyes were included in the estimation of the progression of the area of DDAF. At the first visit, DDAF was present in 224 eyes (58,0%), with a mean (SD) lesion size of 2,2 (2,7) mm^2. The total mean (SD) area of decreased autofluorescence (DDAF and questionably decreased autofluorescence) at first visit was 2,6 (2,8) mm^2. Mean progression of DDAF was 0,51 mm^2/y (95% CI, 0,42-0,61 mm^2/y), and of total decreased fundus autofluorescence was 0,35 mm^2/y (95% CI, 0,28-0,43 mm^2/y). Rates of progression depended on the initial size of the lesion.

CONCLUSIONS AND RELEVANCE In Stargardt disease with DDAF lesions, fundus autofluorescence may serve as a monitoring tool for interventional clinical trials that aim to slow disease progression. Rates of progression depended mainly on initial lesion size.

Supplemental content

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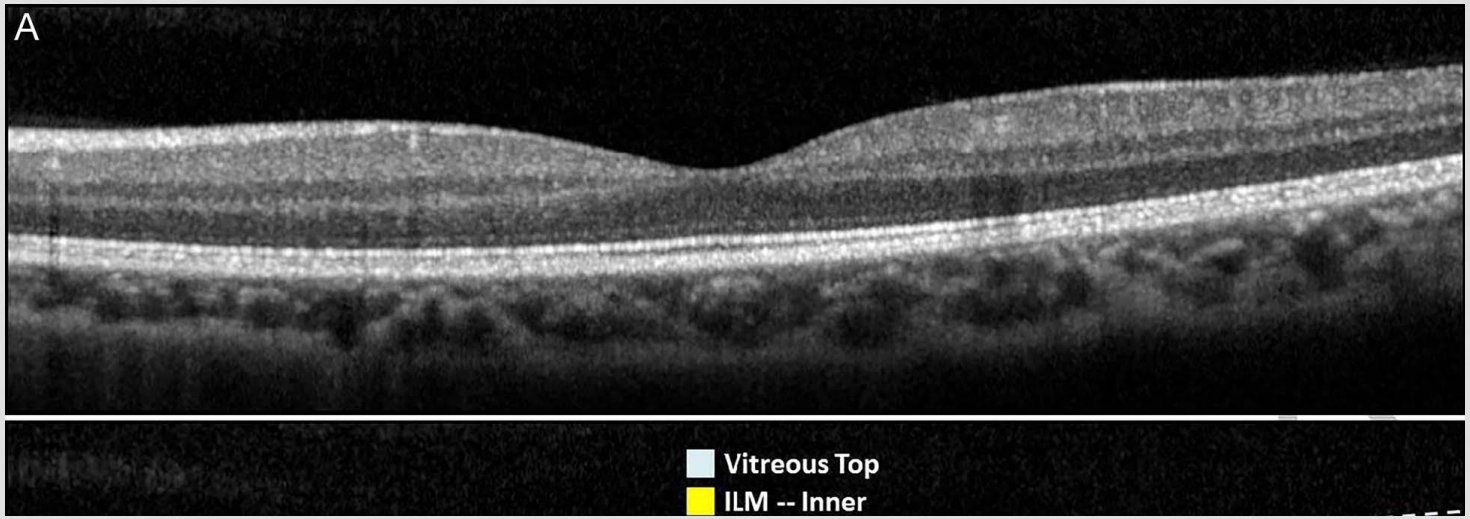
JAMA Ophthalmol. 2017;135(11):1232-1241. doi:10.1001/jamaophthalmol.2017.4152
Published online October 12, 2017.

STAGE SET FOR THERAPEUTIC TRIALS

- ProgSTAR program (funded by Foundation Fighting Blindness) has defined natural history of the disease with respect to:
  - Visual acuity
  - Microperimetric (visual field) sensitivity
  - Loss of RPE/autofluorescence on FAF imaging
  - Loss of photoreceptors on OCT imaging



tvst
https://doi.org/10.1167/tvst.8.3.46
Article

Reproducibility of Measurements of Retinal Structural Parameters Using Optical Coherence Tomography in Stargardt Disease

Xiangrong Kong[1,2], Alexander Ho[3], Beatriz Munoz[1], Sheila West[1], Rupert W. Strauss[1,4,5,6], Anamika Jha[3], Ann Ervin[1,2], Jeff Buzas[7], Mandeep Singh[1], Zhihong Hu[3], Janet Cheetham[8], Michael Ip[3], and Hendrik P. N. Scholl[1,9,10]

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Keywords: reliability; inherited retinal degeneration; structure parameters; outcome measures; repeatability

Citation: Kong X, Ho A, Munoz B, West S, Strauss RW, Jha A, Ervin A, Buzas J, Singh M, Hu Z, Cheetham J, Ip M, Scholl HPN. Reproducibility of measurements of retinal structural parameters using optical coherence tomography in Stargardt disease. Trans Vis Sci Tech. 2019;8(3):46, https://doi.org/10.1167/tvst.8.3.46

Purpose: To assess the reproducibility of retinal measurements from optical coherence tomography (OCT) in *ABCA4*-related Stargardt disease (STGD1).

Methods: The international multicenter Progression of Atrophy Secondary to Stargardt Disease (ProgStar) Study enrolled 259 STGD1 patients. OCT images were graded by the study reading center (RC). Semiautomatic segmentation with manual adjustments was used to segment the layers of retinal pigmentation epithelium, outer segments, inner segments (ISs), outer nuclear layer (ONL), inner retina, and the total retina (TR). The images were overlaid to the Early Treatment Diabetic Retinopathy Study (ETDRS) grid. For each layer, the thickness and the intact area of the ETDRS central subfield, inner ring, and outer ring were recorded, respectively. A different set of RC graders regraded 30 independent ProgStar images to evaluate measurement reproducibility. Reproducibility was assessed graphically and using statistics including intraclass correlation (ICC) and relative absolute difference (RAD).

Results: Across all layers, measurements of the ETDRS central subfield had low ICC and/or large RAD. The outer-ring region was not fully captured in some images. For inner ring, good reproducibility was observed for intact area in the IS (ICC = 0.99, RAD = 4%), thicknesses of the ONL (ICC = 0.93, RAD = 6%), and TR (ICC = 0.99, RAD = 1%).

Conclusions: STGD1's complex morphology made outer retina segmentation challenging. Measurements of the inner ring, including the intact area of IS (i.e., the ellipsoid zone [EZ]) and ONL and TR thicknesses, had good reproducibility and showed anatomical impairment.

Translational Relevance: ONL and TR thicknesses and the EZ intact area in the ETDRS inner ring hold potential as structural endpoints for STGD1 trials. Structure-function relationships need to be further established.

translational vision science & technology

STAGE SET FOR THERAPEUTIC TRIALS

- Understanding the rate and variability of progression has facilitated the design of adequately powered clinical trials of novel therapeutics
- Endpoints acceptable for regulatory agencies

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DOI: 10.1167/tvst.6.5.6

Review

Towards Treatment of Stargardt Disease: Workshop Organized and Sponsored by the Foundation Fighting Blindness

Avery E. Sears[1], Paul S. Bernstein[2], Artur V. Cideciyan[3], Carel Hoyng[4], Peter Charbel Issa[5], Krzysztof Palczewski[1], Philip J. Rosenfeld[6], SriniVas Sadda[7], Ulrich Schraermeyer[8], Janet R. Sparrow[9], Ilyas Washington[9], and Hendrik P.N. Scholl[10,11]

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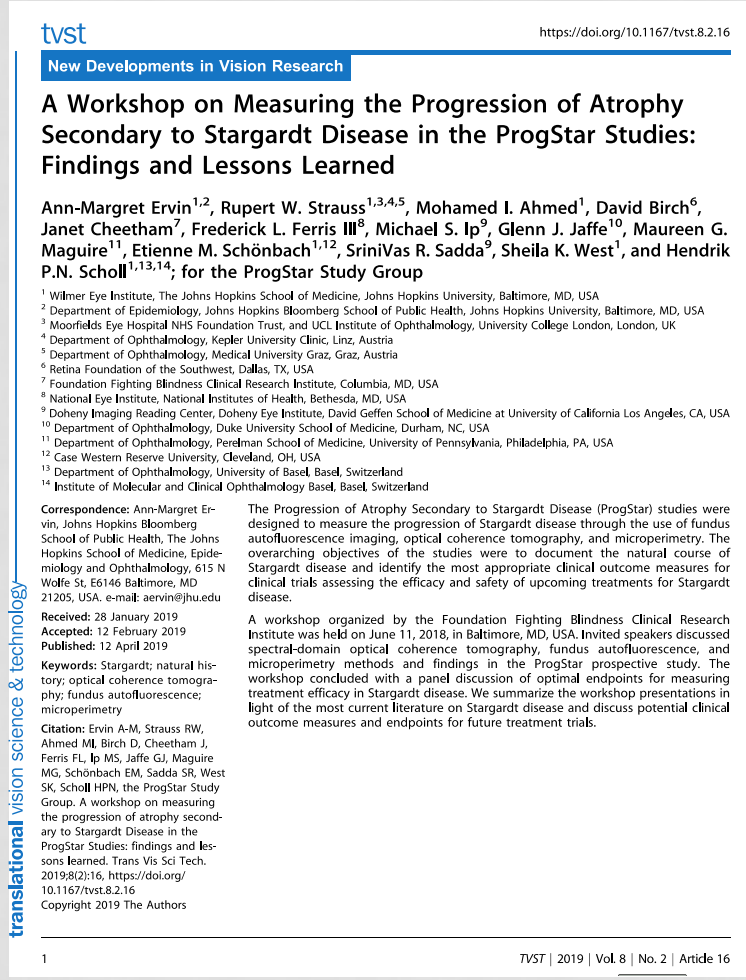
Accepted: 11 July 2017
Published: 14 September 2017

Keywords: Stargardt disease; geographic atrophy; age-related macular degeneration; ABCA4; lipofuscin; A2E, all-*trans*-retinal

Citation: Sears AE, Bernstein PS, Cideciyan AV, Hoyng C, Charbel Issa P, Palczewski K, Rosenfeld PJ, Sadda S, Schraermeyer U, Sparrow JR, Washington I, Scholl HPN. Towards treatment of Stargardt disease: workshop organized and sponsored by the Foundation Fighting Blindness. Trans Vis Sci Tech. 2017;6(5):6, doi:10.1167/tvst.6.5.6

Accumulation of fluorescent metabolic byproducts of the visual (retinoid) cycle is associated with photoreceptor and retinal pigment epithelial cell death in both Stargardt disease and atrophic (nonneovascular) age-related macular degeneration (AMD). As a consequence of this observation, small molecular inhibitors of enzymes in the visual cycle were recently tested in clinical trials as a strategy to protect the retina and retinal pigment epithelium in patients with atrophic AMD.

To address the clinical translational needs for therapies aimed at both diseases, a workshop organized by the Foundation Fighting Blindness was hosted by the Department of Pharmacology at Case Western Reserve University on February 17, 2017, at the Tinkham Veale University Center, Cleveland, OH, USA. Invited speakers highlighted recent advances in the understanding of the pathophysiology of Stargardt disease, in terms of its clinical characterization and the development of endpoints for clinical trials, and discussed the comparability of therapeutic strategies between atrophic age-related macular degeneration (AMD) and Stargardt disease. Investigators speculated that reducing the concentrations of visual cycle precursor substances and/or their byproducts may provide valid therapeutic options for the treatment of Stargardt disease. Here we review the workshop's presentations in the context of published literature to help shape the aims of ongoing research endeavors and aid the development of therapies for Stargardt disease.



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https://doi.org/10.1167/tvst.8.2.16

New Developments in Vision Research

A Workshop on Measuring the Progression of Atrophy Secondary to Stargardt Disease in the ProgStar Studies: Findings and Lessons Learned

Ann-Margret Ervin[1,2], Rupert W. Strauss[1,3,4,5], Mohamed I. Ahmed[1], David Birch[6], Janet Cheetham[7], Frederick L. Ferris III[8], Michael S. Ip[9], Glenn J. Jaffe[10], Maureen G. Maguire[11], Etienne M. Schönbach[1,12], SriniVas R. Sadda[9], Sheila K. West[1], and Hendrik P.N. Scholl[1,13,14]; for the ProgStar Study Group

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Published: 12 April 2019

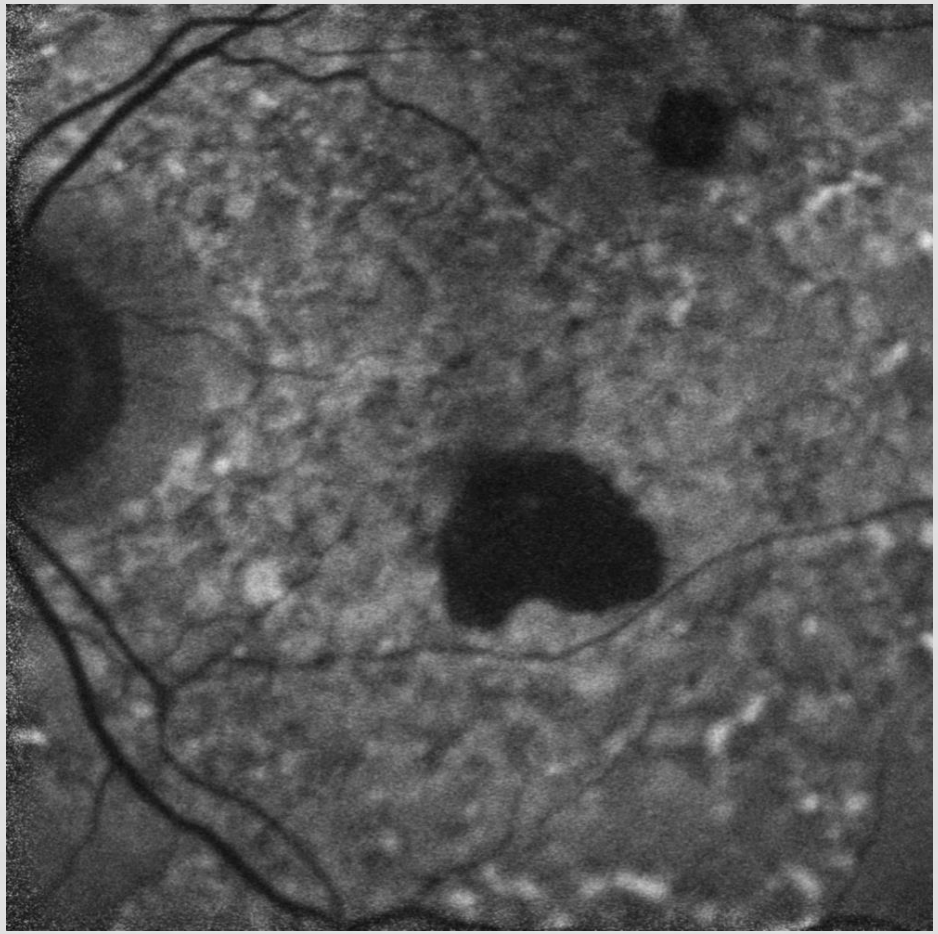
Keywords: Stargardt; natural history; optical coherence tomography; fundus autofluorescence; microperimetry

Citation: Ervin A-M, Strauss RW, Ahmed MI, Birch D, Cheetham J, Ferris FL, Ip MS, Jaffe GJ, Maguire MG, Schönbach EM, Sadda SR, West SK, Scholl HPN, the ProgStar Study Group. A workshop on measuring the progression of atrophy secondary to Stargardt Disease in the ProgStar Studies: findings and lessons learned. Trans Vis Sci Tech. 2019;8(2):16, https://doi.org/10.1167/tvst.8.2.16

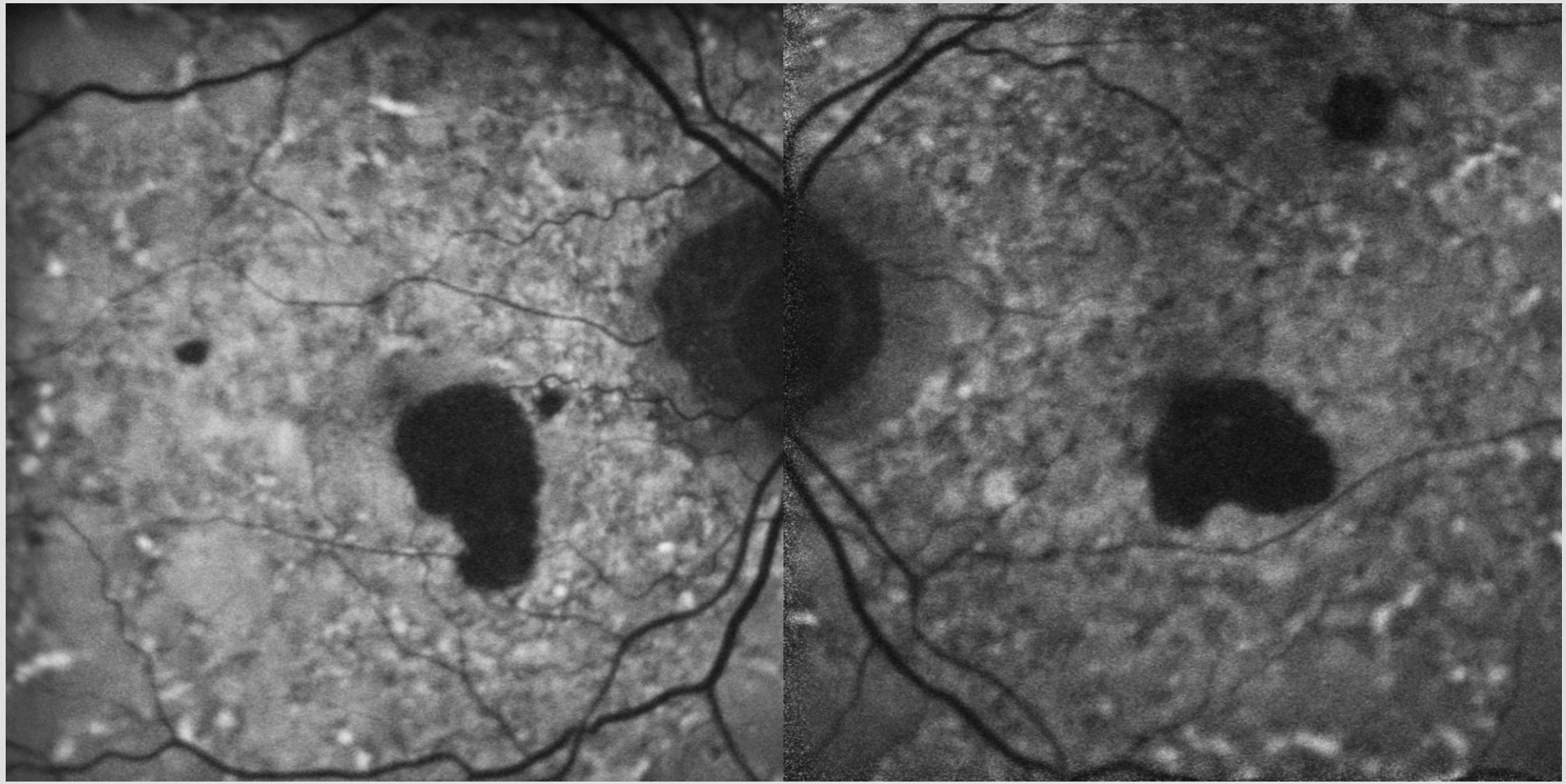
The Progression of Atrophy Secondary to Stargardt Disease (ProgStar) studies were designed to measure the progression of Stargardt disease through the use of fundus autofluorescence imaging, optical coherence tomography, and microperimetry. The overarching objectives of the studies were to document the natural course of Stargardt disease and identify the most appropriate clinical outcome measures for clinical trials assessing the efficacy and safety of upcoming treatments for Stargardt disease.

A workshop organized by the Foundation Fighting Blindness Clinical Research Institute was held on June 11, 2018, in Baltimore, MD, USA. Invited speakers discussed spectral-domain optical coherence tomography, fundus autofluorescence, and microperimetry methods and findings in the ProgStar prospective study. The workshop concluded with a panel discussion of optimal endpoints for measuring treatment efficacy in Stargardt disease. We summarize the workshop presentations in light of the most current literature on Stargardt disease and discuss potential clinical outcome measures and endpoints for future treatment trials.

PROGRESSION OF ATROPHY IN STARGARDT AS SEEN ON FAF IMAGING

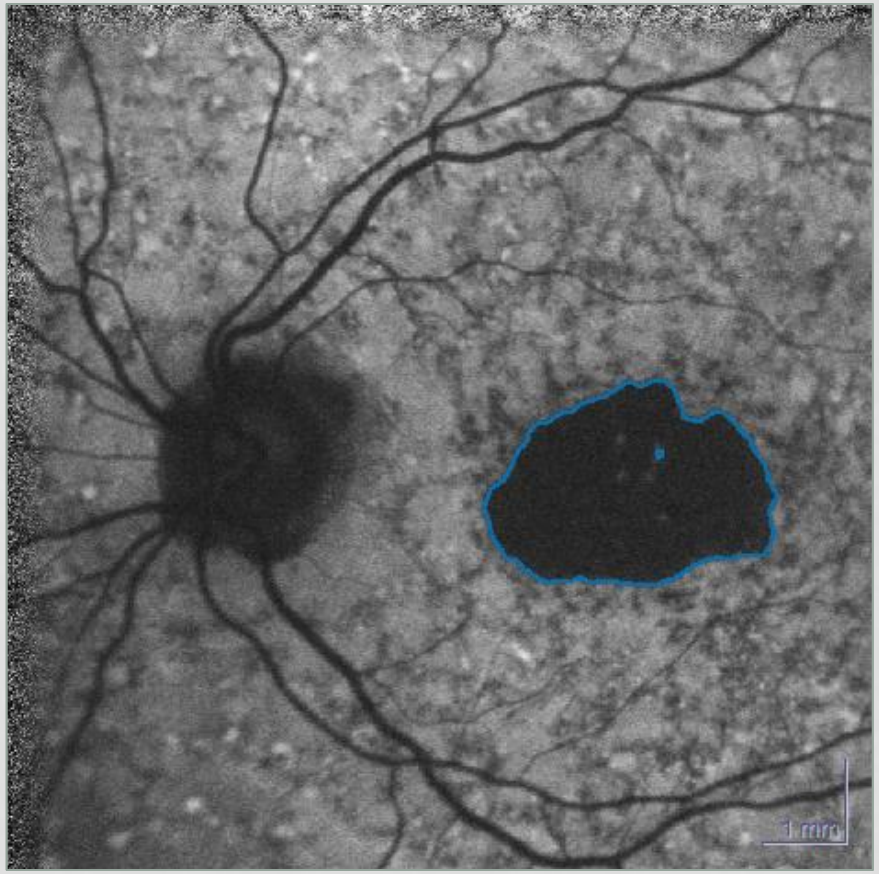


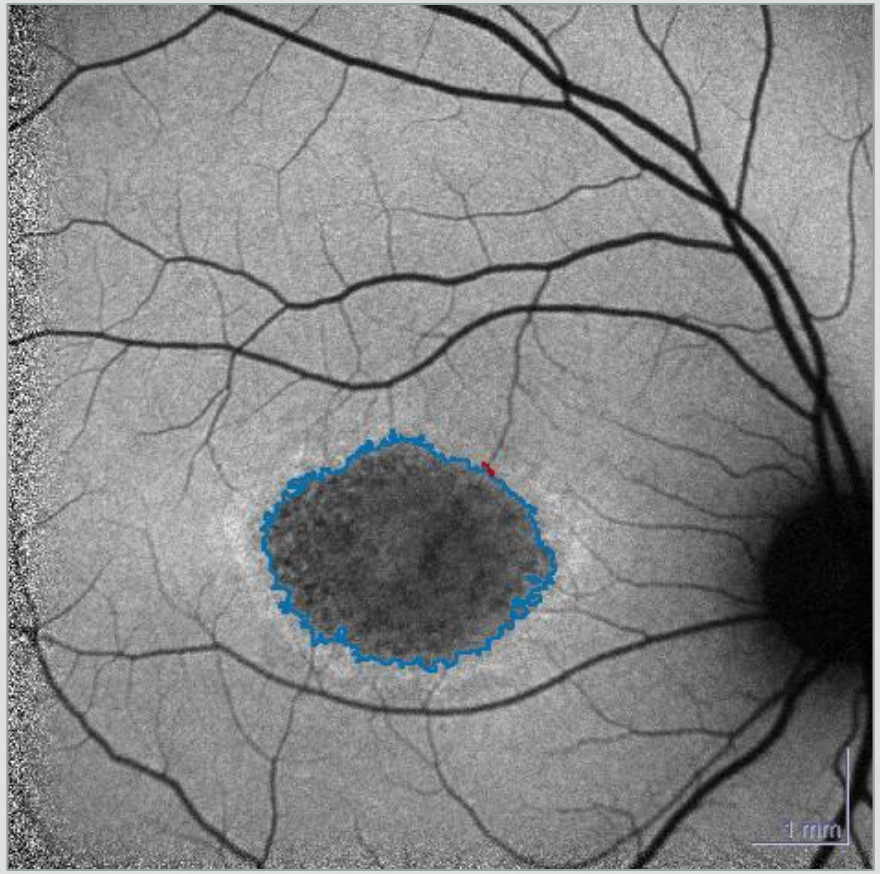
PROGRESSION OF ATROPHY IN STARGARDT AS SEEN ON FAF IMAGING



QUANTIFYING ATROPHY IN STARGARDT BY EXPERT HUMAN GRADERS

Shown to be reliable





COMPARISON OF MANUAL AND SEMIAUTOMATED FUNDUS AUTOFLUORESCENCE ANALYSIS OF MACULAR ATROPHY IN STARGARDT DISEASE PHENOTYPE

LAURA KUEHLEWEIN, MD,*† AMIR H. HARIRI, MD,*† ALEXANDER HO, BS,* LAURIE DUSTIN, MS,‡ YULIA WOLFSON, MD,§ RUPERT W. STRAUSS, MD,§¶ HENDRIK P. N. SCHOLL, MD, MA,§ SRINIVAS R. SADDA, MD*†

Purpose: To evaluate manual and semiautomated grading techniques for assessing decreased fundus autofluorescence (DAF) in patients with Stargardt disease phenotype.

Methods: Certified reading center graders performed manual and semiautomated (region finder—based) grading of confocal scanning laser ophthalmoscopy (cSLO) fundus autofluorescence (FAF) images for 41 eyes of 22 patients. Lesion types were defined based on the black level and sharpness of the border: definite decreased autofluorescence (DDAF), well, and poorly demarcated questionably decreased autofluorescence (WDQDAF, PDQDAF). Agreement in grading between the two methods and inter- and intra-grader agreement was assessed by kappa coefficients (κ) and intraclass correlation coefficients (ICC).

Results: The mean ± standard deviation (SD) area was 3.07 ± 3.02 mm^2 for DDAF (n = 31), 1.53 ± 1.52 mm^2 for WDQDAF (n = 9), and 6.94 ± 10.06 mm^2 for PDQDAF (n = 17). The mean ± SD absolute difference in area between manual and semiautomated grading was 0.26 ± 0.28 mm^2 for DDAF, 0.20 ± 0.26 mm^2 for WDQDAF, and 4.05 ± 8.32 mm^2 for PDQDAF. The ICC (95% confidence interval) for method comparison was 0.992 (0.984–0.996) for DDAF, 0.976 (0.922–0.993) for WDQDAF, and 0.648 (0.306–0.842) for PDQDAF. Inter- and intra-grader agreement in manual and semiautomated quantitative grading was better for DDAF (0.981–0.996) and WDQDAF (0.995–0.999) than for PDQDAF (0.715–0.993).

Conclusion: Manual and semiautomated grading methods showed similar levels of reproducibility for assessing areas of decreased autofluorescence in patients with Stargardt disease phenotype. Excellent agreement and reproducibility were observed for well demarcated lesions.

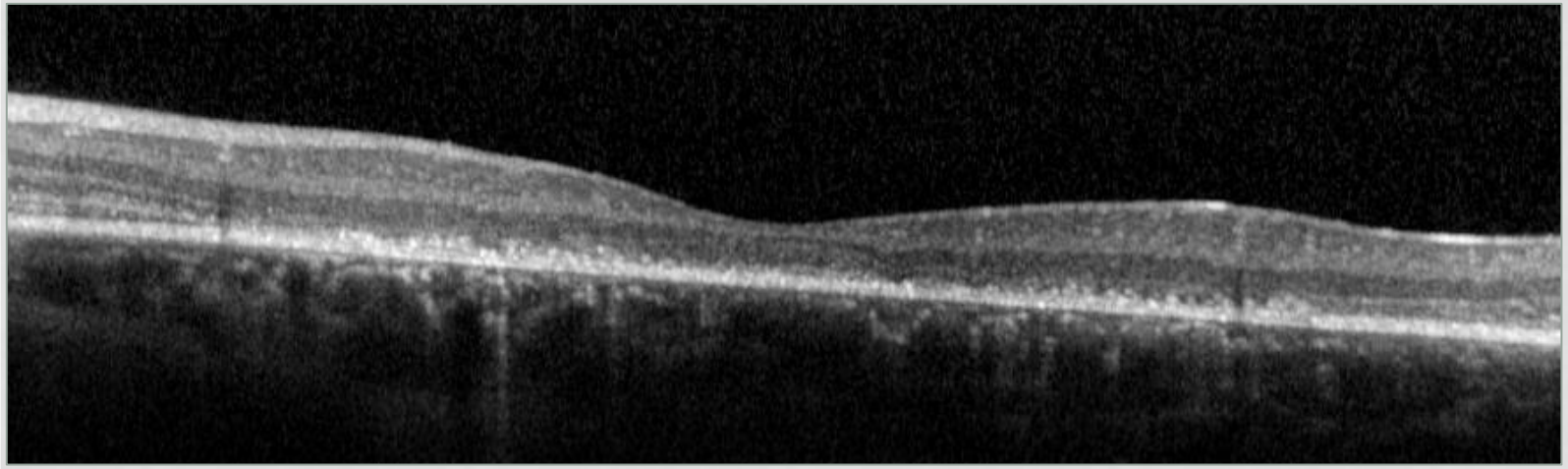
RETINA 36:1216–1221, 2016

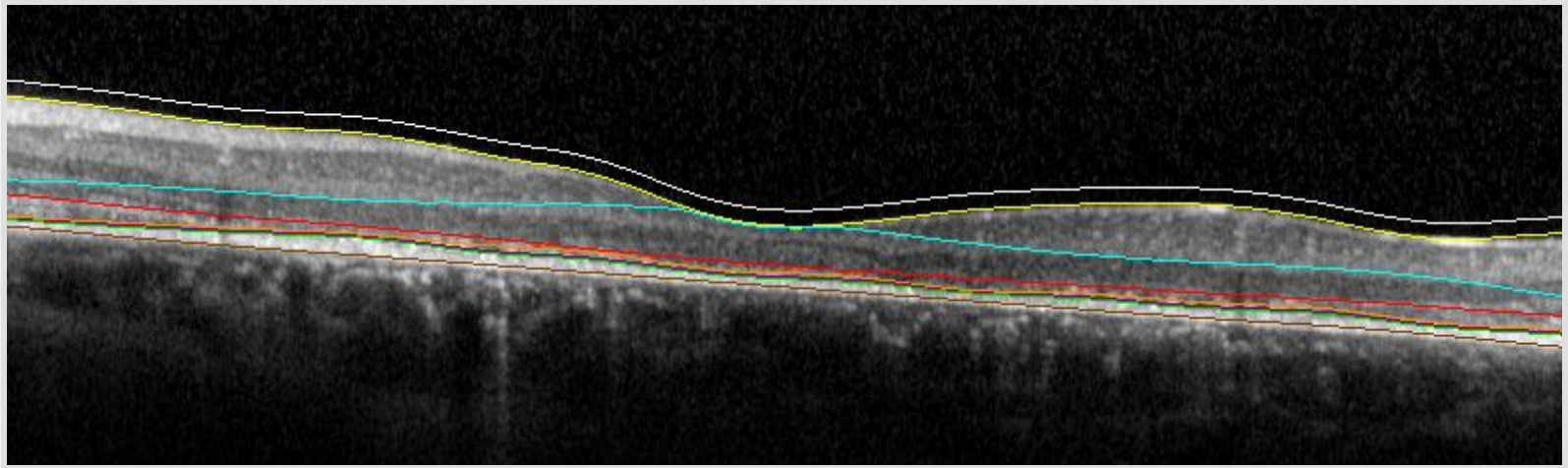
Stargardt disease, the most common form of inherited juvenile macular degeneration, is most commonly caused by a defect in the ABCA4-gene.[1,2] Patients with Stargardt disease usually present between the ages of 10 and 20 with a slowly progressing loss of central vision.[3] Ophthalmoscopy in these individuals typically reveals flecks and atrophy of the retinal pigment epithelium (RPE), but these findings can be subtle in some patients.[4] Identification and quantification of atrophic areas, however, are critical in diagnosing, monitoring and counseling patients with Stargardt disease.

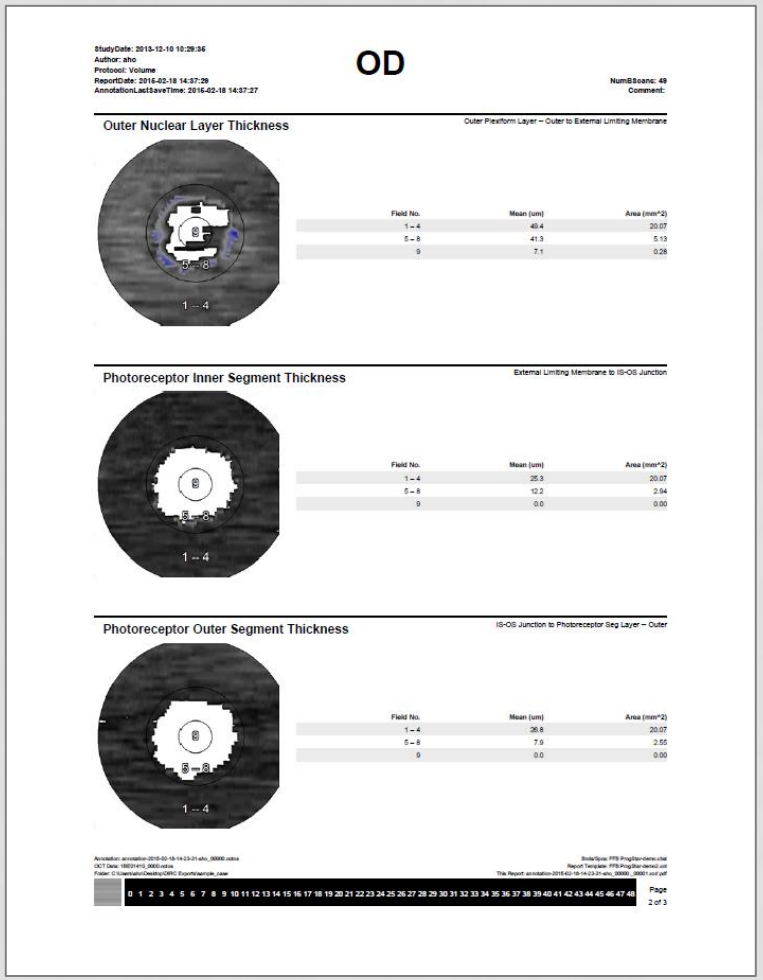
Development and evaluation of potential treatments for Stargardt disease require a careful understanding of the rate of progression of the disease, and its variability.[5,6] The ProgSTAR study (ClinicalTrials.gov Identifier: NCT01977846; http://progstar.org/), a large multicenter, longitudinal natural history cohort study was designed to better define this progression rate, as well as to better understand the correlation between phenotype, genotype, and functional parameters.

The accumulation of lipofuscin in the RPE is a key early feature of Stargardt disease, with eventual

QUANTIFYING ATROPHY IN STARGARDT BY EXPERT HUMAN GRADERS







StudyDate: 2013-12-10 10:29:36
Author: aho
Protocol: Volume
ReportDate: 2016-02-18 14:37:29
AnnotationLastSaveTime: 2016-02-18 14:37:27

OD

NumBScans: 49
Comment:

Outer Nuclear Layer Thickness

Outer Plexiform Layer – Outer to External Limiting Membrane

Field No.	Mean (um)	Area (mm^2)
1 – 4	49.4	20.07
5 – 8	41.3	5.13
9	7.1	0.28

Photoreceptor Inner Segment Thickness

External Limiting Membrane to IS-OS Junction

Field No.	Mean (um)	Area (mm^2)
1 – 4	25.3	20.07
5 – 8	12.2	2.94
9	0.0	0.00

Photoreceptor Outer Segment Thickness

IS-OS Junction to Photoreceptor Seg Layer – Outer

Field No.	Mean (um)	Area (mm^2)
1 – 4	26.8	20.07
5 – 8	7.9	2.55
9	0.0	0.00

Page 2 of 3

SUMMARY

- Stargardt disease is the most common inherited macular dystrophy and is seen worldwide
- Loss of central vision, with the age of onset and rapidity of progression dependent on the severity of the impact of the genetic mutation
- No current treatment –> significant unmet need
- Extensive natural history data now available → facilitates the design of interventional clinical trial

THANK YOU!

Agenda

1. Alnylam ATTR Amyloidosis Franchise Overview
2. Vutrisiran HELIOS-A Phase 3 Topline 18-Month Results
3. Potential Expansion into ATTR Amyloidosis with Cardiomyopathy
4. Advancing Innovation with ALN-TTRsc04
5. Stargardt Disease: Promising New Opportunity for Vutrisiran

Stargardt Disease

Rare, Inherited, Progressive Form of Blindness

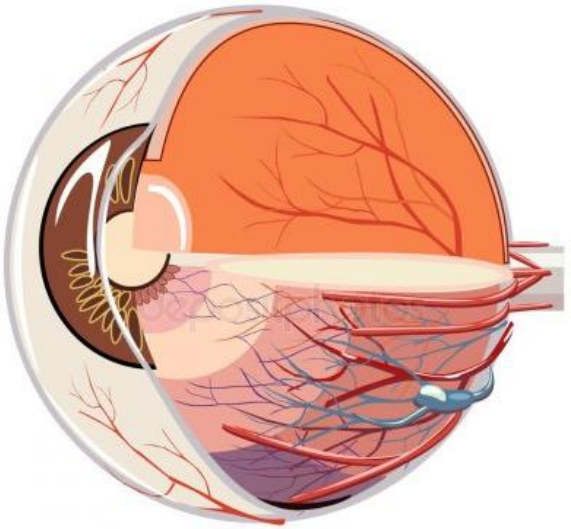
Description

Caused by accumulation of toxic vitamin A metabolites in retina leading to central vision loss

High unmet medical need with no approved treatments

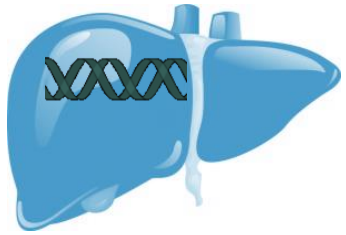
Incidence of 1 in 8,000-10,000

Leading cause of blindness in children from inherited, retinal disease - almost all legally blind as adults

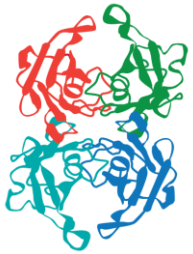


Stargardt Disease: Disease Cascade

Accumulation of Toxic Vitamin A Metabolites Leads to Central Vision Loss



Liver Production of TTR



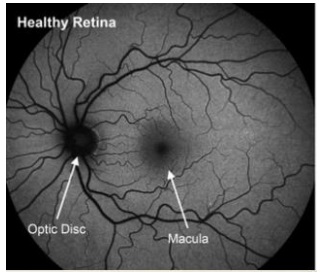
TTR/ RBP4 Vitamin A complex

Healthy People

Vitamin A delivered to eye

Visual Cycle

ABCA4



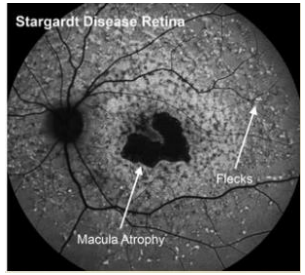
Vitamin A delivered to eye

Stargardt Disease Patients

Visual Cycle

ABCA4

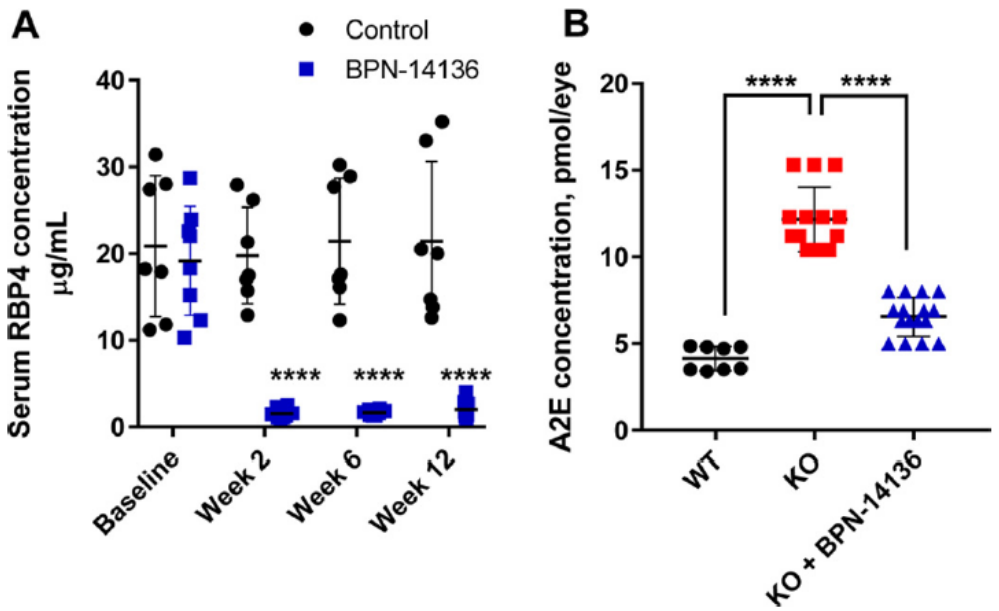
toxic metabolites

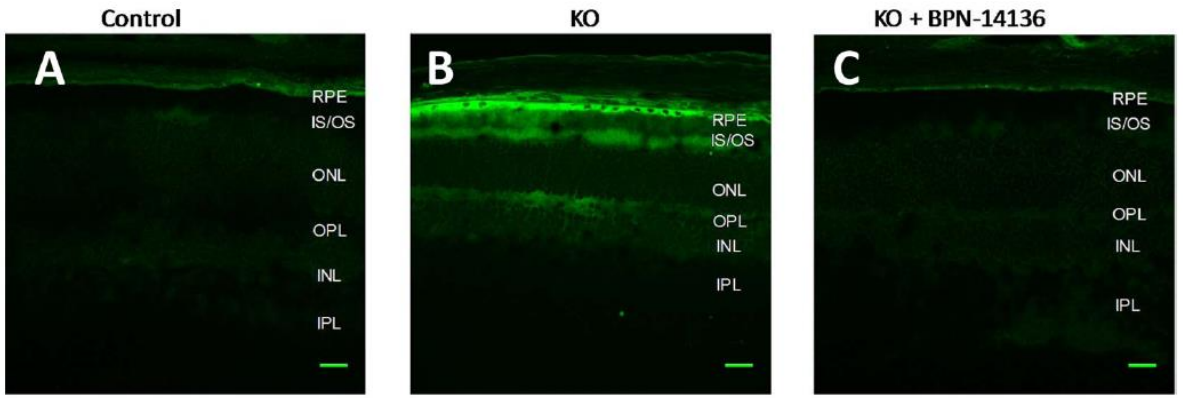


Decreasing Vitamin A Delivery to Eye via RBP4 Antagonist Efficacious in Stargardt Mouse Model (Published Data)

Points to Potential Applicability for Vutrisiran in Disease Treatment

Decrease in RBP4 (key transporter of Vitamin A) leads to decreased accumulation of toxic vitamin A metabolites in eye of Abca4$^{-/-}$ mice[1]





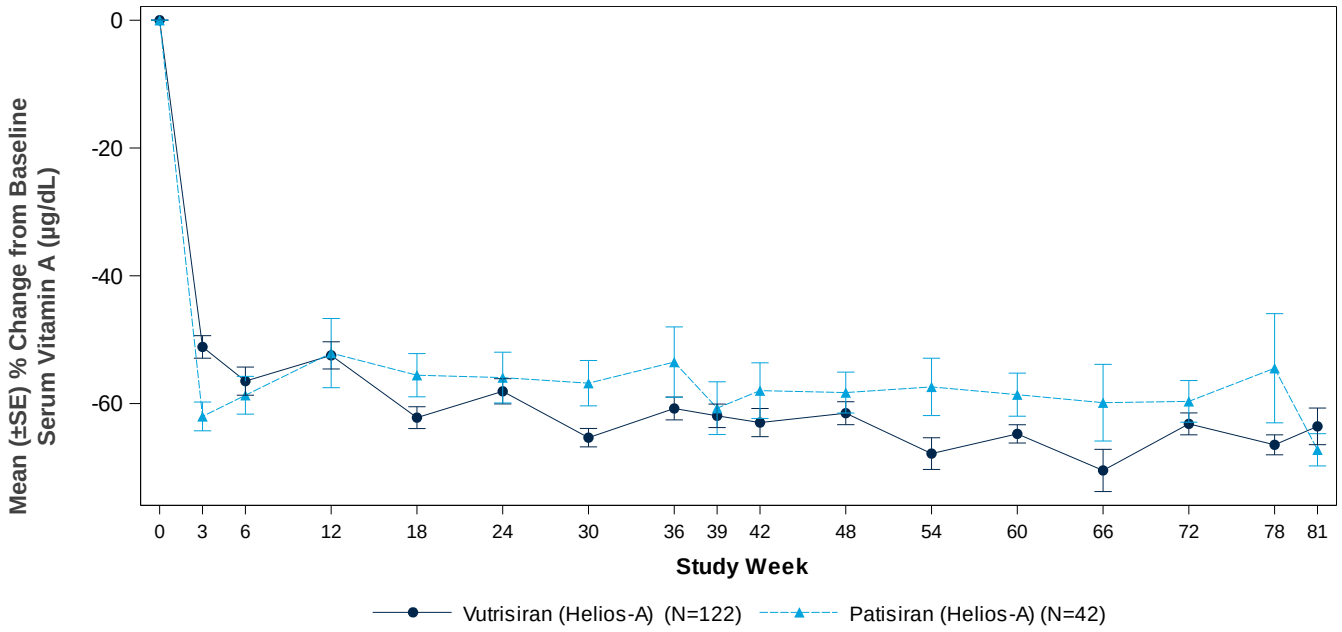
Treatment with RBP4 antagonist was not associated with inhibition of visual cycle

[1] J. Biol. Chem. (2018) 293(29) 11574–11588

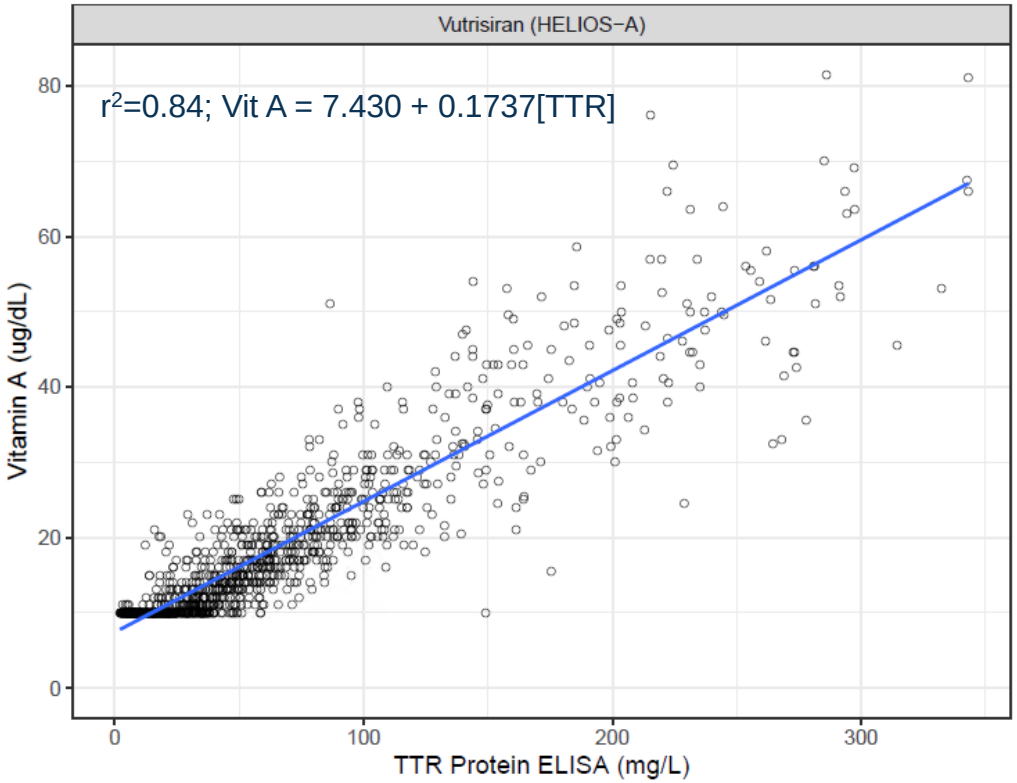
HELIOS-A: Observed Reduction in Vitamin A with Vutrisiran Treatment

Serum Vitamin A and TTR Levels are Highly Correlated

Mean Percent Change from Baseline in Vitamin A over Time During 18-Month Treatment Period



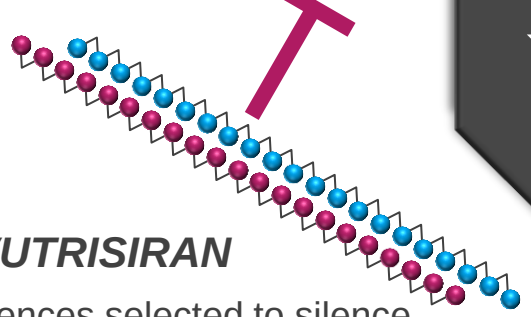
Serum Vitamin A Correlation with Serum TTR Protein*



*HELIOS-A vutrisiran-treated patients at Month 9 analysis

RNAi Therapeutic Hypothesis in Stargardt Disease

Silencing TTR Gene Expression Can Potentially Address Disease



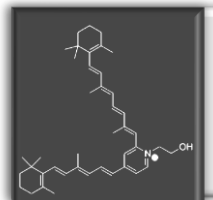
VUTRISIRAN

siRNA sequences selected to silence both mutant and wild-type TTR

Production of TTR in liver*

Reduce

circulating TTR / RBP4 / Vitamin A Complex



Reduce

build-up of toxic metabolites in retina

Halt Progression

of vision loss

* >95% of TTR in circulation produced in liver

Opportunity to Address High Unmet Medical Need and Expand TTR Franchise

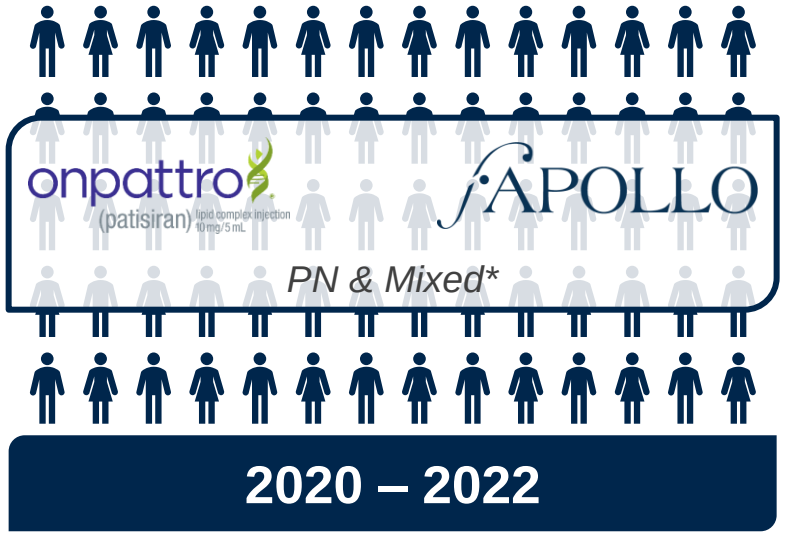
Alnylam Well Positioned to Investigate Stargardt Disease

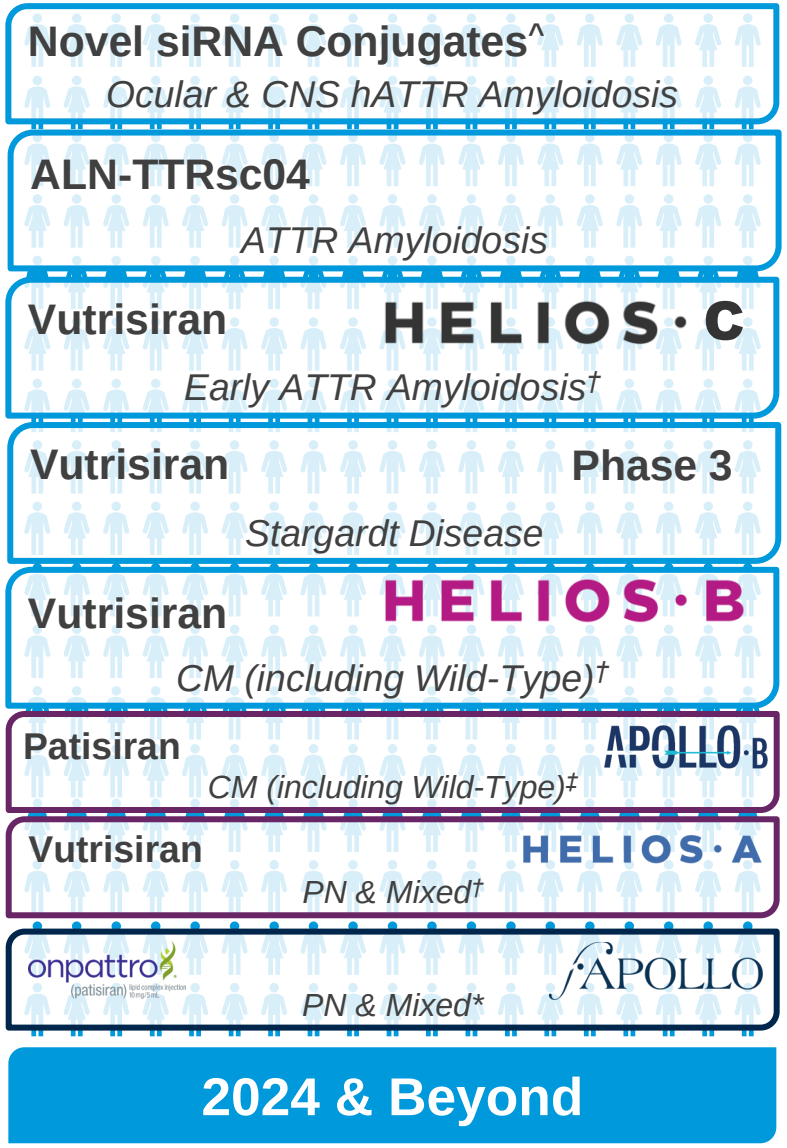
- Expertise in TTR lowering with multiple RNAi therapeutics
- Track record in relevant aspects of drug development
  - Platform and organization with history of treating young patients
  - History of *substrate reduction therapy* for diseases with high unmet need (AHP, PH1)
- Other promising approaches exist, but none are approved – all have limitations
  - Except stem cell therapy, none expected to restore vision
  - siRNA dosing profile unmatched vs. daily pills, IVT or subretinal injection
  - No evidence others taking TTR approach; stabilizers not expected to work because of disease pathophysiology
- Potential to move directly to pivotal trial with vutrisiran

Phase 3 start targeted for
Late 2022

Alnylam ATTR Amyloidosis Franchise

Potential to Expand Value to Patients Globally for Many Years to Come





* ONPATTRO is approved in the U.S. and Canada for the treatment of the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or 2 PN; ‡ ONPATTRO has not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in this population

† Vutrisiran is an investigational agent and has not been approved by the FDA, EMA, or any other regulatory agency and no conclusions can or should be drawn regarding its safety or effectiveness; additional studies and future development possible; ^ Novel siRNA conjugate development candidates for ocular or CNS hATTR amyloidosis not yet selected

Intended to be illustrative and not intended to represent specific estimates of patient numbers

Reimagining the Treatment of Hypertension with Zilebesiran, an Investigational RNAi Therapeutic

Weinong Guo, M.D., Ph.D., FACC
Senior Vice President, Clinical Development

Alnylam® PHARMACEUTICALS

RNAi Therapeutics Could Potentially Reimagine Treatment of Hypertension

Opportunity for Tonic Blood Pressure (BP) Control

Disease Overview

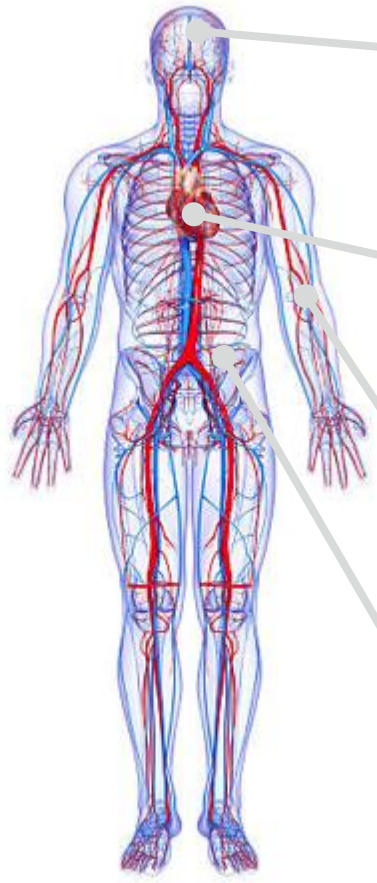
Primary Hypertension[1]	Hypertension at high CV risk[2]
~108 Million in U.S.	**~38 Million** in U.S.

>71% of patients have uncontrolled hypertension (>130/80 despite treatment)[3]

Hypertension risk further exacerbated by variability in BP **control**, lack of nighttime **dipping**, and poor medication **adherence**

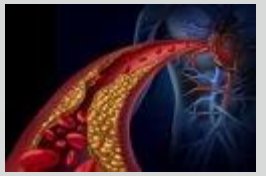
Together, contribute to substantial risk of CV morbidity and mortality

Potential Complications of Uncontrolled Hypertension



Stroke

Heart Attack



Arteriosclerosis

Kidney Failure

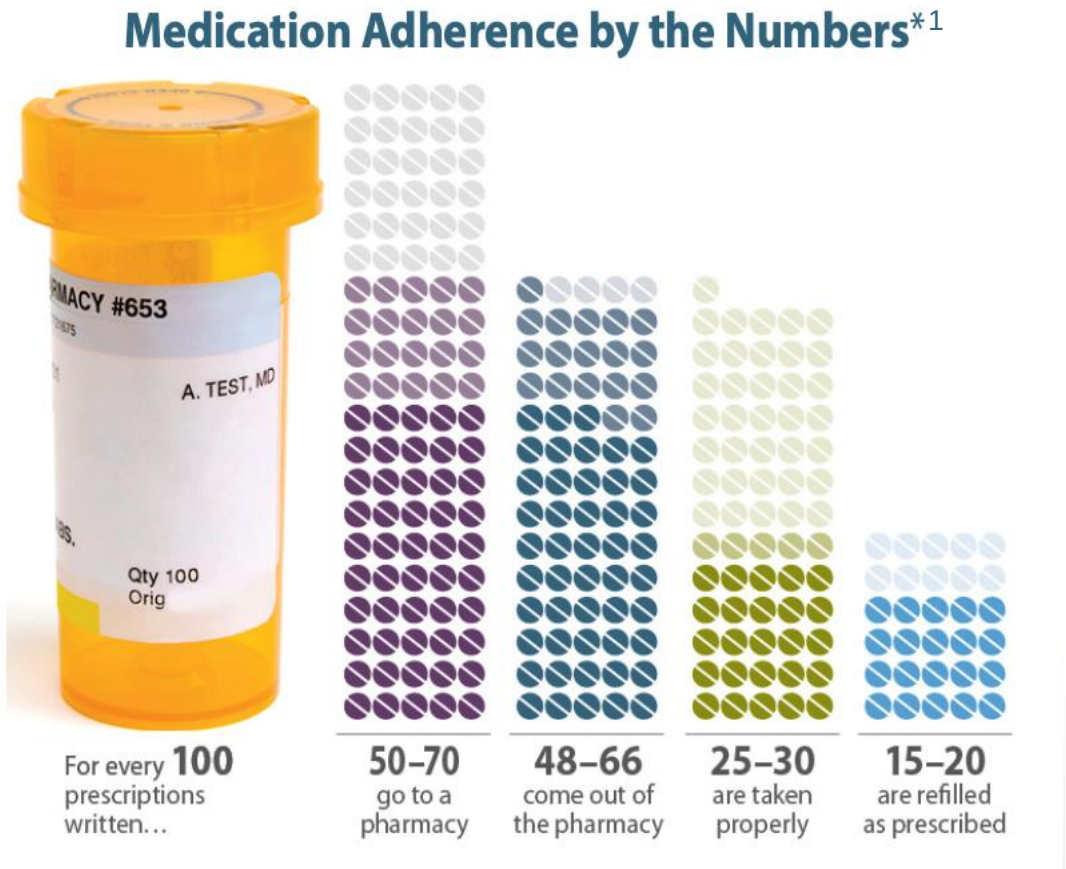
[1] Centers for Disease Control and Prevention (CDC). Hypertension Cascade: Hypertension Prevalence, Treatment and Control Estimates Among US Adults Aged 18 Years and Older Applying the Criteria From the American College of Cardiology and American Heart Association's 2017 Hypertension Guideline—NHANES 2013–2016. Atlanta, GA: US Department of Health and Human Services; 2019.

[2] Estimated from multiple sources and internal estimates: Dorans. JAHA. 2018; Al Kibria. Hypertens Res. 2019; CDC Hypertension Cascade. 2019; High CV risk: ASCVD risk score ≥20% and/or history of CVD

[3] U.S. Department of Health and Human Services. The Surgeon General's Call to Action to Control Hypertension. Washington, DC: U.S. Department of Health and Human Services, Office of the Surgeon General; 2020.

Poor Medication Adherence Adds to Cardiovascular Risk

Improving Medication Adherence, Including Among Patients with Hypertension, is Significant Challenge



* These data apply to all medication types, not only hypertension medication

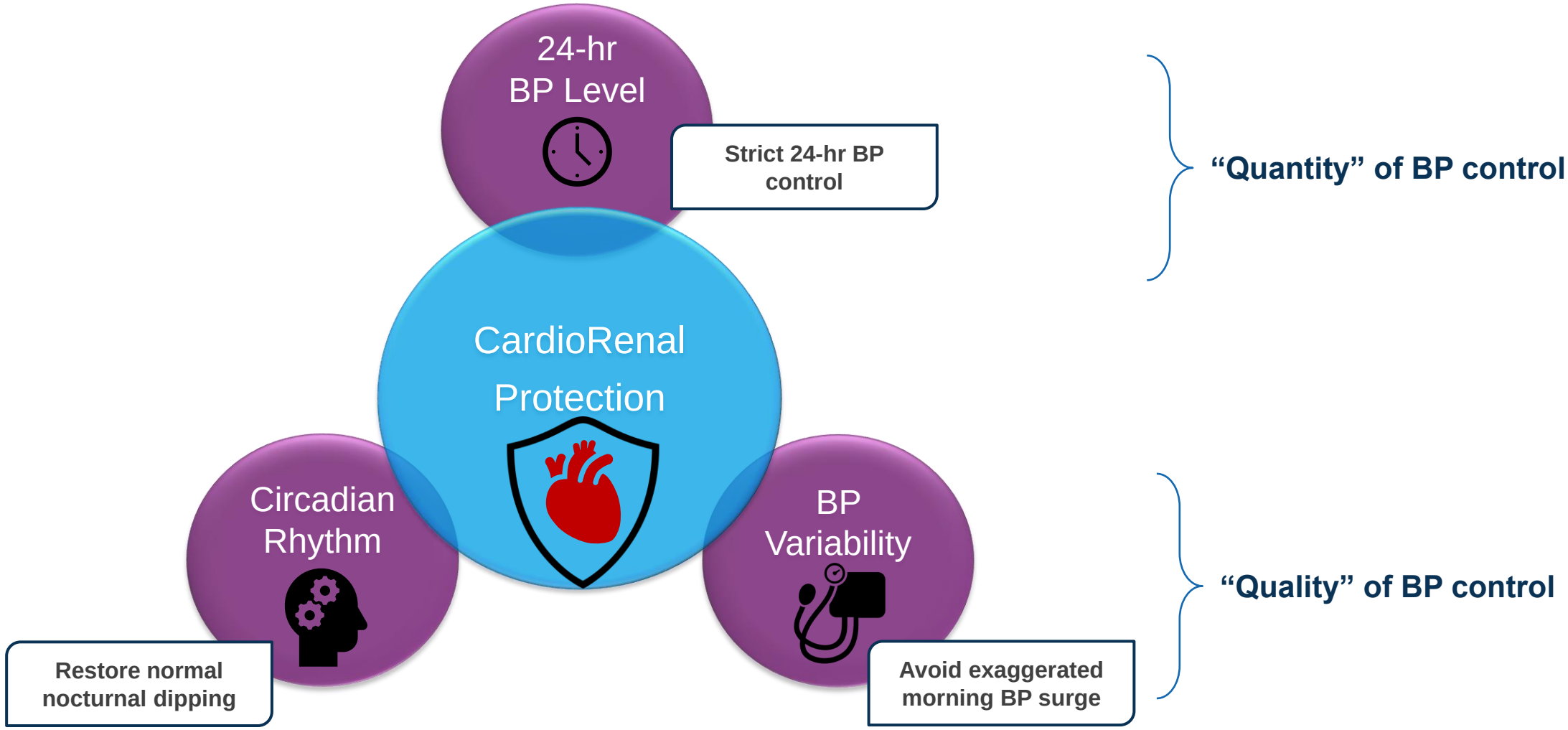
"Drugs don't work in patients who don't take them."

- C. Everett Koop, MD, US Surgeon General, 1985

Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. Circulation. 2009;119:3028-3035.
[1] https://millionhearts.hhs.gov/data-reports/factsheets/adherence.html, accessed 24Jun2021

Targeting “Tonic” BP Control to Reduce Cardiorenal Risks

Achieving Triad Could Reduce Risk of Organ Damage and Risk of CVD Events

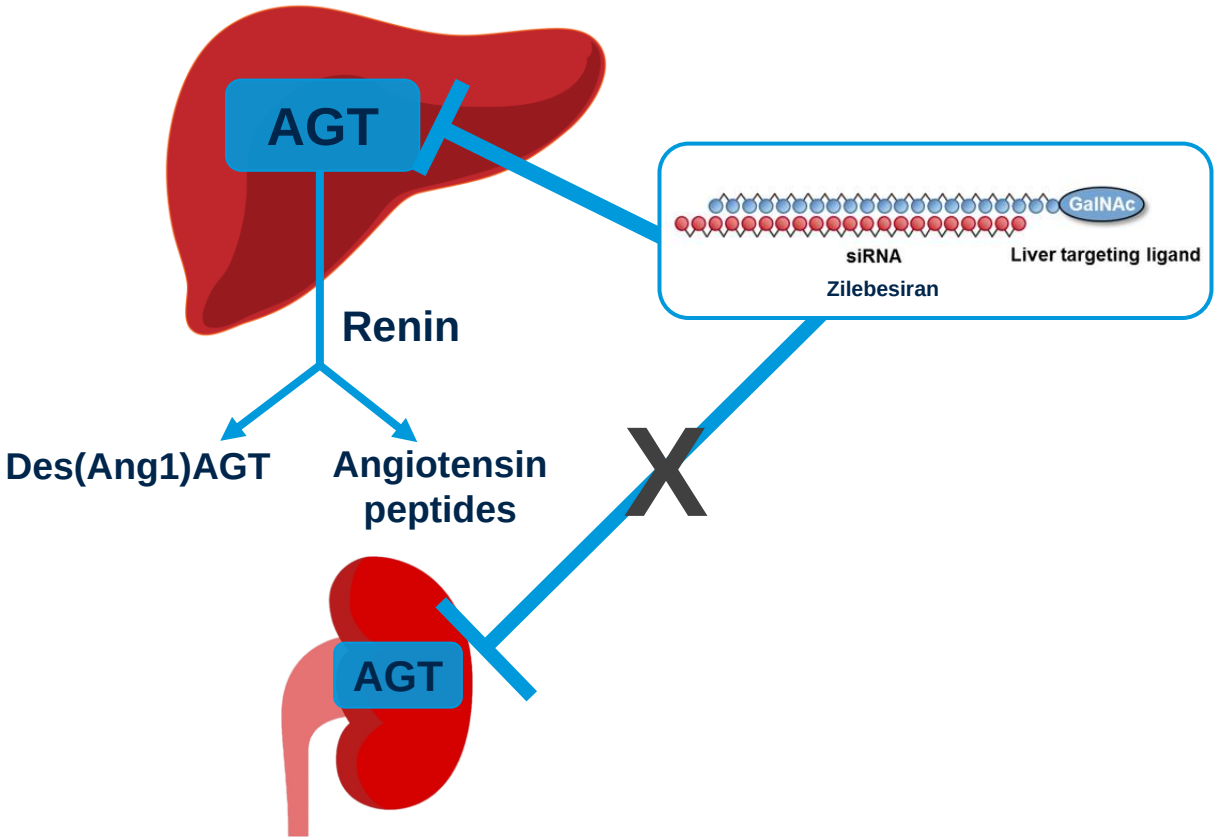


Kario K. Evidence and Perspectives on the 24-hour Management of Hypertension: Hemodynamic Biomarker-Initiated 'Anticipation Medicine' for Zero Cardiovascular Event. Prog Cardiovasc Dis. 2016 Nov-Dec;59(3):262-281.

CV: cardiovascular; CVD: cardiovascular disease; BP: blood pressure

Zilebesiran Therapeutic Hypothesis

Liver-specific AGT Knockdown



Potential Mechanistic Advantages

- **Liver-specific silencing of AGT**
- **Prolonged duration of action**
  - Consistent and durable BP response
  - Infrequent dose administration
  - Potential for improved adherence

AGT, angiotensinogen; BP, blood pressure; GalNAc, N-acetylgalactosamine; siRNA, small interfering ribonucleic acid

Zilebesiran Clinical Development

Phase 1 Study Data

Part A: SAD

Single-Ascending Dose

Part B: Salt Deprivation

Low- and High-Salt Diet

Part E: Combo

Co-Administration of ARB

Phase 2 Study Designs

KARDIA$_1$

Monotherapy

KARDIA$_2$

Concomitant Therapy

Zilebesiran Clinical Development

Phase 1 Study Data

Part A: SAD

Single-Ascending Dose

Part B: Salt Deprivation

Low- and High-Salt Diet

Part E: Combo

Co-Administration of ARB

Phase 2 Study Designs

KARDIA-1

Monotherapy

KARDIA-2

Concomitant Therapy

Zilebesiran Phase 1 Study

Multicenter Phase 1 study designed to evaluate safety, tolerability, PK/PD effects of subcutaneous administration of zilebesiran in patients with mild-to-moderate hypertension

Study is conducted in 4 parts

Part A: *Randomized, placebo-controlled, single ascending dose study*

Proof-of-Concept

Part B: *Randomized, placebo-controlled, single dose study with modified salt intake*

Safety / tolerability under volume depletion

Part D: *Randomized, active-controlled, multiple-dose study in obese patients*

Metabolic effect

Part E: *Open-label, single dose study with co-administration of Irbesartan*

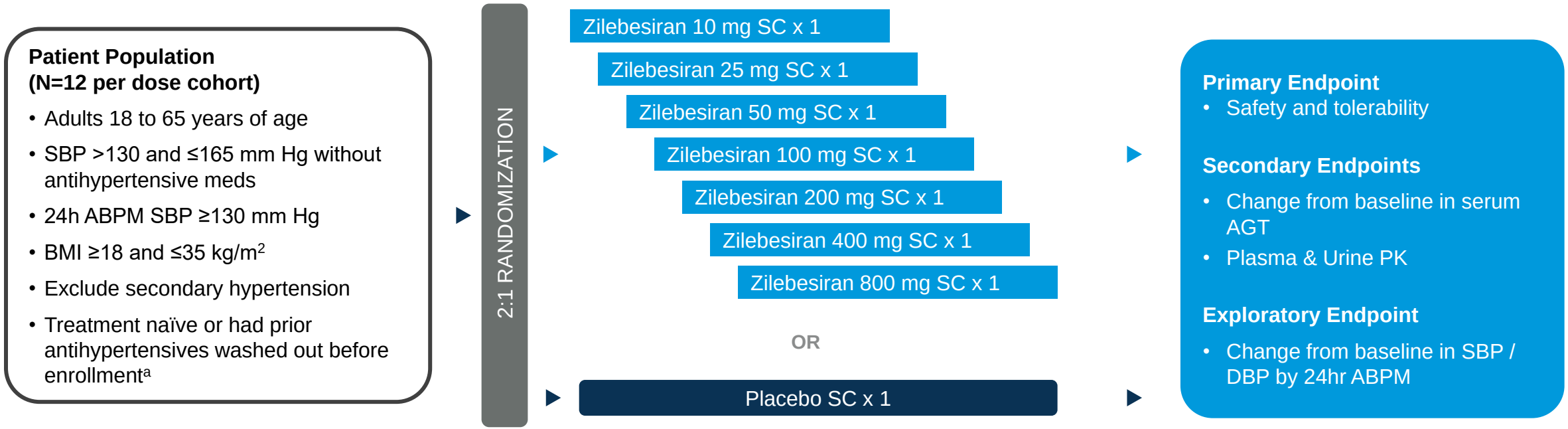
Safety / tolerability in combination with a potent ARB

Part C of multi-dose cohort was removed in Study Protocol Amendment 6

Zilebesiran Single Ascending Dose Phase 1 Study

Part A

- Patients received either zilebesiran (N=8 per cohort) or Placebo (N=4 per cohort)
- Study conducted in outpatient setting with usual activity and dietary sodium intake



[a] Patients previously taking medication for hypertension must be without antihypertensives for ≥2 weeks prior to screening

ClinicalTrials.gov Identifier: NCT03934307

ABPM, ambulatory blood pressure monitoring; AGT, angiotensinogen; BMI, body mass index; DBP, diastolic blood pressure; PD, pharmacodynamics; PK, pharmacokinetics; SBP, systolic blood pressure; SC, subcutaneous

Primary Endpoint: Safety & Tolerability Over 12 Weeks

Zilebesiran was Generally Well Tolerated, Supporting Continued Development

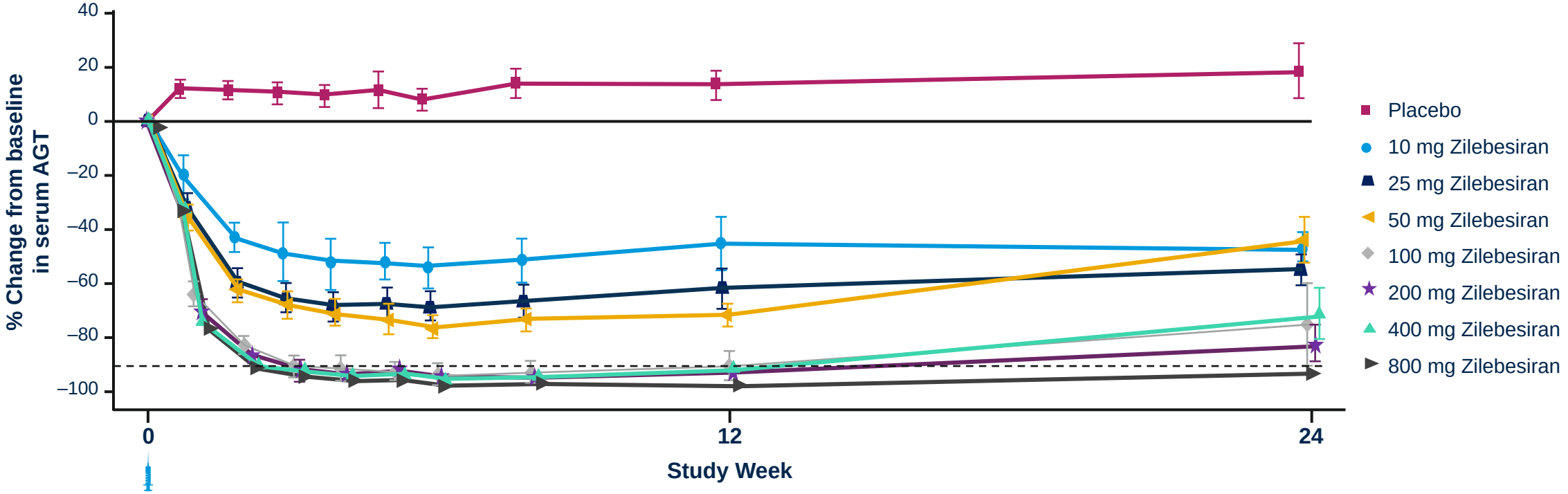
At Least One Event, n	Placebo (N=28)	Zilebesiran Dose Cohort							All Zilebesiran (N=56)
		10 mg (N=8)	25 mg (N=8)	50 mg (N=8)	100 mg (N=8)	200 mg (N=8)	400 mg (N=8)	800 mg (N=8)	
Adverse Event	24	5	7	6	7	7	4	6	42
Serious Adverse Event	1	0	0	0	0	1	0	0	1
Severe Adverse Event	2	0	0	0	0	1	0	0	1

- Most AEs mild or moderate in severity and resolved without intervention
- No deaths or AEs leading to study withdrawal
- No treatment-related Serious AEs (SAEs)
  - Severe and serious AE of prostate cancer reported in 1 patient who received 200 mg zilebesiran, based upon biopsy performed in screening period and reported as positive after dosing
- No patient has required intervention for low blood pressure
- No clinically significant elevations in serum ALT, serum creatinine, or serum potassium
- 5 patients treated with zilebesiran had injection site reactions, all mild and transient

AE, adverse event; ALT, alanine aminotransferase; SAE, serious adverse event

Durable Dose-Dependent Lowering of Serum AGT

- A reduction of ≥90% in serum AGT from baseline was observed with single doses of zilebesiran ≥100 mg from Week 3 and sustained to Week 12
- All patients who received a single dose of zilebesiran 800 mg maintained >90% reduction in serum AGT through Week 24

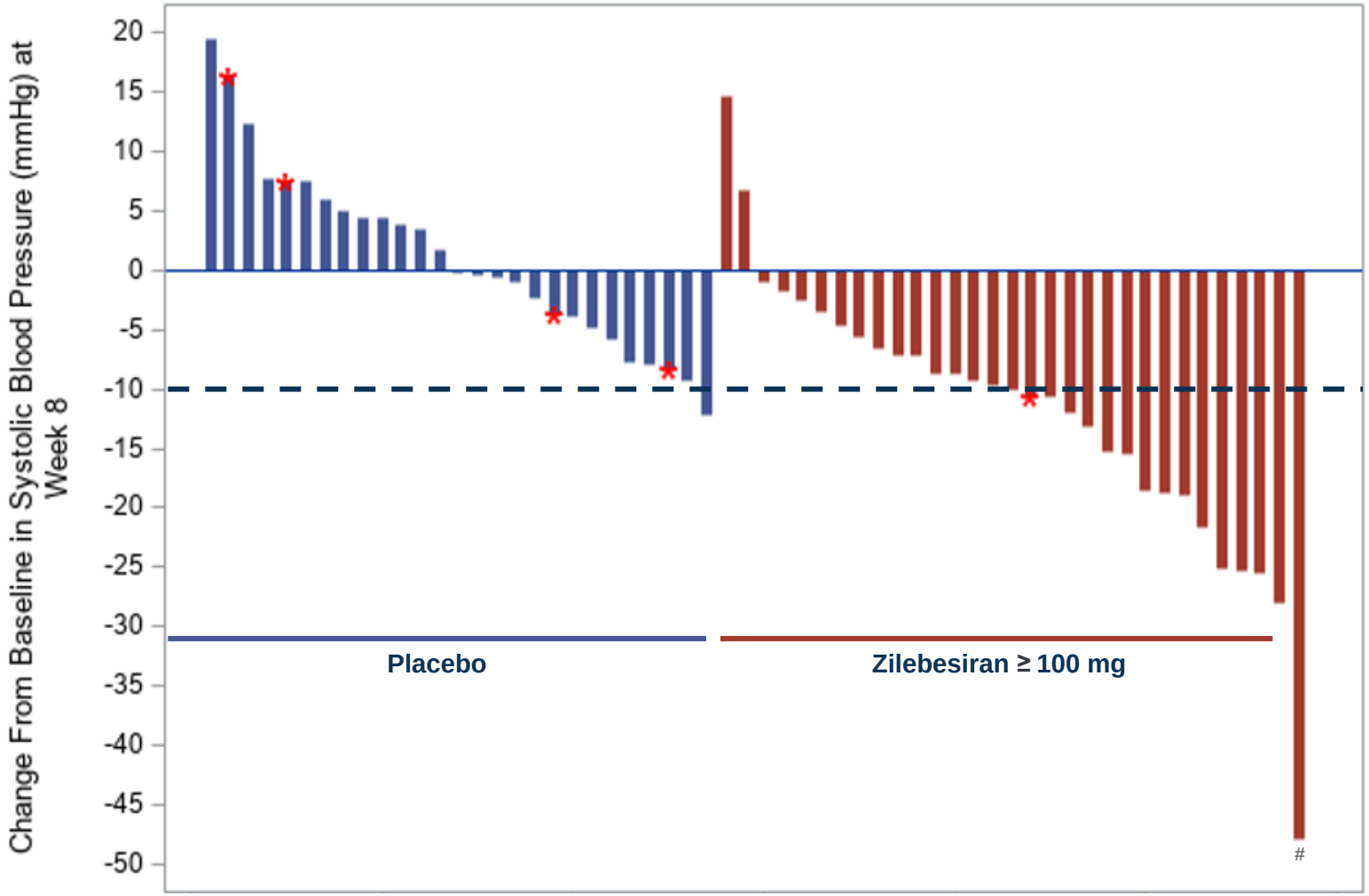


Placebo	28	28	12
10 mg	8	8	5
25 mg	8	8	8
50 mg	8	7	7
100 mg	8	7	7
200 mg	8	8	8
400 mg	8	8	8
800 mg	8	8	8

Huang AH, Taubel J, Casey S, et al., AHA Scientific Sessions 2021
AGT, angiotensinogen

Exploratory Endpoint: Changes in 24-Hour Mean Systolic BP

Individual Patient Reductions in 24-Hour Mean SBP 8 Weeks After Single Dose of Zilebesiran



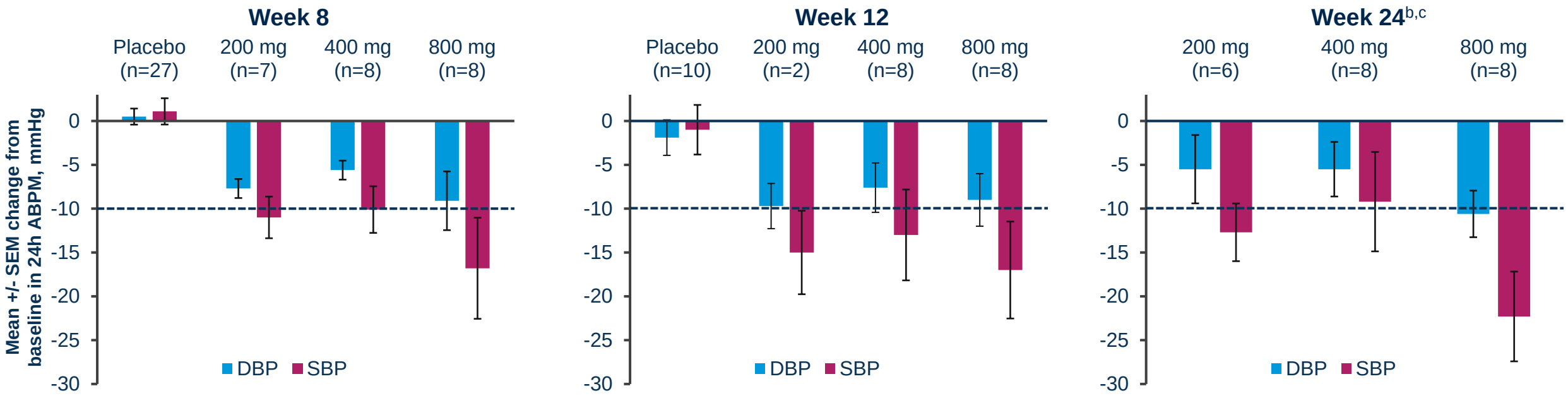
* Patient receiving oral antihypertensive medication; # Baseline 24-hour mean SBP of 167 mmHg for this patient

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure

Durable Antihypertensive Effect of Single Dose Zilebesiran

- A mean 24-hr SBP reduction of >10 mmHg was achieved at Week 8 across dose groups ≥200 mg
  - Clinically meaningful reductions in BP were maintained through Week 24
- After a single dose of 800 mg zilebesiran, a mean 24-hr SBP reduction of >20 mmHg was observed at Week 24
  - Of the 8 patients in this group, 6 achieved a mean 24-hr SBP reduction of >20 mmHg at Week 24 without add-on antihypertensives

Mean Change From Baseline in ABPM[a]



Huang AH, Taubel J, Casey S, et al., AHA Scientific Sessions 2021

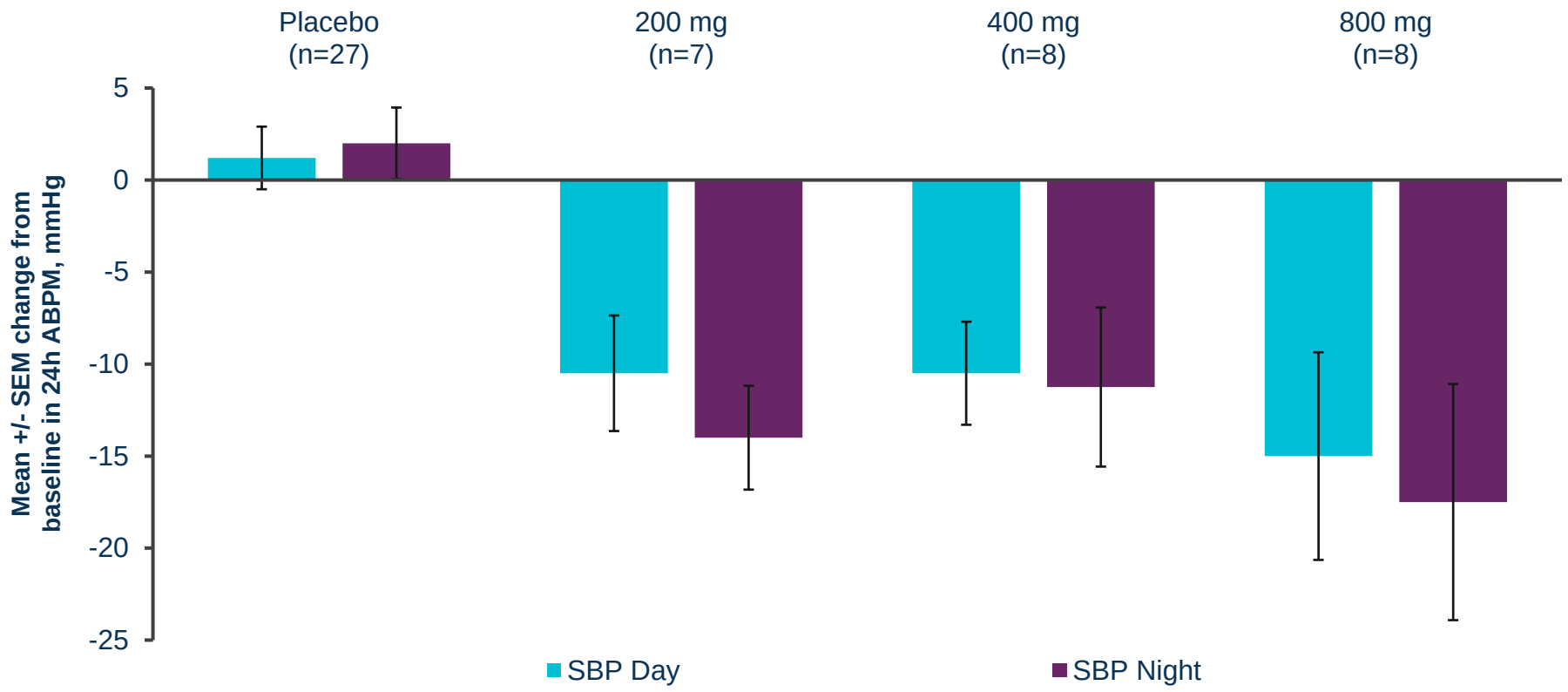
[a] Median SBP/DBP at baseline: Placebo - 142/88 mmHg; 200 mg - 139/83 mmHg; 400 mg - 138/90 mmHg; 800 mg - 142/88 mmHg.

[b] After Week 12, patients on placebo were not required to be followed. [c] 2 patients in the 200 mg dose group, 1 patient in 400 mg, and 2 patients in 800 mg received add-on antihypertensive therapy.

ABPM, ambulatory blood pressure monitoring; AGT, angiotensinogen; BP, blood pressure; DBP, diastolic blood pressure; SAD, single ascending dose; SBP, systolic blood pressure; SEM, standard error of the mean.

Consistent BP Reduction Over 24 Hours of Single Dose Zilebesiran

Mean Change from Baseline in Daytime/Nighttime Blood Pressure at Week 8[a,b,c]



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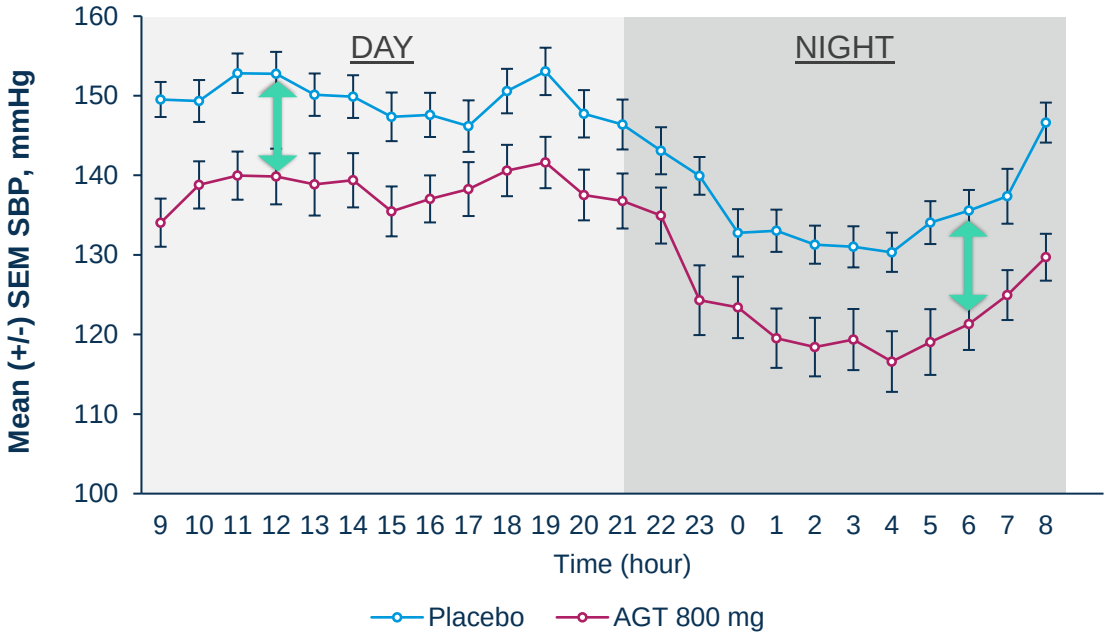
[a] All patients at Week 8 were receiving zilebesiran only (no rescue antihypertensives). [b] Hourly adjusted mean: Daytime [9 am to 9 pm], Nighttime [1 am to 6 am].

[c] Median SBP/DBP at baseline: Placebo - 142/88 mmHg; 200 mg - 139/83 mmHg; 400 mg - 138/90 mmHg; 800 mg - 142/88 mmHg

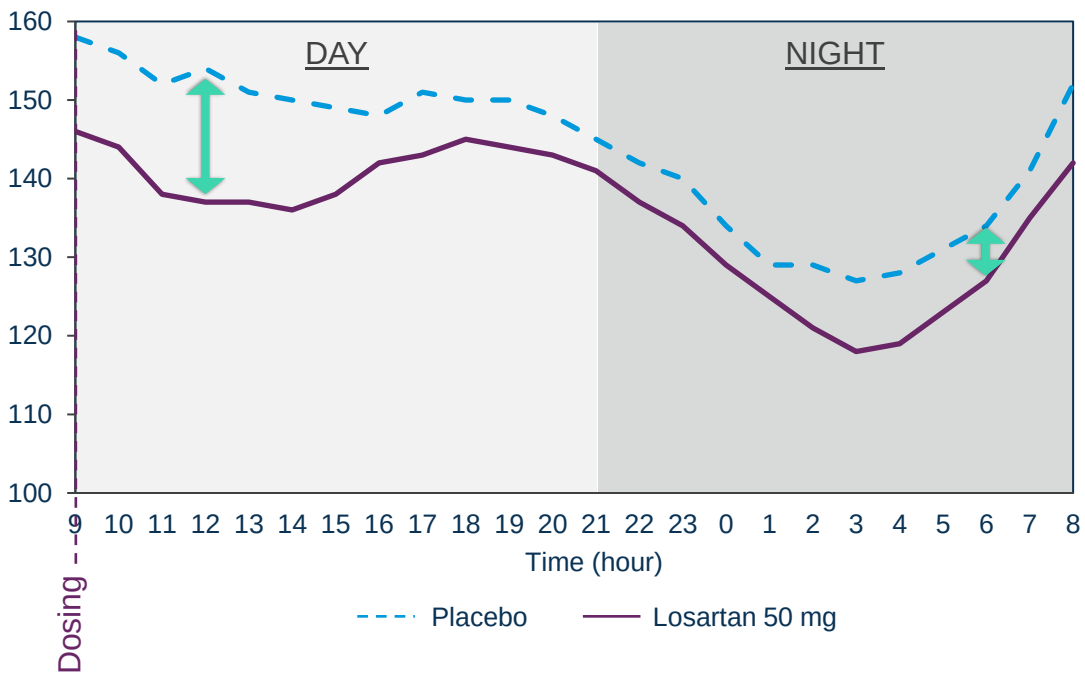
ABPM, ambulatory blood pressure monitoring; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; SEM, standard error of the mean.

Early Evidence of Tonic BP Control over 24 Hours with Zilebesiran

Zilebesiran: 24-Hour SBP at Week 6



Losartan: 24-Hour SBP at Week 4[a]



[a] Adapted from Fogari et al. (1999) Current Therapeutic Research 60(4):195-206

AGT, angiotensinogen; BP, blood pressure; SBP, systolic blood pressure

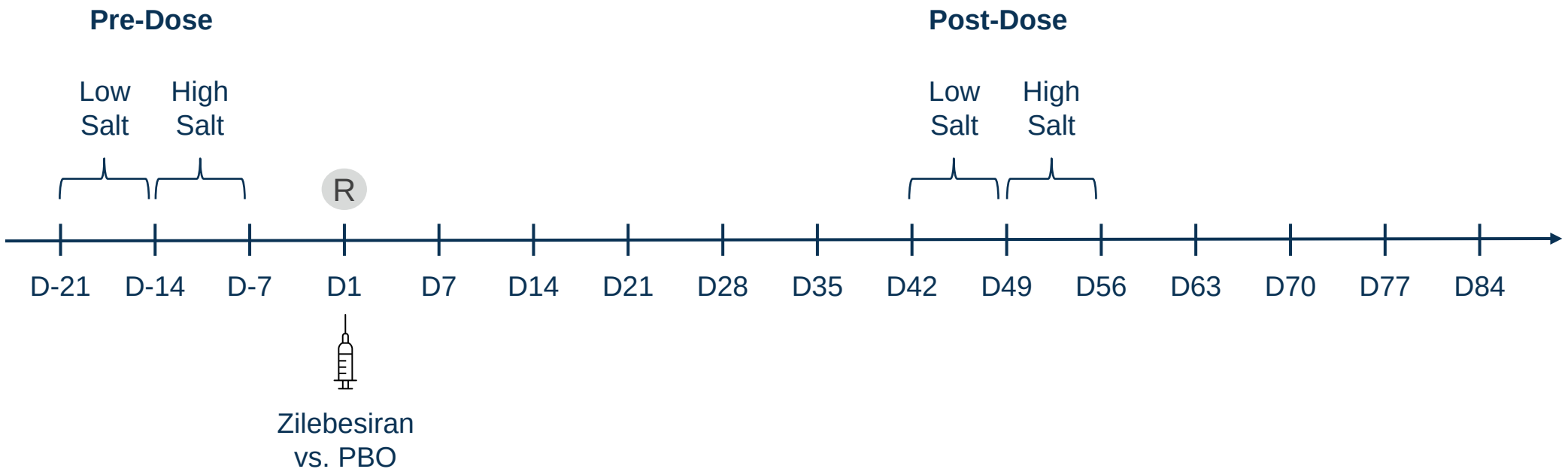
Part A: Summary and Conclusions

- A single dose of zilebesiran SC administration was generally well tolerated in patients with mild-to-moderate hypertension, with no treatment-related SAEs
- Durable reductions in serum AGT >90% were sustained for 24 weeks after a single SC dose of zilebesiran 800 mg
- Zilebesiran led to >10 mmHg reduction in 24-hour mean SBP at Week 8 across all doses ≥200 mg, with the clinically meaningful BP reduction maintained through Week 24
- Zilebesiran produced consistent BP reduction during both daytime and nighttime, showing early evidence of potential for tonic BP control at all timepoints over 24-hour period that is sustained during the entire dosing interval(s)
- These data support further evaluation of both quarterly and biannual dose administration of zilebesiran in hypertension

AGT, angiotensinogen; BP, blood pressure; SBP, systolic blood pressure; SAE, serious adverse event; SC, subcutaneous

Randomized, Placebo-Controlled, Single Dose Study with Controlled Salt Intake (Part B)

Objective: Assess Safety/Tolerability of Zilebesiran During Salt Deprivation



- A cohort of 12 patients randomized 2:1 to receive zilebesiran (800 mg) or Placebo subcutaneous on Day 1
- Two-week controlled salt intake of low-salt diet (0.23 g sodium per day) followed by high-salt diet (5.75 g sodium per day) during the pre-defined pre-dose and post-dose periods

Safety and Tolerability in Low/High-Salt Diet

Zilebesiran was Generally Well Tolerated with No Drug-Related SAEs

- All AEs mild in severity and resolved without intervention
- No deaths or SAEs were reported
- No AEs leading to study withdrawal
- No AEs of injection site reaction or hypotension
- No patient required intervention for low blood pressure, including during the sodium deprivation period
- No clinically significant elevations in ALT, serum creatinine or serum potassium in zilebesiran group were reported
- One patient receiving placebo had transient ALT elevation >3x ULN attributed to alcohol consumption

Summary of Adverse Events

Number of Patients with at Least One Event, n	Placebo (N=4)	Zilebesiran (N=8)
Adverse Event	4	3
Serious Adverse Event	0	0
Severe Adverse Event	0	0

Huang AH, Taubel J, Desai AS, et al., AHA Scientific Sessions 2021

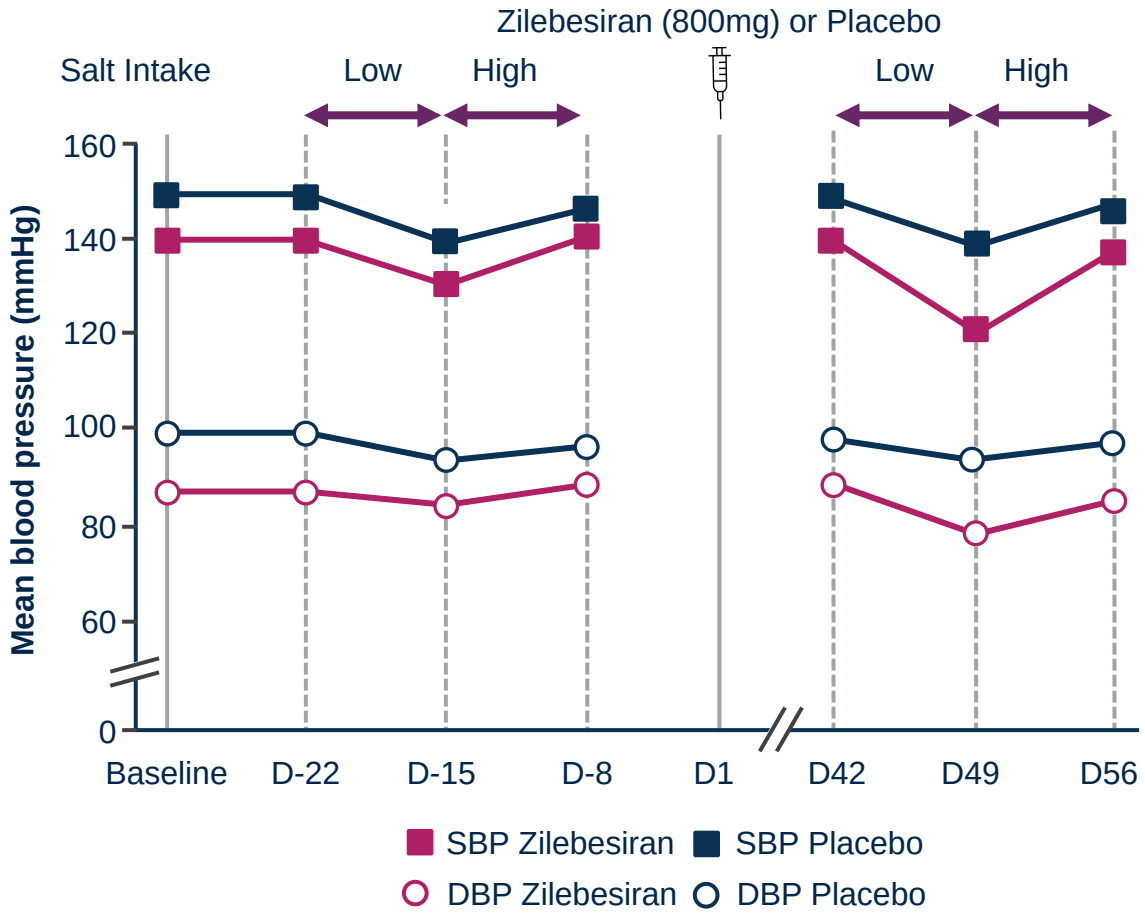
AE, adverse event; ALT, alanine aminotransferase; PBO, placebo; SAE, serious adverse event; ULN, upper limit of normal.

Data transfer date: May 28, 2021 (all patients completed low- and high-salt diets before data transfer). Safety reported from start of study drug to Day 85.

Changes in 24-hr BP in Low/High Salt Diet

- Pre-dose: A reduction in 24-hr SBP/DBP was observed for all patients at day -15 following a low-salt diet; BP increased at day -8 upon switching to a high-salt diet
- Post-dose: Changes in mean BP were more profound following a low-salt diet for patients receiving zilebesiran (-19.8 mmHg) vs. placebo (-10.0 mmHg); a high-salt diet modulated the BP lowering effect of zilebesiran
- *Zilebesiran 800 mg resulted in a reduction in serum AGT levels of >90%, sustained between Week 2 and Week 12 (data not shown)*

Changes in ABPM during Controlled Salt Intake

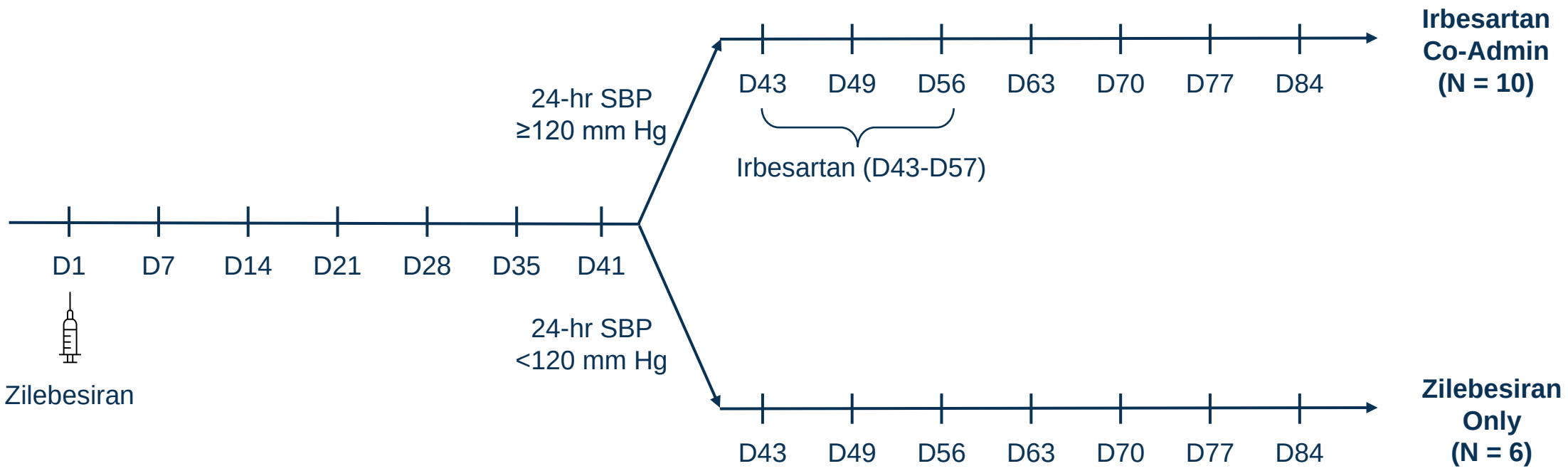


Huang AH, Taubel J, Desai AS, et al., AHA Scientific Sessions 2021

ABPM, ambulatory blood pressure monitoring; AGT, angiotensinogen; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure

Open-Label, Single Dose Study with Co-Administration of Irbesartan (Part E)

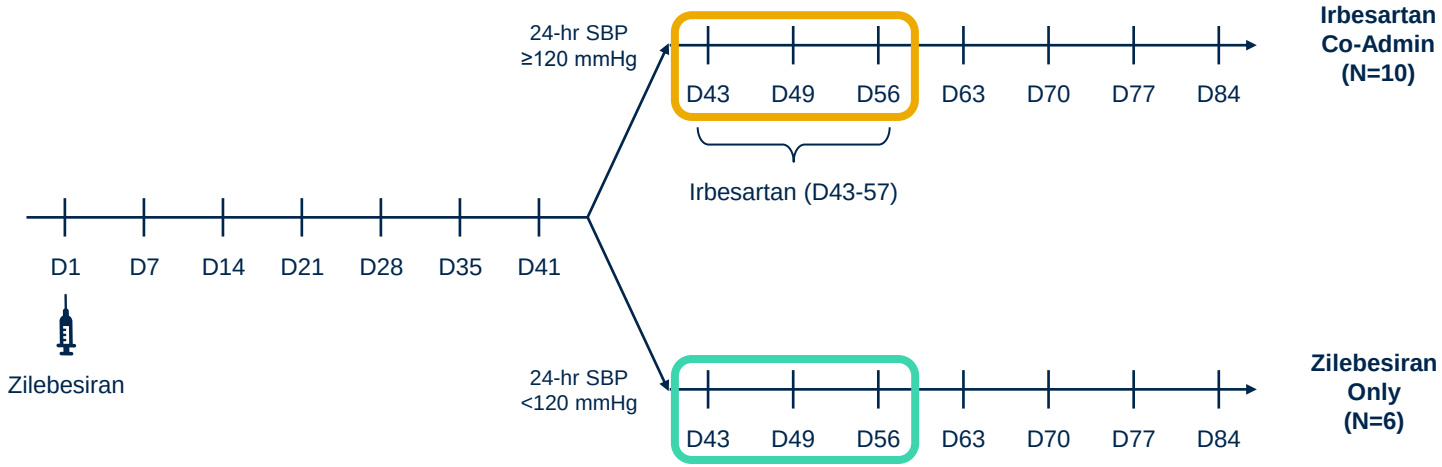
Objective: Assess Tolerability of Zilebesiran during ARB (Irbesartan) Co-Administration



- All patients (N = 16) received open-label treatment with zilebesiran 800 mg SC on Day 1
- On Day 41, patients with 24-hr mean SBP ≥120 mm Hg (N = 10) proceeded to receive Irbesartan 300 mg PO qD for 14 days (Day 43 to Day 57)

ARB: angiotensin receptor blocker; SBP: systolic blood pressure; SC: subcutaneous

Irbesartan Further Reduced BP without Clinically Significant Changes in Creatinine or Potassium



	Δ 24-hr SBP mmHg; mean (SEM)			Δ 24-hr DBP mmHg; mean (SEM)		
Time Period	**Zilebesiran Only (N=6)**	**Irbesartan Co-Admin (N=10)**	**All Patients (N=16)**	**Zilebesiran Only (N=6)**	**Irbesartan Co-Admin (N=10)**	**All Patients (N=16)**
Day 41 *vs*. Day 1	**-22.0** (2.9)	**-7.7** (2.5)	**-13.1** (2.6)	**-14.3** (2.3)	**-3.3** (1.0)	**-7.4** (1.7)
Day 57 *vs*. Day 41	**0.4** (2.9)	**-6.4** (3.1)	**-3.9** (2.3)	**-0.5** (1.6)	**-3.2** (1.9)	**-2.2** (1.3)

- **No clinically significant elevations in serum creatinine or potassium during zilebesiran treatment or co-administration with Irbesartan**

Huang AH, Taubel J, Desai AS, et al., AHA Scientific Sessions 2021
BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure

Parts B & E: Conclusions

- Subcutaneous administration of zilebesiran 800 mg was safe and well-tolerated in patients with mild-to-moderate hypertension, with no SAEs/AEs of hypotension or low BP requiring interventions reported during low-salt diet or co-administration with ARB
- High-salt diet modulated BP lowering effect of zilebesiran, providing early evidence that standard intervention could be effective to treat potential hypotensive adverse events
- Addition of Irbesartan to zilebesiran further reduced BP without clinically significant changes in creatinine or potassium
- These data support further investigation of zilebesiran for treatment of hypertension in patients with uncontrolled BP despite standard-of-care antihypertensive treatment

Huang AH, Taubel J, Desai AS, et al., AHA Scientific Sessions 2021
SAE: severe adverse event; AE: adverse event; BP: blood pressure; ARB: angiotensin receptor blocker

Zilebesiran Clinical Development

Phase 1 Study Data

Part A: SAD

Single-Ascending Dose

Part B: Salt Deprivation

Low- and High-Salt Diet

Part E: Combo

Co-Administration of ARB

Phase 2 Study Designs

KARDIA-1

Monotherapy

KARDIA-2

Concomitant Therapy

Phase 2 Clinical Development Plan

KARDIA$_1$

Monotherapy Phase 2 Study (N ~ 375)

- Evaluate efficacy and safety of zilebesiran as a monotherapy in patients with mild-to-moderate hypertension
- Exploring both quarterly and biannual dosing regimens
- First patient randomized in August 2021

KARDIA$_2$

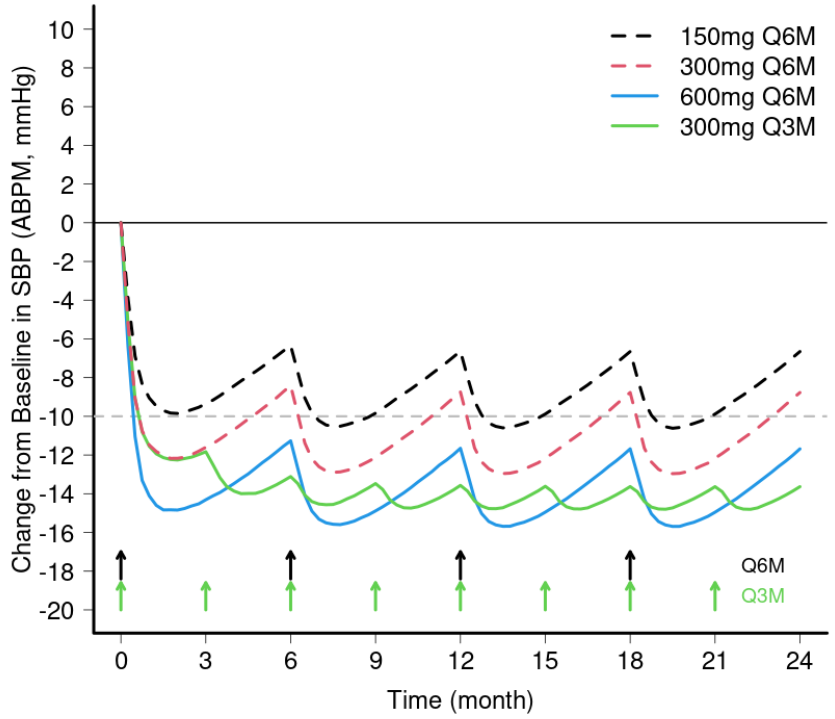
Combination Phase 2 Study (N ~ 800)

- Evaluate efficacy and safety of zilebesiran as concomitant therapy
- Background treatment standardized with ARB, calcium channel blocker or diuretic
- Study initiated in November 2021

Projected Change in 24-Hour ABPM with Different Dosing Regimens

Modeling Based on Phase 1 SAD Data Suggests Potential for Quarterly or Biannual Dosing of Zilebesiran

Modeled Systolic BP



Modeled Parameters

Dosing Regimen	Serum AGT Reduction (%)		SBP Reduction (mmHg)	DBP Reduction (mmHg)
	Peak	Trough (M12)	Trough (M12)	Trough (M12)
150 mg q6M	93.2	81.7	6.6	3.8
300 mg q6M	96.3	89.3	8.7	5.0
600 mg q6M	98.1	94.9	11.7	6.7
300 mg q3M	97.7	96.9	13.6	7.8

Modeling of Quarterly (q3M) & Biannual (q6M) Dosing

SAD: Single ascending dose; SBP: systolic blood pressure; DBP: diastolic blood pressure; HTN: hypertension; q3M: every 3 months (quarterly); q6M: every 6 months (semiannual); ABPM: ambulatory blood pressure measurement

Zilebesiran KARDIA-1 Phase 2 Study

Randomized, Double-Blind, Placebo-Controlled Study in Patients with Mild-to-Moderate Hypertension

N ~ 375
Patient Population

Key Inclusion Criteria:
- 18 - 75 years of age
- Daytime SBP ≥135 & ≤160 mm Hg
- Treatment naive or prior antihypertensives washed out before enrollment

Key Exclusion Criteria:
- Secondary HTN
- eGFR <30 ml/min/1.73m^2

ClinicalTrials.gov Identifier: NCT04936035

4-Week Washout

1:1:1:1:1 RANDOMIZATION

- **Zilebesiran** 150 mg SC q6M
- **Zilebesiran** 300 mg SC q6M
- **Zilebesiran** 300 mg SC q3M
- **Zilebesiran** 600 mg SC q6M
- **Placebo*** SC q3M

Primary Endpoint
- Change in SBP from baseline to Month 3 assessed by ABPM

Secondary Endpoints Include (through Month 6)
- Change in SBP and DBP by ABPM
- Time-adjusted change in SBP and DBP by office BP

Exploratory Endpoints Include (through Month 12)
- Change in 24h average, daytime average, and nighttime average SBP and DBP
- Time-adjusted change in SBP and DBP assessed by office BP, home BP monitoring, and ABPM

Study Initiated
June 2021

* Placebo randomized across 4 zilebesiran treatment arms after 6 months on study

SBP: systolic blood pressure; DBP: diastolic blood pressure; HTN: hypertension; q3M: every 3 months (quarterly); q6M: every 6 months (semiannual); ABPM: ambulatory blood pressure measurement

Zilebesiran KARDIA-2 Phase 2 Combination Study

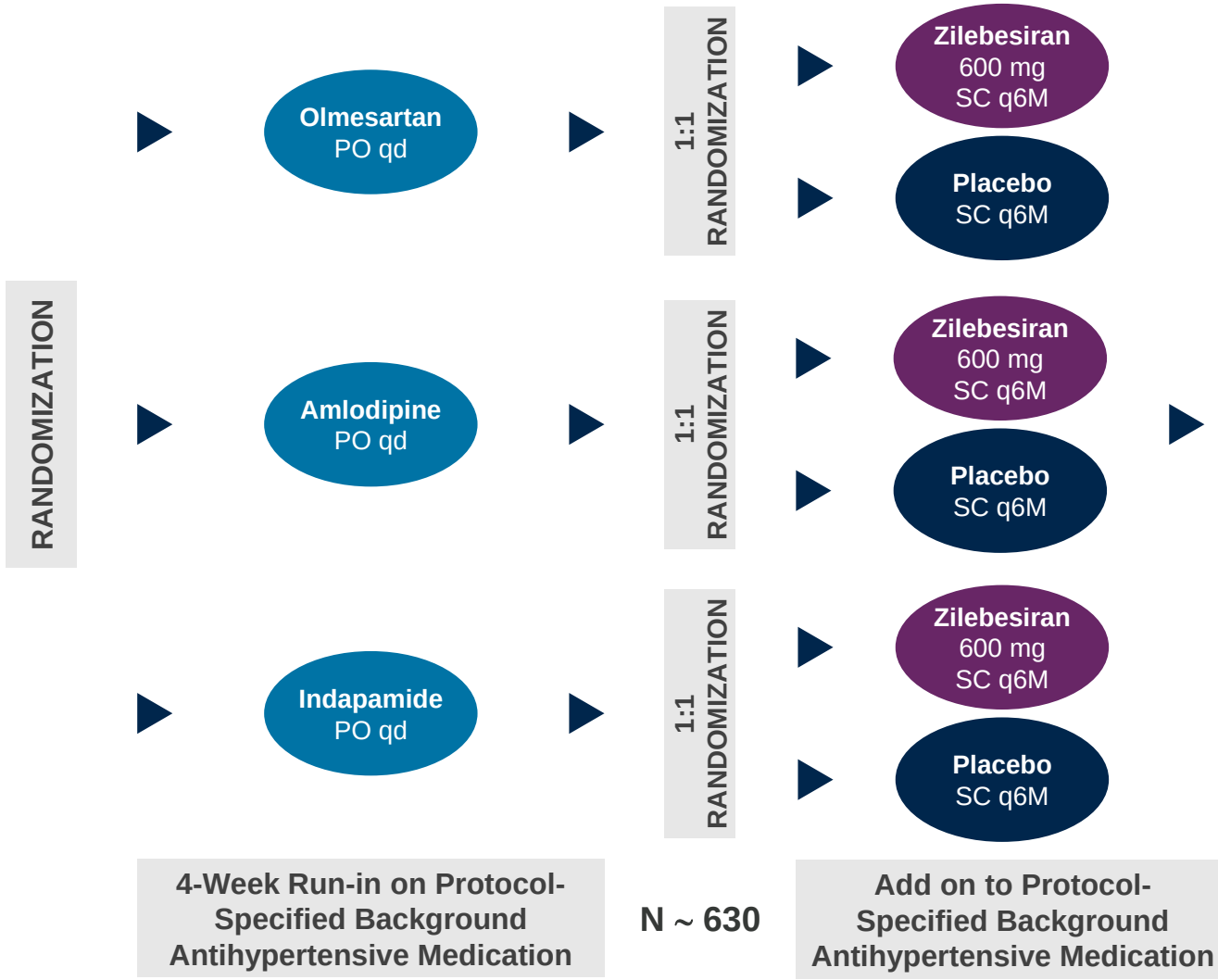
Randomized, Double-Blind, Placebo-Controlled Study in Patients with Hypertension Not Adequately Controlled on Standard-of-Care Antihypertensive Medication

N ~ 800
Patient Population

Key Inclusion Criteria:
- 18 - 75 years of age
- 24h mean SBP ≥130 & ≤160 mmHg
- Treatment naive or on stable therapy before enrollment

Key Exclusion Criteria:
- Secondary HTN
- eGFR <30 ml/min/1.73m^2

ClinicalTrials.gov Identifier: NCT05103332



Primary Endpoint
- Change in SBP from baseline to Month 3 assessed by ABPM

Secondary Endpoints Include (through Month 6)
- Change in SBP and DBP by office BP
- Change in SBP and DBP by ABPM

Exploratory Endpoints Include (through Month 6 or Month 18)
- Change in 24h average, daytime average, and night-time average SBP and DBP
- Time-adjusted change in SBP and DBP assessed by office BP, home BP monitoring, and ABPM

Study initiated
November 2021

SBP: systolic blood pressure; DBP: diastolic blood pressure; HTN: hypertension;
q3M: every 3 months (quarterly); q6M: every 6 months (semiannual); ABPM: ambulatory blood pressure measurement; PO: oral; qd: once daily

Summary and Next Steps in Zilebesiran Development

Significant unmet need for treatment of hypertension in patients with uncontrolled blood pressure could potentially be addressed by zilebesiran

- Tonic BP control with infrequent dosing could benefit patients with difficult to treat hypertension or patients with uncontrolled blood pressure at risk for CV events
- Potential to become new antihypertensive treatment for patients with primary hypertension

Current data from ongoing Phase 1 study in patients with mild-to-moderate hypertension supports continued development

- Interim results include encouraging safety and tolerability profile
- ≥10 mmHg persistent reduction in 24-hr mean SBP at Week 8 at single doses ≥100mg, with clinically meaningful BP reduction maintained through Week 24
- Durability supportive of exploring once quarterly and biannual dosing

Initiation of KARDIA Phase 2 Program

- KARDIA-1 study of zilebesiran as monotherapy is open and actively enrolling patients
- KARDIA-2 study of zilebesiran as concomitant therapy with standard antihypertensive agents has initiated

Alzheimer's Disease and Cerebral Amyloid Angiopathy

Alnylam R&D Day

Sharon Cohen, MD FRCPC

November 19, 2021

Disclosures

Consultant to (no personal fees received):

- Alzheimer Society Toronto, Alnylam, Biogen, Conference Board of Canada, Cogstate, Cassava, Eisai, Eli Lilly, INmuneBio, PROmis Neurosciences, RetiSpec, Roche

Research grants (paid to institution only):

- AgeneBio, Alector, Alzheon, Anavex, Biogen, Cassava, Eli Lilly, Eisai, Green Valley, Janssen, Novo Nordisk, RetiSpec, Roche, Vielight

Objectives

To provide insights regarding Alzheimer's disease (AD) and cerebral amyloid angiopathy (CAA):

- Clinical presentation
- Etiology/pathophysiology/genetics
- Current treatment options
- Unmet need
- Future directions

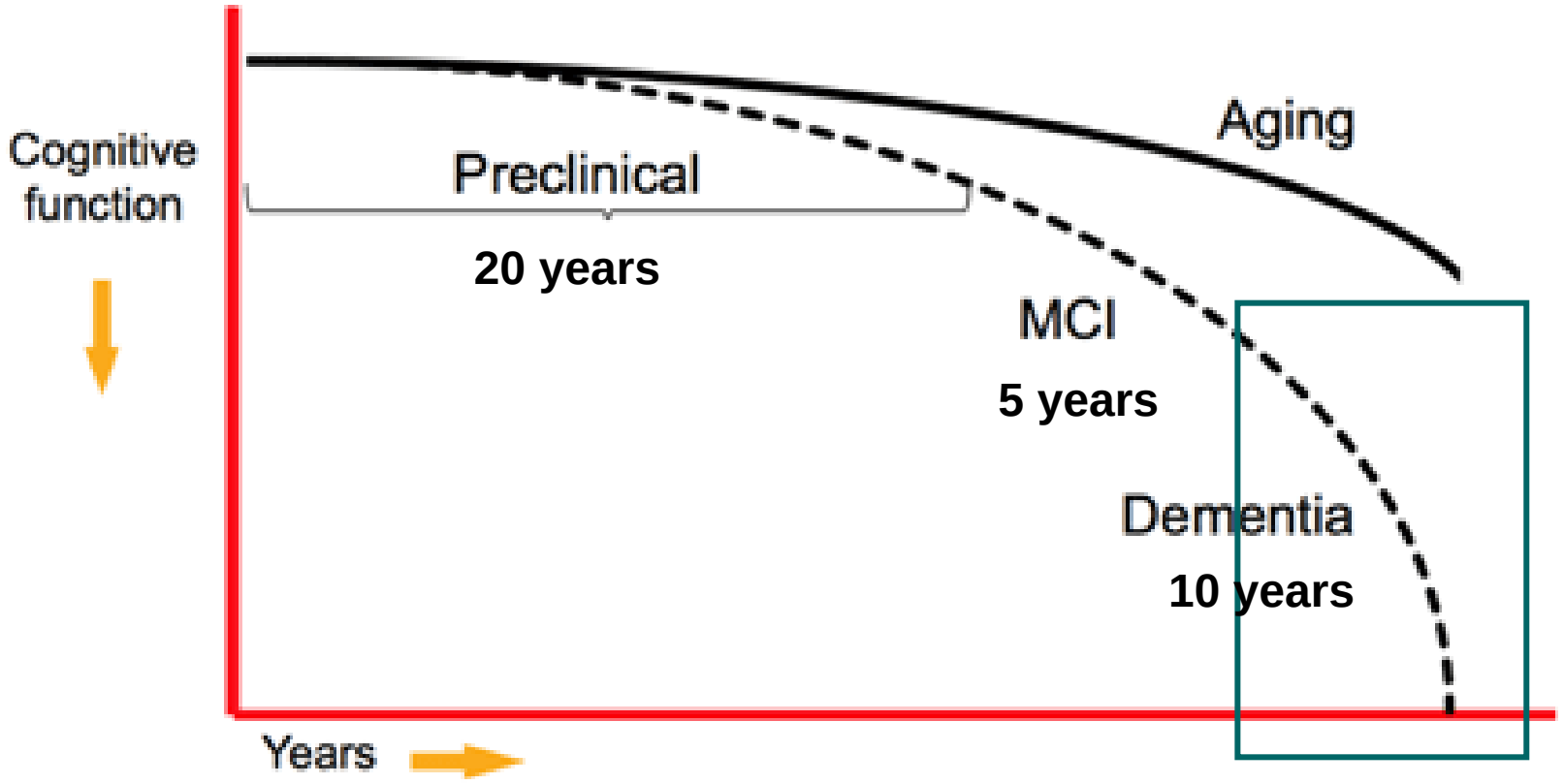
AD: An Urgent Health Care Priority

- An irreversible, fatal neurodegenerative disease
- The commonest cause of dementia in seniors
- 50 million cases worldwide; 150 M by 2050
- Enormous cost of care (formal and informal costs)
- No prevention or cure; modest symptom treatments; limited disease modifying treatment
- A major unmet medical need of our time

AD: A Clinical Continuum

- Cognitive and functional decline develop gradually over years and progress relentlessly; psychiatric symptoms are common and disabling
- 3 stages of AD recognized: preclinical, MCI, and dementia (NIA-AA 2011 Diagnostic Criteria)
- Typical and atypical presentations include:
  - Amnestic versus non-amnestic variants
  - Late onset versus young onset of symptoms
  - Pure AD versus AD with co-pathologies (e.g., AD plus cerebrovascular disease)

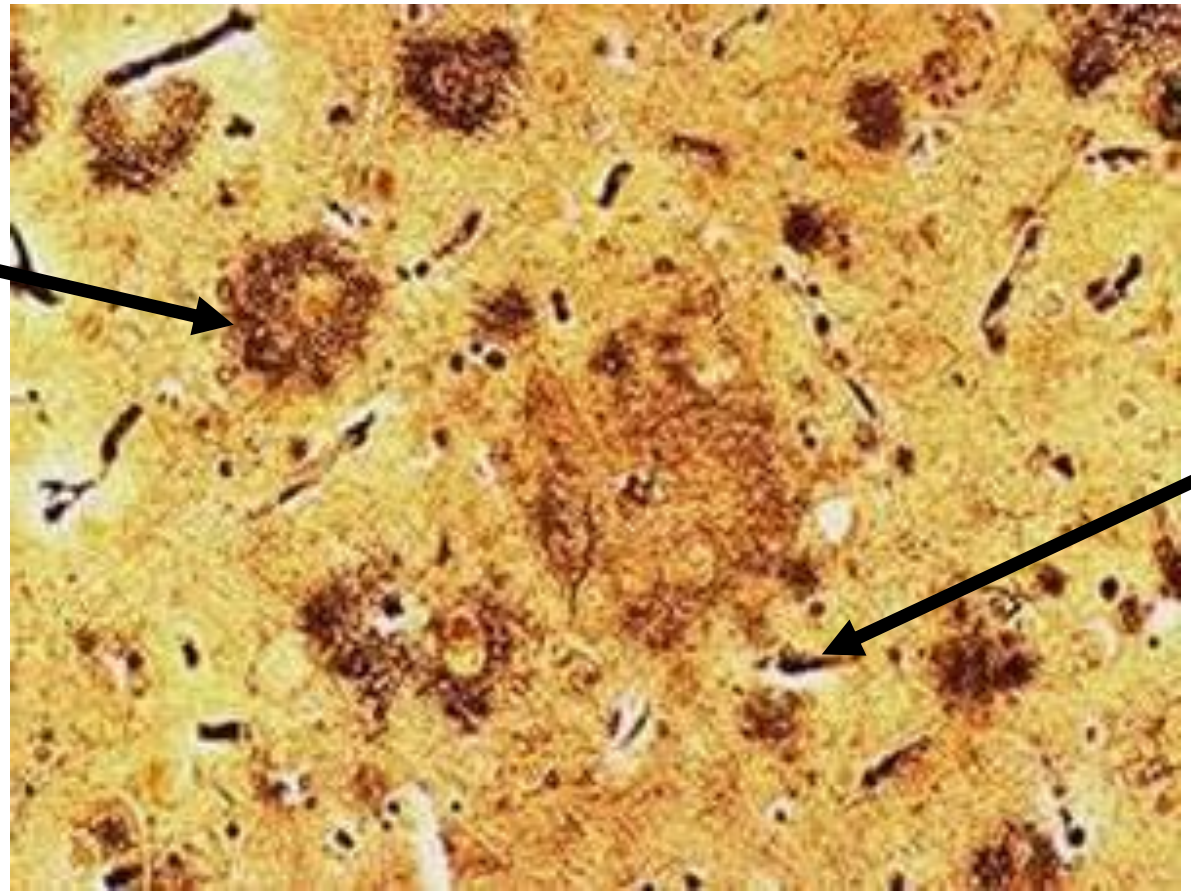
The Alzheimer's Continuum



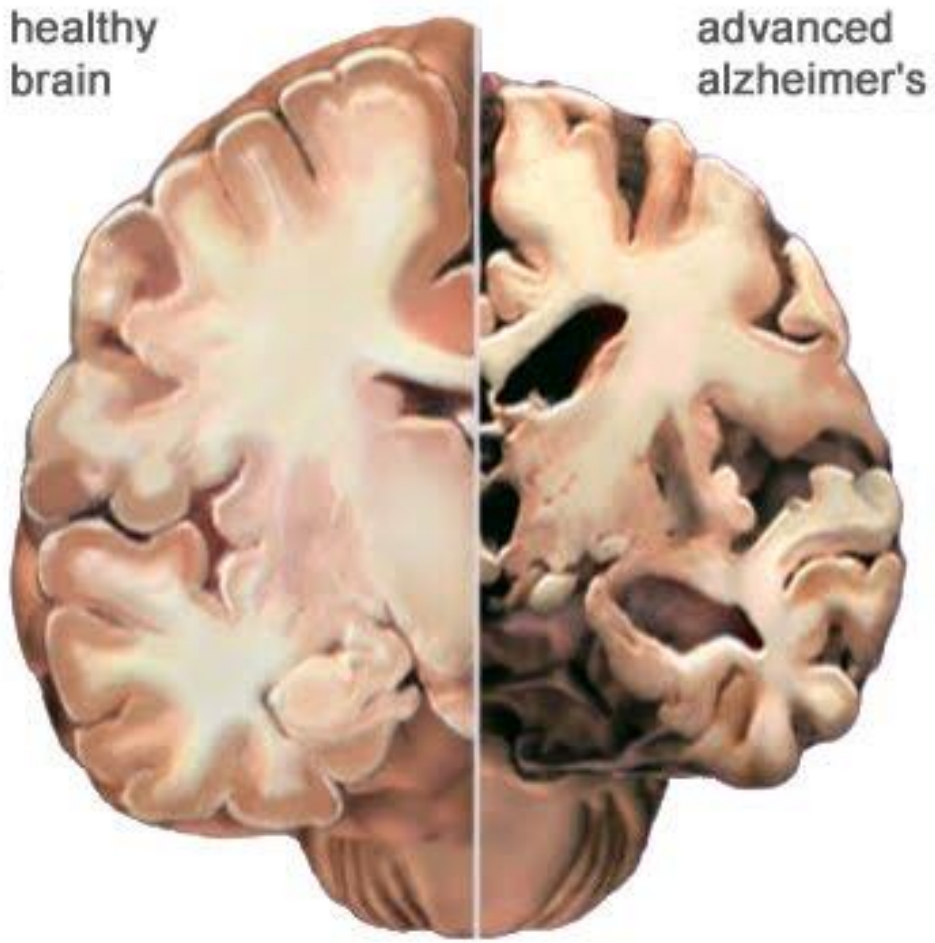
A 30 yr disease: 15 + 5 + 10

After Sperling 2011

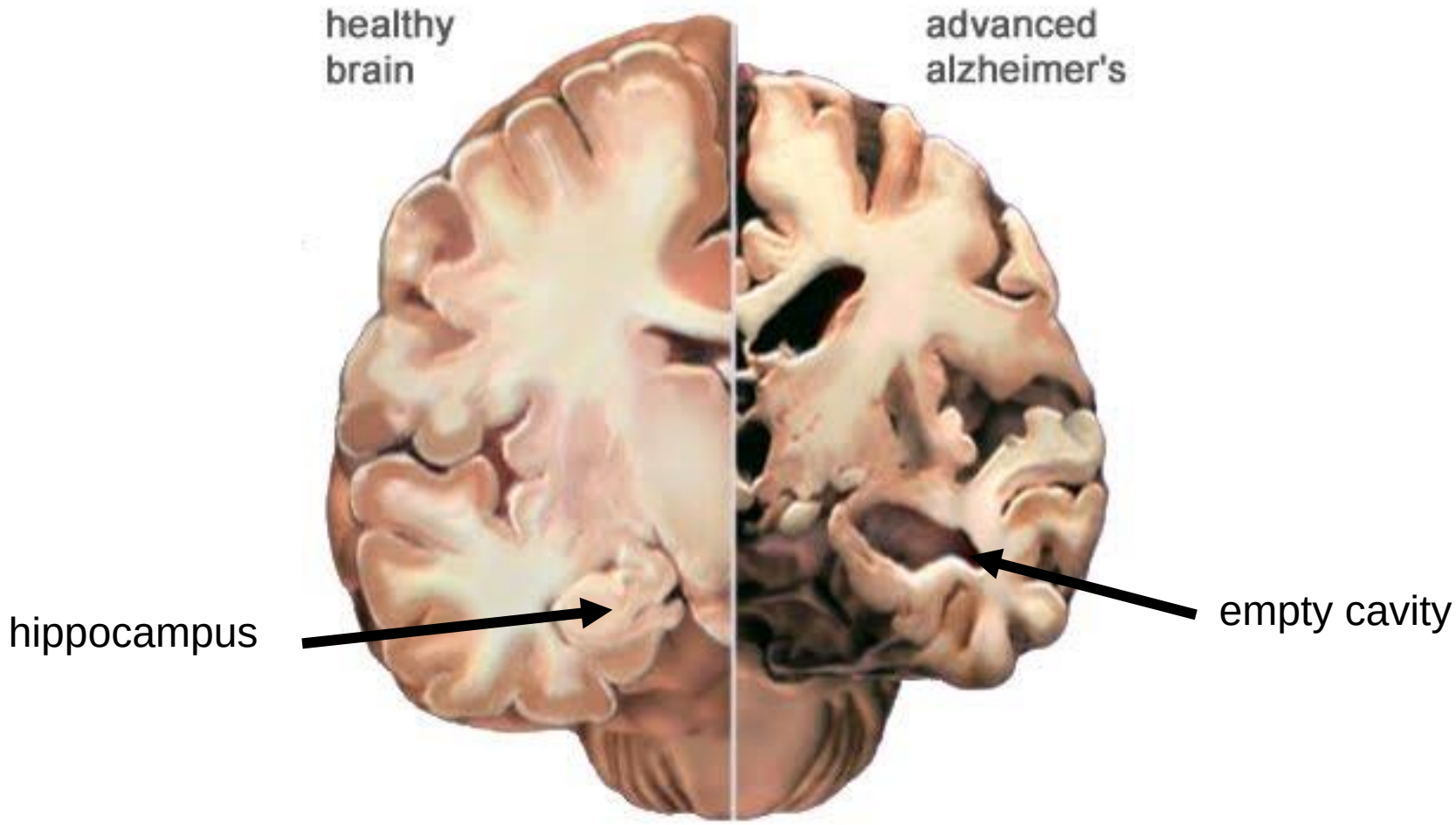
Amyloid Plaque and Tau Tangles



Profound Loss of Brain Cells



Profound Loss of Brain Cells



The Burden of AD

This is not a disease for the faint at heart

AD: A Disease of Personal Frustration and Despair

- Stigma, loneliness, loss of self, loss of dignity and autonomy over a very long period of time
- Progressive loss of knowledge, skills, and eventually, one's own biography
- Loss of decision-making and self-determination
- Psychiatric symptoms (e.g., delusions, agitation, wandering) further impact quality of life

AD: Significant Impact on Family

- Psychological distress of seeing a loved one deteriorate relentlessly
- Loss of key relationships (spouse; parent)
- Stress of juggling work and caregiving
- Financial burden of providing care
- Sleep deprivation; higher rate of depression, physical illness, injury, hospitalization

AD: Etiology/Pathophysiology

- Sporadic (99% cases); Inherited (1% cases)
- A complex pathobiology
- APP-derived amyloid-beta (Aβ42) accumulates early
  - Multiple “species” of AB42, soluble and insoluble, each with various toxicity
- Hyperphosphorylated tau impairs intraneuronal function
  - Spreads to adjacent cells causing regional neuronal death
- Additional pathologies:
  - Immune dysfunction; neuro-inflammation; others

Role of Genetics in AD

- Deterministic gene mutations on APP, PSEN1, PSEN2, cause autosomal dominant AD
  - All mutations increase Aβ production, especially Aβ42
  - Age of symptom onset typically under age 65
- Trisomy 21 (Down's syndrome) causes AD in mid-life
  - Extra copy of APP on chromosome 21 increases Aβ production
- In Sporadic AD, multiple risk genes play a role
  - Most risk genes deal with immunity and lipid metabolism
  - ApoE gene (ApoE4 allele) confers the greatest risk
  - A protective mutation on APP (Icelandic mutation) reduces Aβ production and risk for AD

Young Onset AD

Still Alice (2014)

8% of those with AD are under 65

Additional Burden For Those With Young Onset AD

- Greater financial impact on patient and family
- Greater delays in diagnosis
- Fewer services available
- Additional hours of care-giving required
- Increased rates of depression and severe psychiatric distress in patients and family

Existing AD Medications for Symptoms

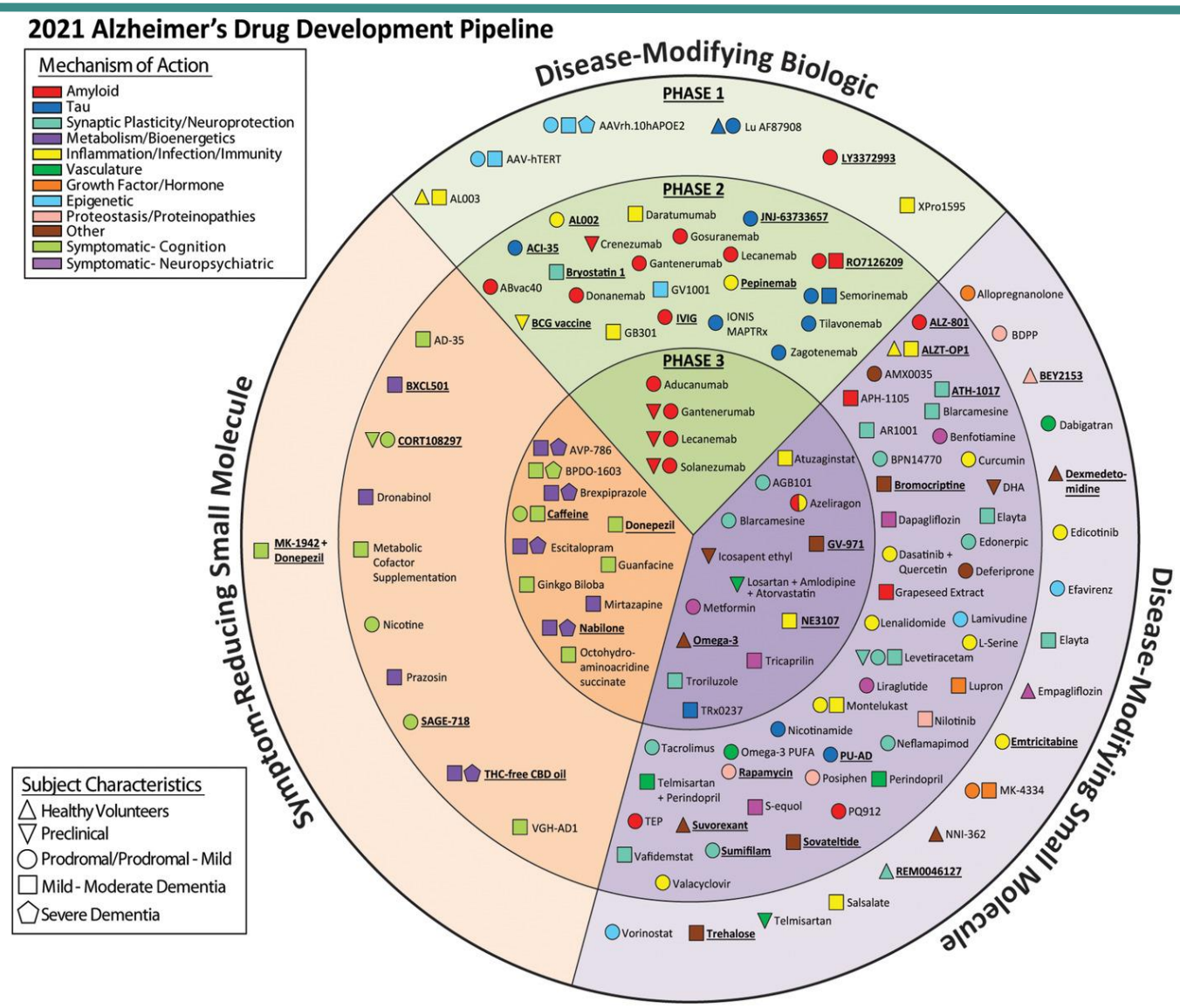
- Two classes available (for past 20+ years):
  - CHEIs: donepezil, galantamine, rivastigmine
  - Glutamate modulator: memantine
- Target downstream neurotransmitter loss
- Achieve modest impact on neurotransmitter levels and modest benefit to symptoms
- Do not address amyloid or tau
- Do not prevent or slow disease progression
- Are not approved for MCI stage of AD

Current Disease Modifying Medication

- First disease modifying drug for AD (aducanumab) approved by FDA in June 2021
- Accelerated approval based on robust amyloid lowering felt reasonably likely to yield clinical benefit; confirmatory trial required
- Since then, 3 other anti-amyloid mabs received breakthrough therapy designation and may be approved within the next few years
- These may, at best, slow decline by 20-30%; hence other approaches will remain necessary

The Current AD Pipeline

Cummings et al 2021



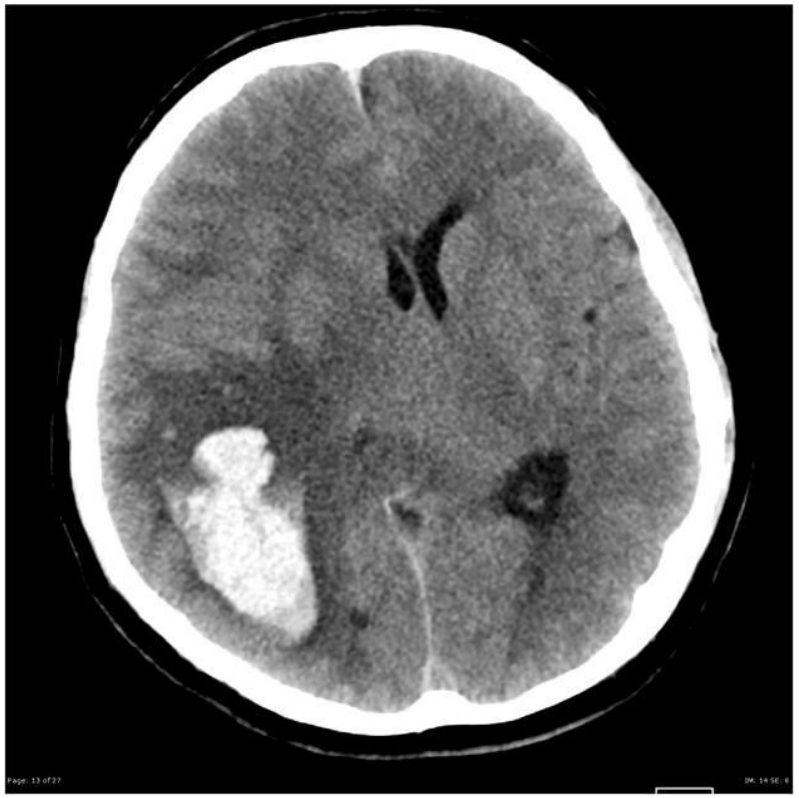
Cerebral Amyloid Angiopathy

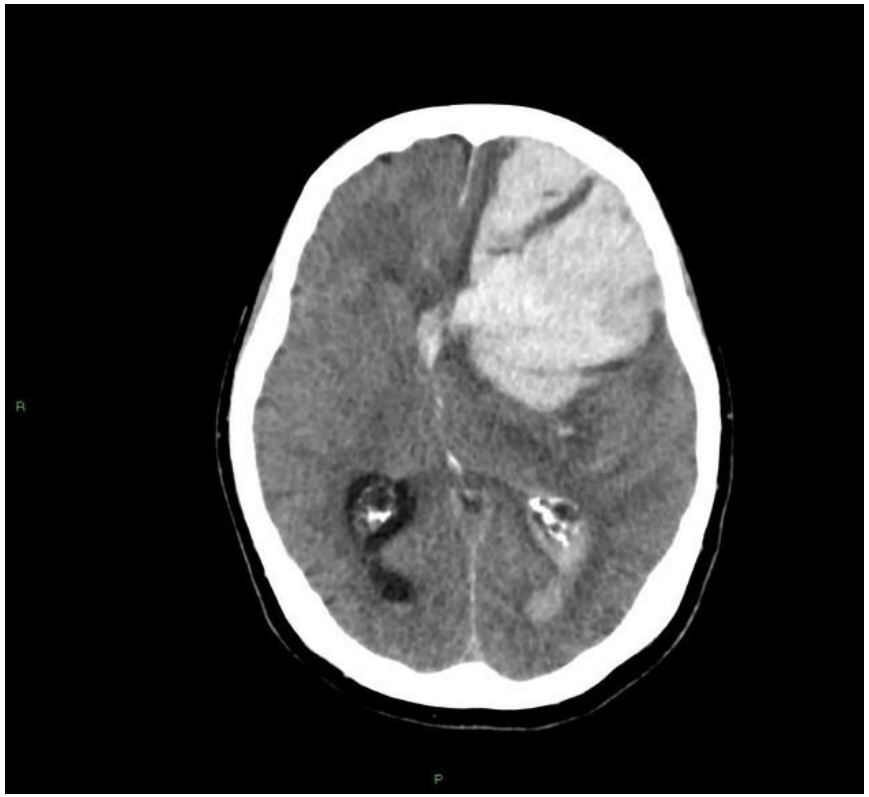
- A cerebrovascular disease caused by deposition of APP-derived Aβ40 in cerebral blood vessel walls
- CAA selectively involves cerebral vasculature unlike systemic amyloidosis which involves the heart and other organs
- All layers of the blood vessel wall are injured in CAA; vessels lose elasticity; microaneuryms form; vessels leak and rupture

CAA - Clinical Presentations

- Lobar hemorrhage most common
  - Affinity for temporal and occipital regions
  - Sudden headache and focal neurological deficits +/- loss of consciousness, seizure, death
- Convexal subarachnoid hemorrhage
  - Typically presents as a TIA with motor or sensory symptoms
  - Increases risk of future lobar hemorrhage
- Cerebral microbleeds (MBs)
  - Typically multiple and lobar in distribution
  - Increases risk for hemorrhage, ischemic stroke, dementia, shorter survival

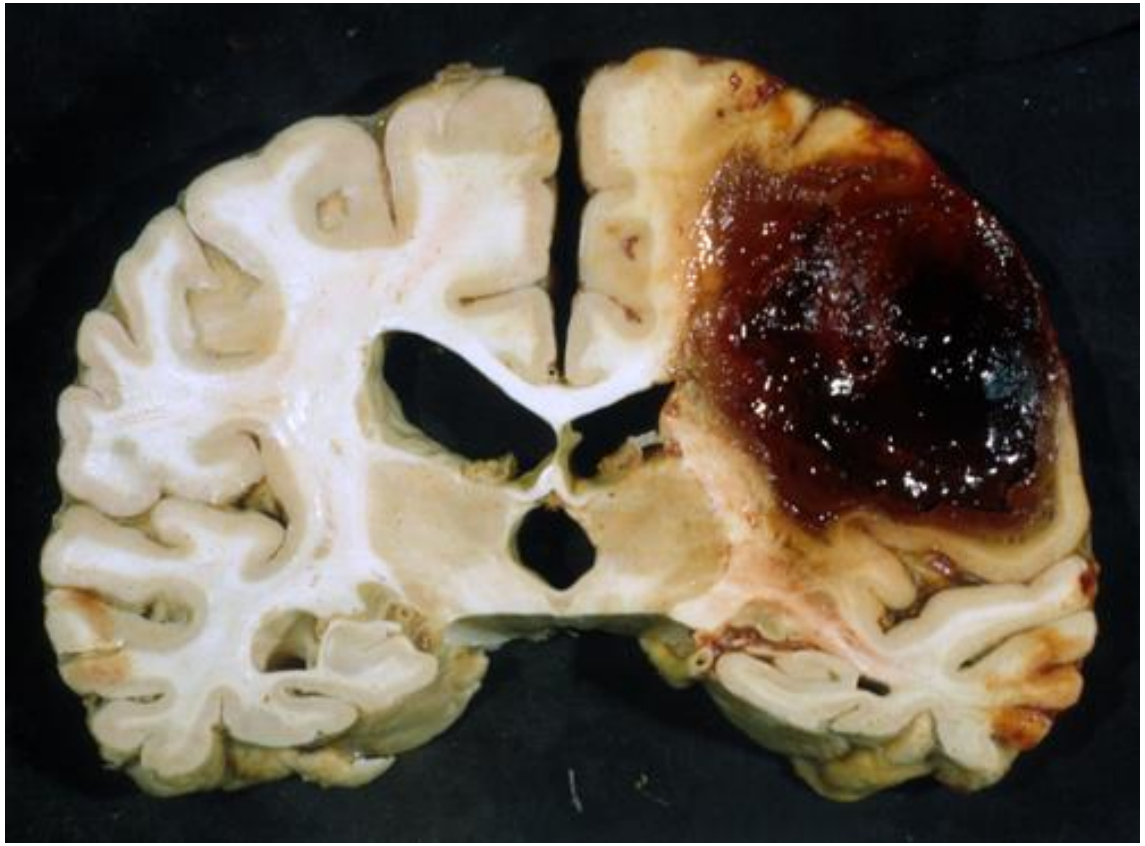
Lobar Hemorrhage in CAA





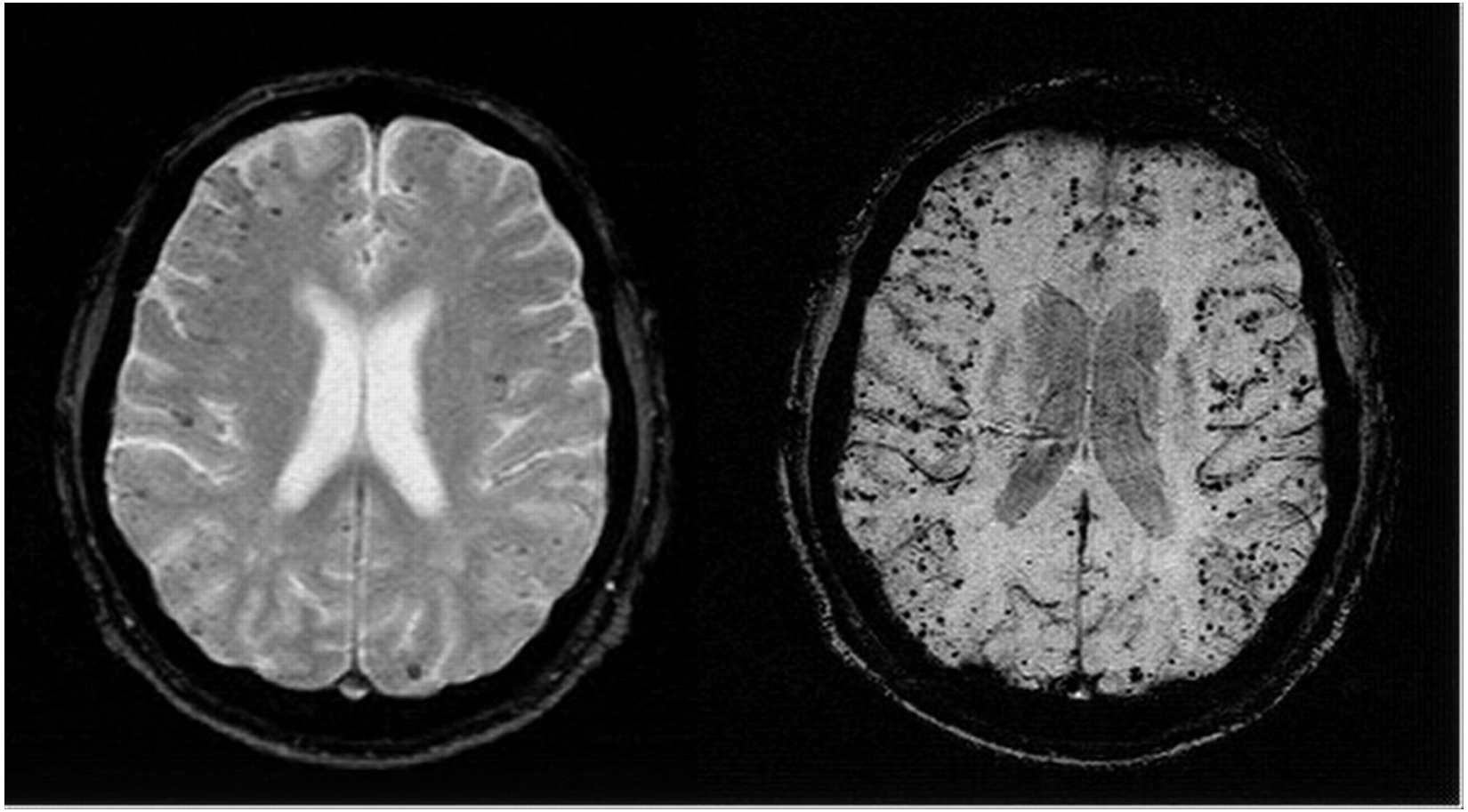
Radiopaedia.org.(accessed 8Nov/21) https://doi.org/10.53347/rID-24877
Radiopaedia.org. (accessed 8Nov/21) https://doi.org/10.53347/rID-5875

Lobar Hemorrhage in CAA



Neuropathology: An interactive course 2017 DIMITRI AGAMANOLIS

Cerebral Microbleeds in CAA



E.M. Haacke et al. AJNR Am J Neuroradiol 2007;28:316-317

Cerebral Amyloid Angiopathy

- Sporadic and inherited types
- Sporadic type is common and presents in the elderly as hemorrhagic stroke
- Hereditary forms (Dutch type most common)
  - Most due to mutations in APP gene; autosomal dominant
  - Increased production and deposition of Aβ40 in vessels
  - Stroke and dementia begin in mid-adult life (50s)
  - Recurrent strokes are common. Seizures may also occur
  - Death usually within a decade of first symptoms
- Current treatment consists of supportive care

In Summary

- AD and CAA are devastating brain diseases with distinct abnormalities downstream of APP metabolism
- APP is a genetically validated target as evidenced by multiple gene mutations that directly cause AD and CAA
- AD is a slowly progressing dementing illness in which Aβ42 accumulates in brain parenchyma; CAA is a cerebrovascular disease with Aβ40 accumulation in vessel walls leading to brain hemorrhage +/- dementia
- Both have a common sporadic form with late-life onset, as well as hereditary forms with younger age of onset

In Summary (continued)

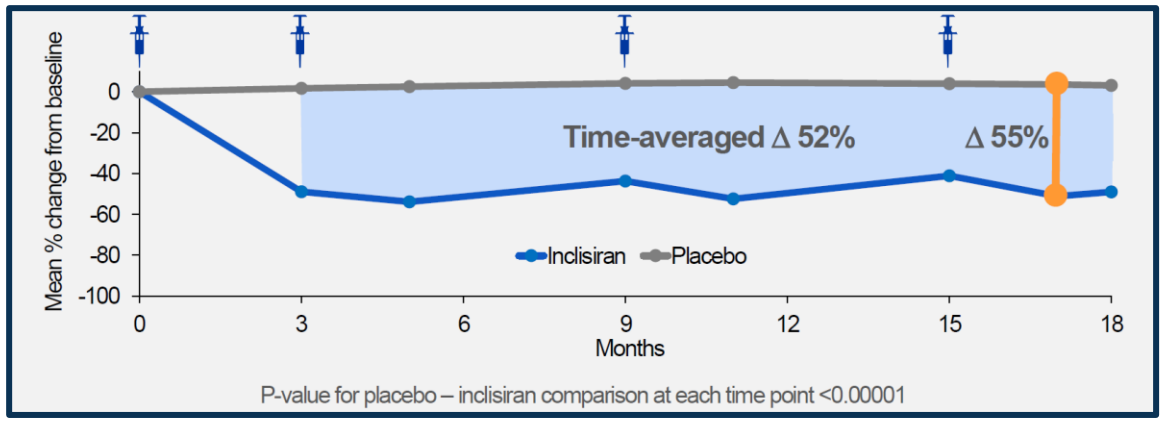
- Current AD treatments are largely symptomatic, only modestly effective, and downstream of key pathology
- Newer disease modifying treatment for AD with anti-amyloid antibodies will alone be insufficient to prevent, cure, or stabilize AD
- No specific therapies are currently available for CAA
- Upstream approaches with potential to block proximal mechanisms, such as APP metabolism, are of high interest as they may address a broad cascade of intra-cellular and extra-cellular pathological processes

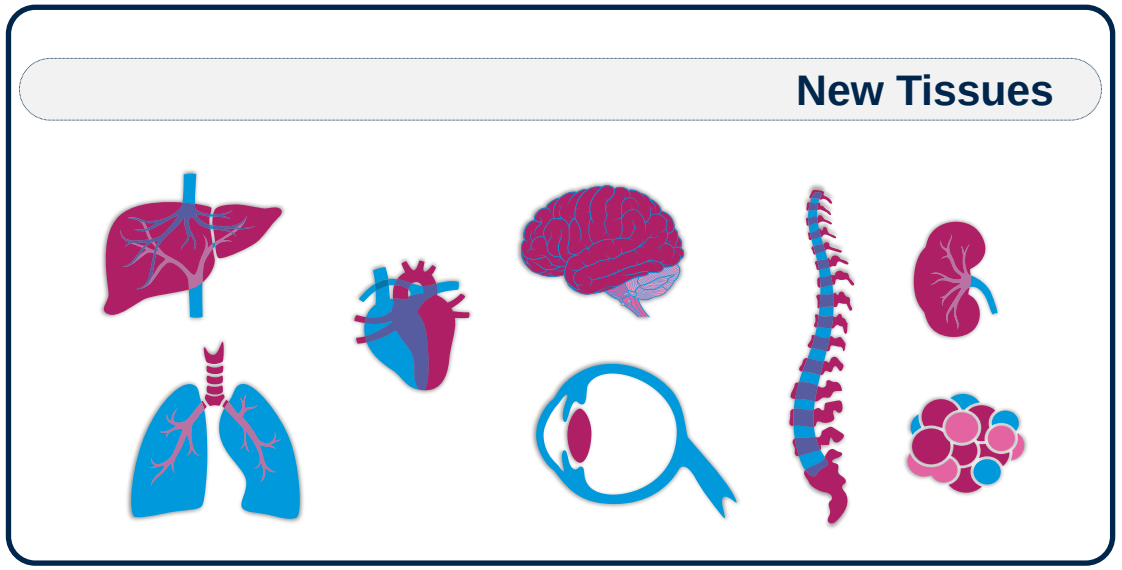
Beyond the Liver with RNAi Therapeutics

Kevin Fitzgerald, Ph.D.
Chief Scientific Officer

Alnylam PHARMACEUTICALS

Alnylam Platform Expands Potential Opportunities for Novel RNAi Therapeutics





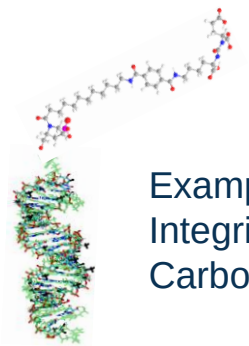
- siRNA/AGO2 mechanism well conserved in all tissues studied to date
- PK/PD relationships with RNAi therapeutics are also conserved across tissues
  - Similar duration of effect in CNS, Ocular as in the liver

Alnylam Strategy: GalNAc-Like Ligands for Tissues of Medical Importance

Focus on tissues/cell types with high value targets → ID suitable cell surface receptor(s) → Ligand selection (library screen) → Conjugation and RLP evaluation → In vivo proof-of-concept, conjugate optimization → Species translation, safety → Transition to development

Ligand platforms to support identification of novel receptor ligand pairs

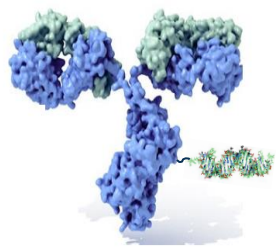
Small Molecules



Examples:
Integrin ligands,
Carbohydrates

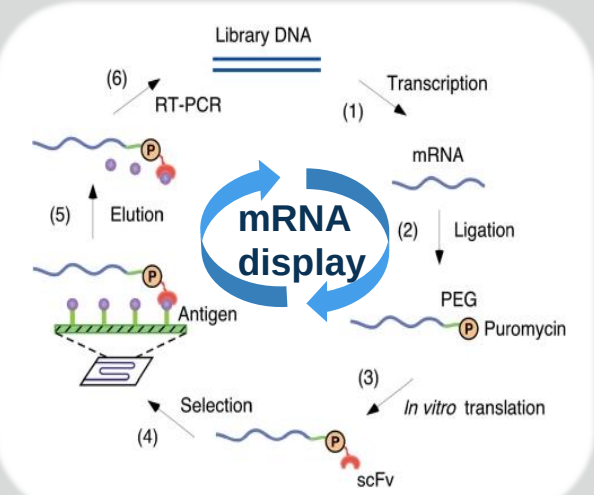
Ex. GalNAc
C16, others

Antibodies/Nanobodies



Ex. Ongoing Collaborations

Peptides



Ex. PeptiDream

Alliances in Extrahepatic Discovery and Development

REGENERON

- Landmark alliance with Regeneron focused on CNS & ocular RNAi therapeutics
  - Leverages Alnylam R&D expertise and scientific excellence in RNAi therapeutics, in combination with Regeneron's world-leading capabilities in human genetics
  - 50-50 structure in CNS, with Regeneron leading development and commercialization of all programs targeting eye diseases.

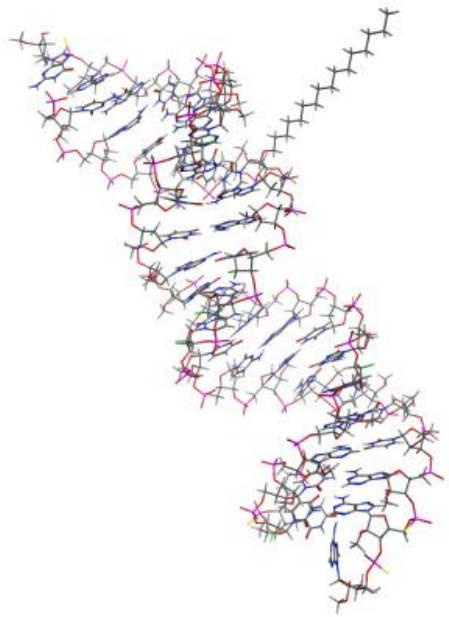
PeptiDream

- Collaboration to discover and develop peptide-siRNA conjugates for targeted delivery of RNAi therapeutics to a broad range of extrahepatic tissues
  - PeptiDream to select, optimize, and synthesize peptides for Alnylam-selected receptors utilizing its peptide discovery platform
  - Final peptide selection to be supported by *in vitro* and *in vivo* studies evaluating novel peptide-siRNA conjugates

CNS Platform Objectives

Potential for Best-in-Class CNS Oligonucleotide Delivery Platform

- **Robust knockdown**
- **Wide biodistribution in CNS**
- **Long duration of action**
- **Favorable benefit / risk profile**



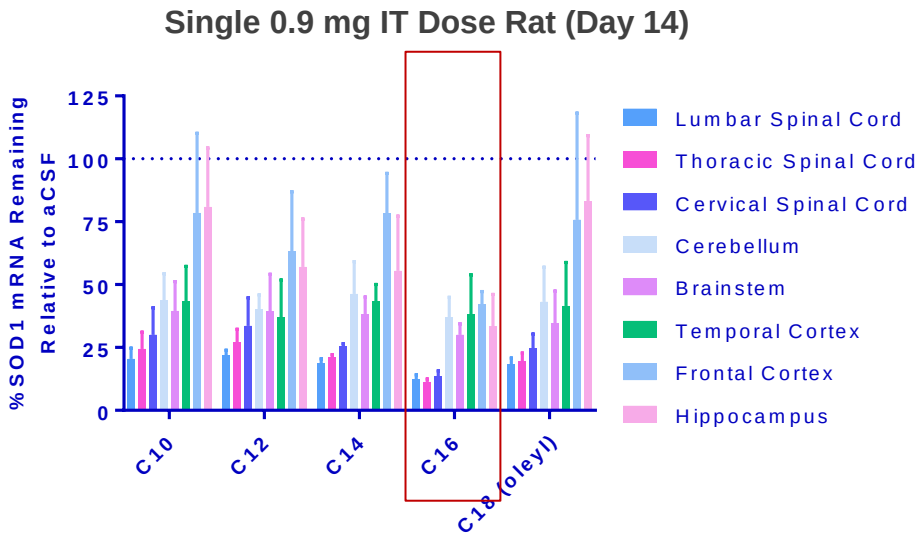
C16 Conjugate

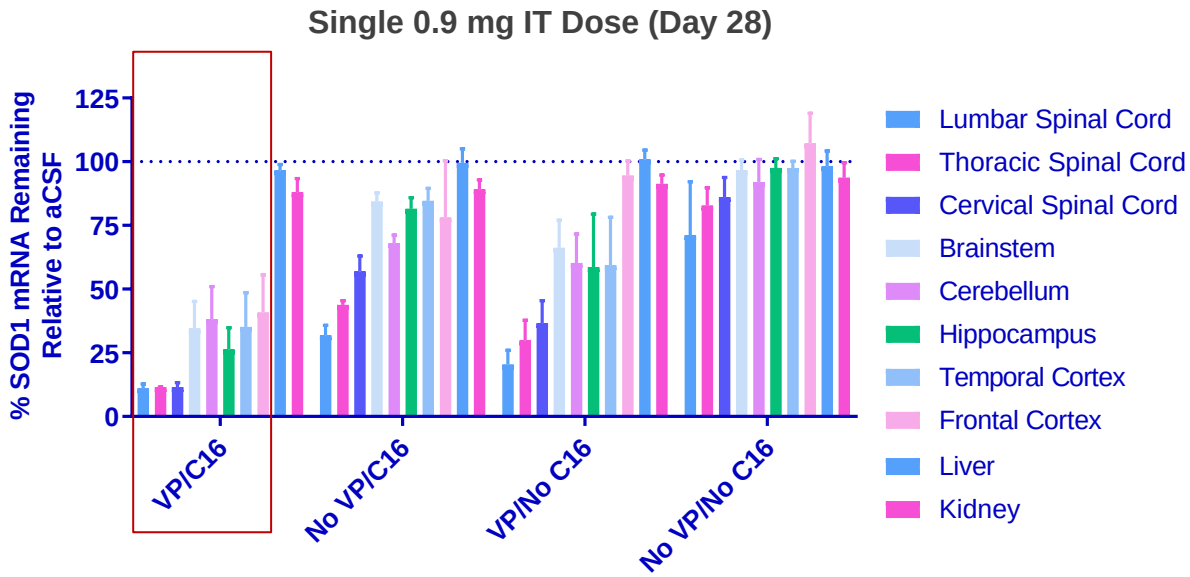
C16 Conjugate Platform

Optimized for CNS Delivery of RNAi Therapeutics

C16 conjugate platform designed to optimize potency, durability, and safety

- Exhaustive optimization of siRNA lipophilic moiety, position, and design chemistry
- Backbone modifications to enable similar metabolic stability to liver platform (e.g., ESC+)
- Vinylphosphonate (VP) modification improves potency through enhanced RISC-binding

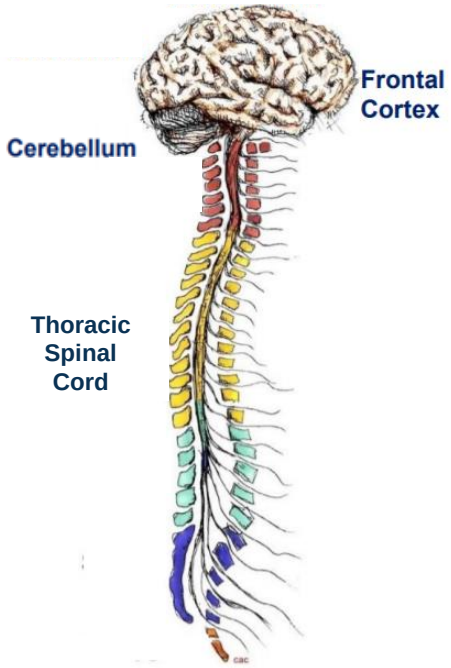


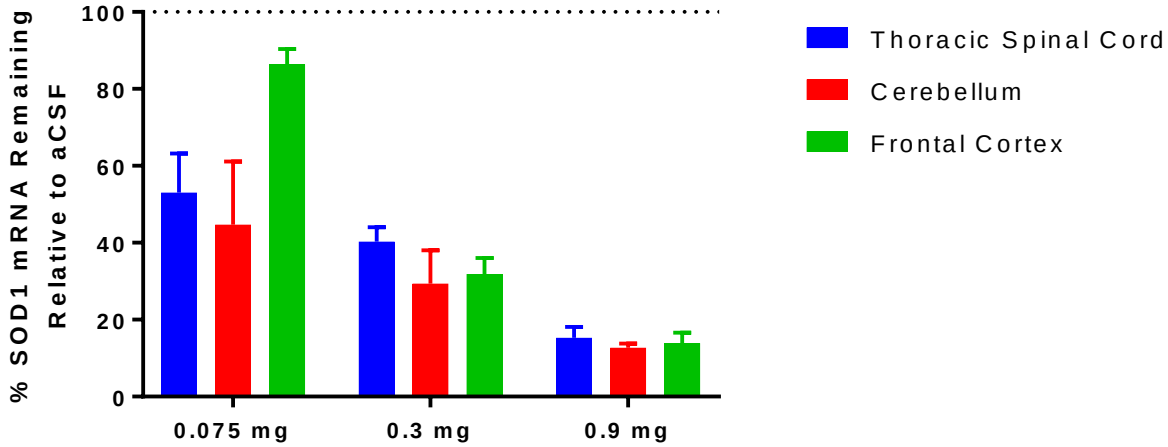


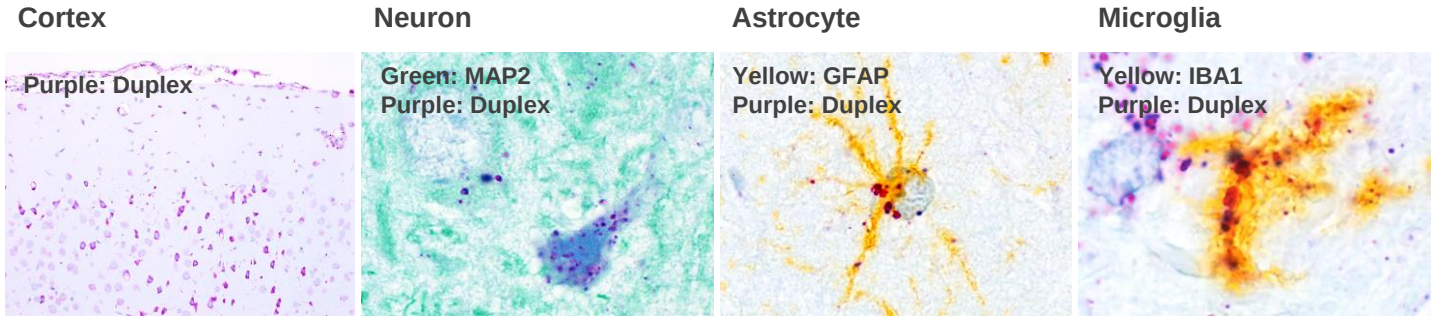
Robust Silencing Throughout Brain and Spinal Cord

Intrathecal Delivery of siRNA to Cell Types and Tissues Throughout CNS

Potent, dose dependent knockdown in cell types and tissues of rat spinal cord and brain







APP as a Target for Alzheimer's Disease (AD)

Alzheimer's Disease is Most Common Cause of Dementia Worldwide

High prevalence and high unmet need for new therapies

- Over 5M people affected by AD in the US (over 30M worldwide); population continues to grow as the population ages
- Life expectancy for those diagnosed after age 65 is 4-8 years
- Early-onset and genetic forms impact cognition earlier in life
- Limited progress in development of disease modifying therapies

Genetically Validated Target	✓	• Mutations that increase APP production or alter APP processing cause early-onset AD • Mutations decreasing APP processing are protective
Biomarker In Phase 1	✓	• Target engagement: sAPPα, sAPPβ in CSF • Disease progression: Fluid biomarkers (Aβ, tTau, pTau, NfL, etc.), neuroimaging
Definable Path to Approval	✓	• Multiple populations for potential development • High unmet need for disease modifying therapy • Emerging regulatory pathways

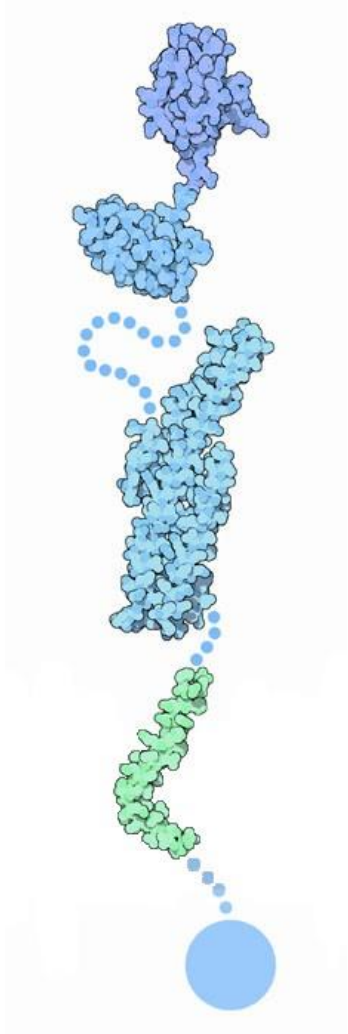
Multiple Development Opportunities

- **Early Onset AD (<65 yo) (EOAD)**
  - Autosomal Dominant AD (ADAD)
  - Non-familial early onset AD (nf-EoAD)
  - Down Syndrome AD
- **Late Onset AD (>65 yo) (LOAD)**
- **Sporadic AD (All non-familial AD)**

2020 AD Facts and Figures, *Alzheimer's Dementia* (2020); WHO Dementia Fact Sheet (2021); Tom SE, et al., Am J Public Health (2015)

Amyloid Precursor Protein (APP)

Alzheimer's Disease and Cerebral Amyloid Angiopathy



One target, two distinct pathological processes

- APP is an 87 kDA membrane-associated protein produced in many tissues, but with the highest expression in the nervous system
- APP is processed via serial cleavage by various enzymes (α-, β-, and γ-secretase) to produce a variety of peptides, including Aβ
- APP is a genetically validated target for both Alzheimer's Disease and Cerebral Amyloid Angiopathy

Alzheimer's Disease (AD)

- APP mutations and duplications cause Early Onset AD
- Amyloid deposits in brain tissue, tau tangles in neurons, neurodegeneration

Cerebral Amyloid Angiopathy (CAA)

- APP mutations cause hereditary CAA
- Amyloid deposits in the walls of the arteries in the brain and causes cerebral hemorrhages and dementia

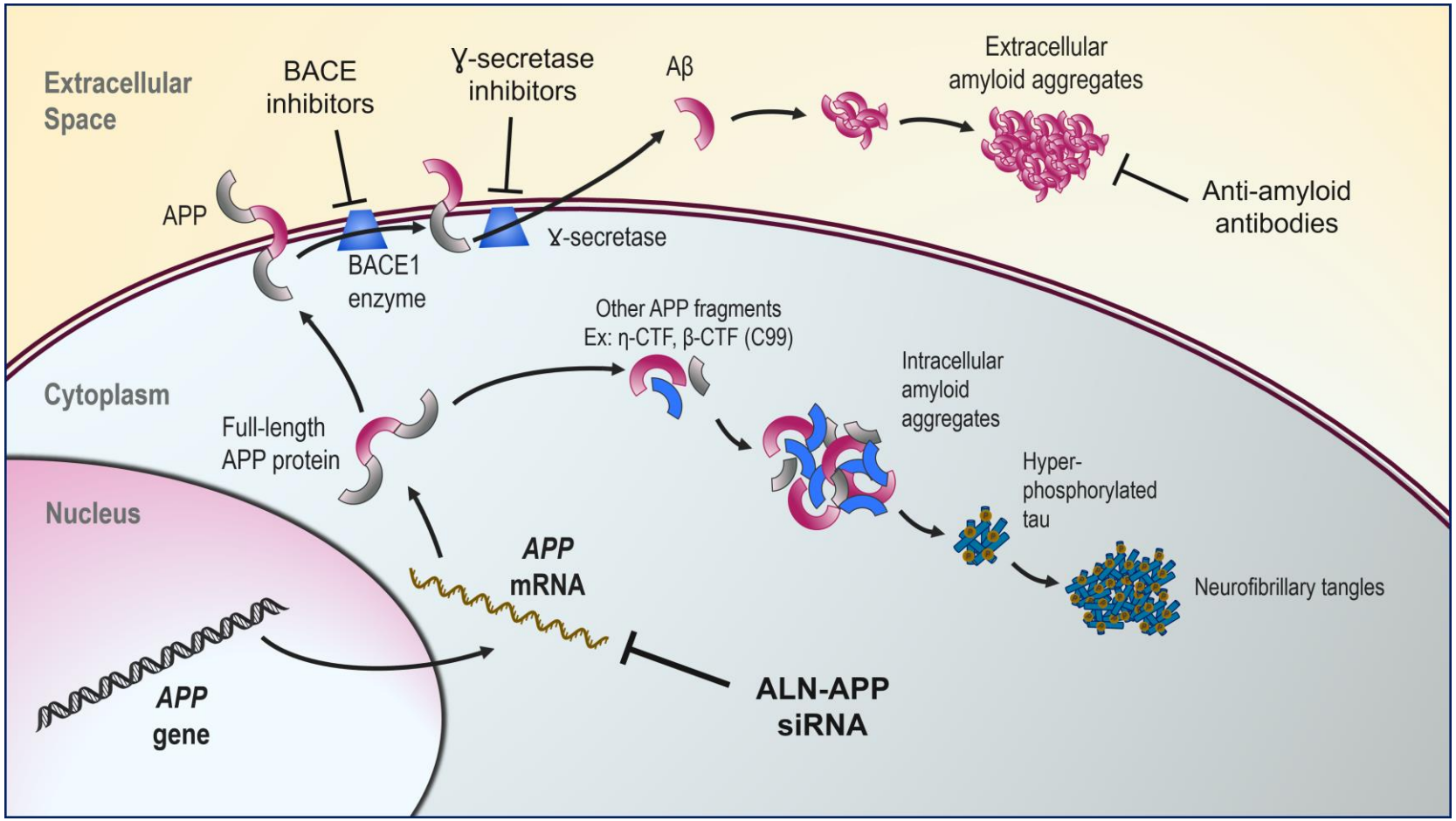
APP Protein Structure courtesy of David S. Goodsell and the RCSB Protein Data Bank

Therapeutic Hypothesis: Alzheimer's Disease

A New Approach: Targeting the APP Protein

Lower APP production *at its source*, upstream of the pathogenic process

- Reduce ***both intracellular and extracellular*** drivers of disease pathology
- ***Reduce all APP cleavage products*** including all species of Aβ
- Removing substrate for amyloid deposit formation and ***potentially enabling natural clearance***



What About the Role of INTRAcellular Aβ in Alzheimer's Pathogenesis?

NATURE REVIEWS | NEUROSCIENCE

Intracellular amyloid-β in Alzheimer's disease

Frank M. LaFerla, Kim N. Green and Salvatore Oddo

PNAS

Mechanism of amyloid plaque formation suggests an intracellular basis of Aβ pathogenicity

Ralf P. Friedrich[a,1,3], Katharina Tepper[a,b,1], Raik Rönicke[c], Malle Soom[a], Martin Westermann[d], Klaus Reymann[c], Christoph Kaether[a], and Marcus Fändrich[a,b,e,2]

RESEARCH Open Access

Intracellular amyloid β oligomers impair organelle transport and induce dendritic spine loss in primary neurons

Tomohiro Umeda[1,2], Elisa M. Ramser[3], Minato Yamashita[1], Koichi Nakajima[4], Hiroshi Mori[2,5], Michael A. Silverman[3*] and Takami Tomiyama[1,2*]

frontiers in AGING NEUROSCIENCE

REVIEW ARTICLE
published: 10 March 2010
doi: 10.3389/fnagi.2010.00008

Intracellular accumulation of amyloid-beta – a predictor for synaptic dysfunction and neuron loss in Alzheimer's disease

*Thomas A. Bayer and Oliver Wirths**

Division of Molecular Psychiatry and Alzheimer Ph.D. Graduate School, Department of Psychiatry, University of Göttingen, Göttingen, Germany

OPEN ACCESS Freely available online

PLOS ONE

Accumulation of Intraneuronal β-Amyloid 42 Peptides Is Associated with Early Changes in Microtubule-Associated Protein 2 in Neurites and Synapses

Reisuke H. Takahashi[1,2]*, Estibaliz Capetillo-Zarate[2], Michael T. Lin[2], Teresa A. Milner[2,3], Gunnar K. Gouras[2,4]*

Intracellular Accumulation of Amyloid-β (Aβ) Protein Plays a Major Role in Aβ-Induced Alterations of Glutamatergic Synaptic Transmission and Plasticity

Cristian Ripoli,[1]* Sara Cocco,[1]* Domenica D. Li Puma,[1] Roberto Piacentini,[1] Alessia Mastrodonato,[1] Federico Scala,[1] Daniela Puzzo,[2] Marcello D'Ascenzo,[1] and Claudio Grassi[1]

THE JOURNAL OF BIOLOGICAL CHEMISTRY Vol. 277, No. 18, Issue of May 3, pp
© 2002 by The American Society for Biochemistry and Molecular Biology, Inc.

Intracellular Amyloid-β1–42, but Not Extracellular Soluble Amyloid-β Peptides, Induces Neuronal Apoptosis*

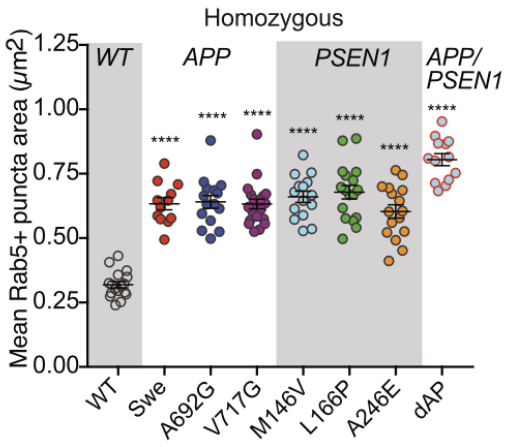
Prion-like seeding and nucleation of intracellular amyloid-β

Tomas T. Olsson*, Oxana Klementieva, Gunnar K. Gouras*

Experimental Dementia Research Unit, Dept. of Experimental Medical Science, Lund University, Lund, Sweden

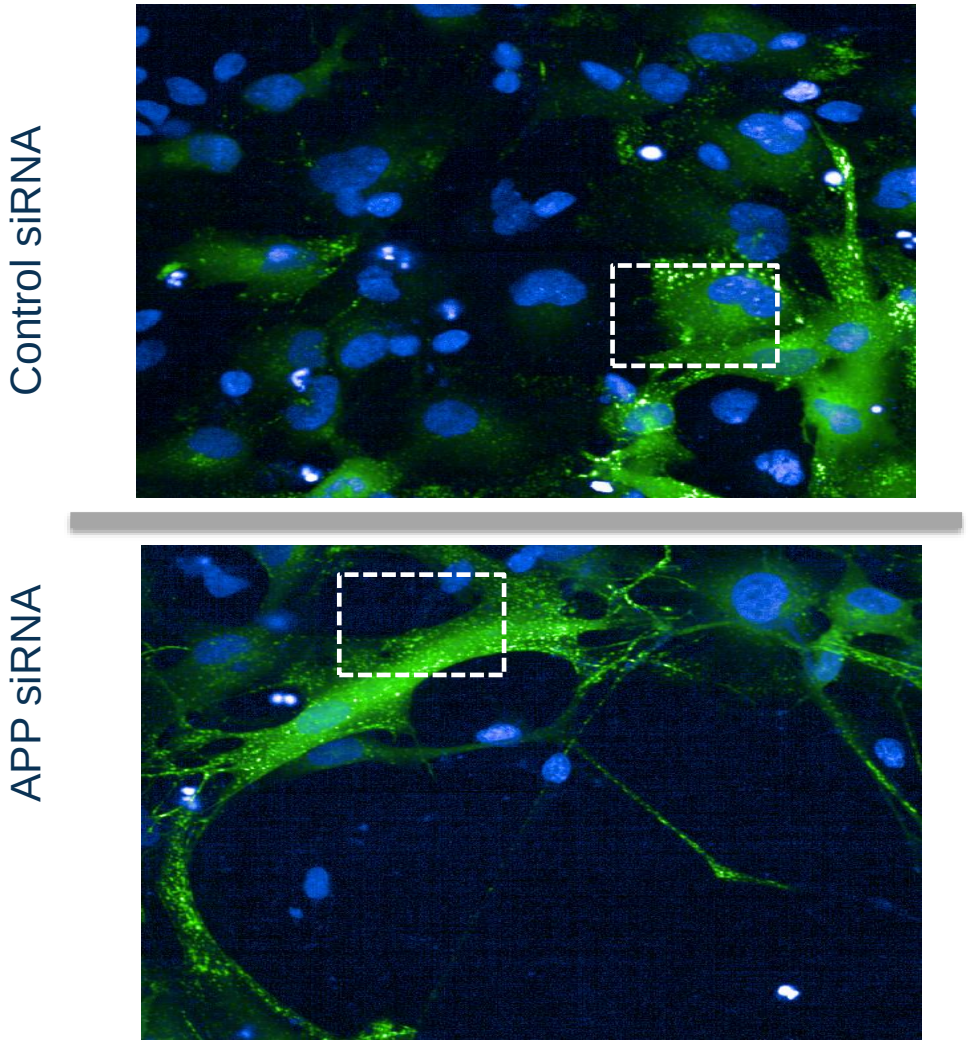
1. LaFerla, et al. Nat Rev Neurosci 8, 499–509 (2007)
2. Bayer et al. Front Aging Neurosci. 2010
3. Ripoli et al Neurobioilogy of Disease 2014
4. Umeda et al. Acta Neuropathologica Communications (2015)
5. Friedrich et al PNAS 2010
6. Kienlen-Campard et al 2002
7. Olsson et al. Neurobiology of disease 2018
8. Takahashi et al. PLOS One 2013

PSEN1 ^{A246E} Patient iPSC-Derived Neurons Treated with APP siRNA Show Reduction in Rab5+ Early Endosome Size

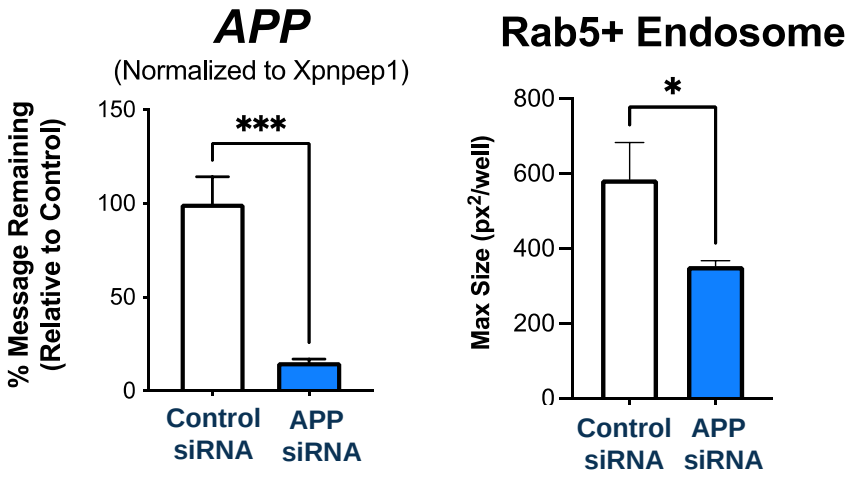


Mutations in APP and PSEN1 cause enlargement of Rab5+ Early Endosomes in human iPSC derived Neurons

Kwart et al., Neuron 2019

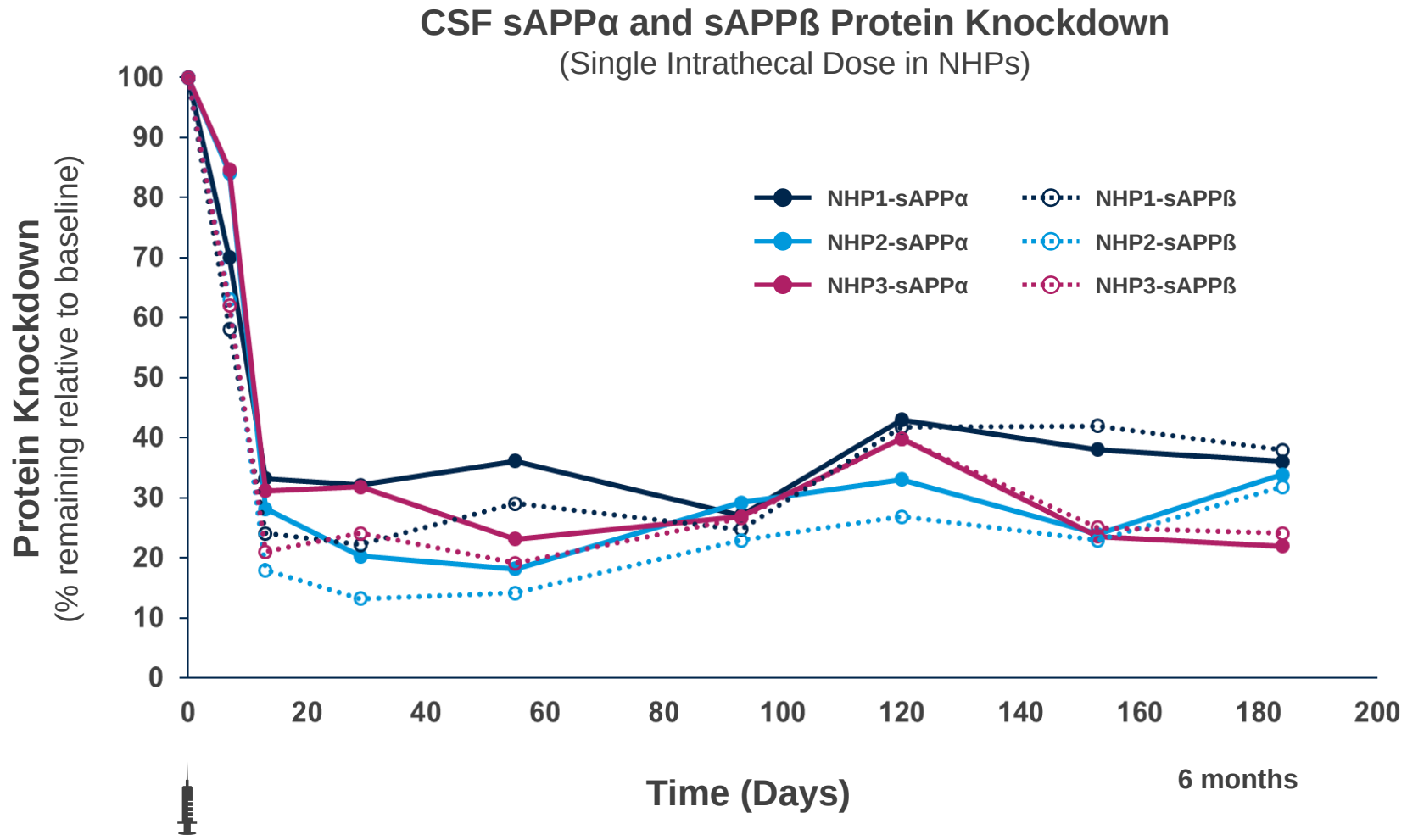


Phenix High Content Imaging, 63X, analysis on Harmony



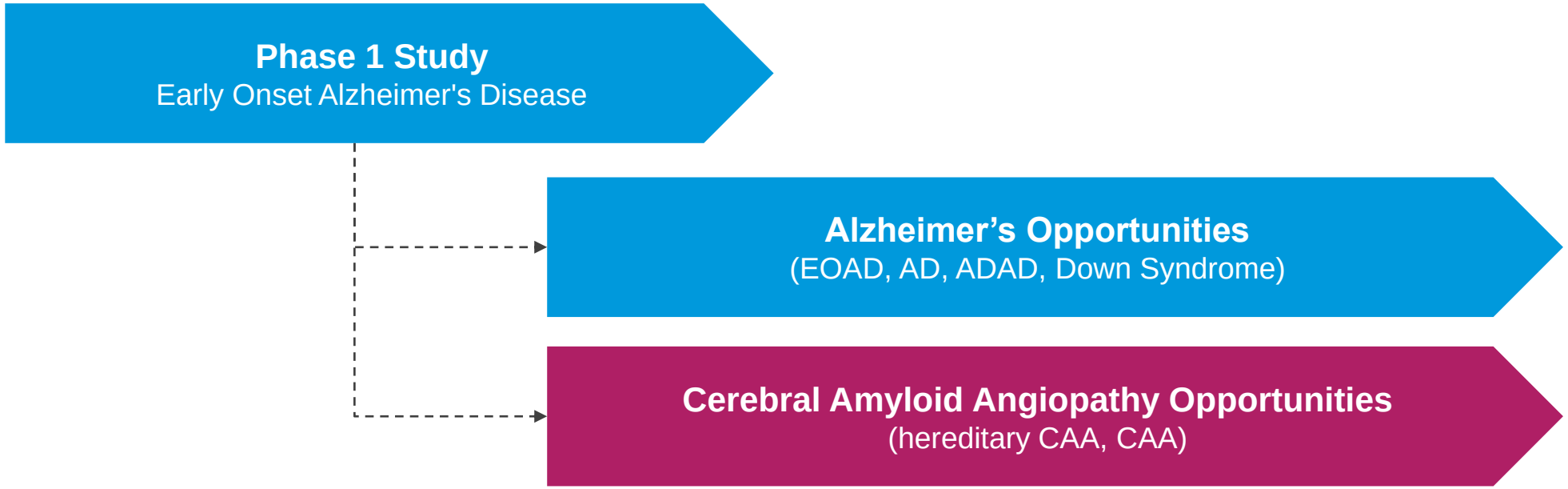
Lowering of Amyloid Precursor Protein in NHPs (APP)

Target Knockdown with Single Dose siRNA in NHP



Multiple Opportunities for Expansion

Phase 1 for Investigational ALN-APP to Inform Late-Stage Development Plan



Significant opportunity for both Alzheimer's Disease and Cerebral Amyloid Angiopathy

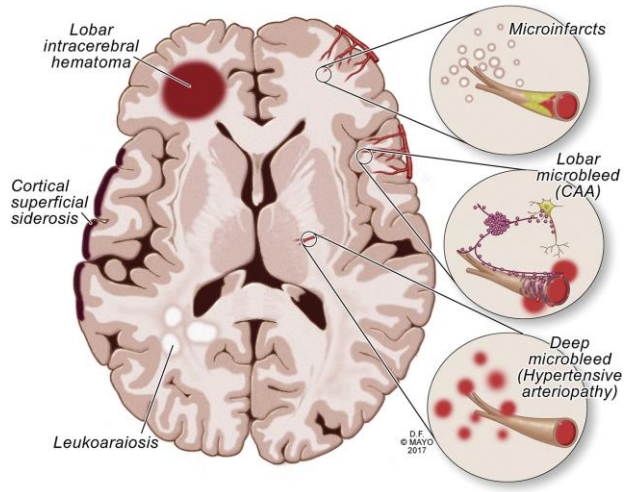
- Multiple disease area opportunities with the same target; different disease processes, development strategies, competitive environment enable strategic options for future development

APP as a Target for Cerebral Amyloid Angiopathy (CAA)

Cerebral Amyloid Angiopathy is an Underdiagnosed Cause of Stroke and Dementia

Increasing awareness and diagnosis, but no targeted therapies

- >20% of the general elderly population have moderate-to-severe CAA pathology and higher risk of stroke and dementia
- CAA is the second most common risk factor for intracerebral hemorrhage (ICH) after hypertension
- Diagnosis increasing with increased neuroimaging
- No targeted therapies have been developed for CAA



Genetically Validated Target	✓	• Mutations that alter APP cleavage and Aβ aggregation cause hereditary CAA
Biomarker In Phase 1	✓	• Target engagement: sAPPα, sAPPβ • Disease progression: Measures of vascular reactivity (BOLD fMRI)
Definable Path to Approval	✓	• High unmet need for disease modifying therapy • Biomarkers for vascular reactivity • Orphan population with hereditary CAA

Multiple Development Opportunities

Hereditary CAA: Ultra-orphan genetically defined population found primarily in the Netherlands and Australia; onset in 40s/50s

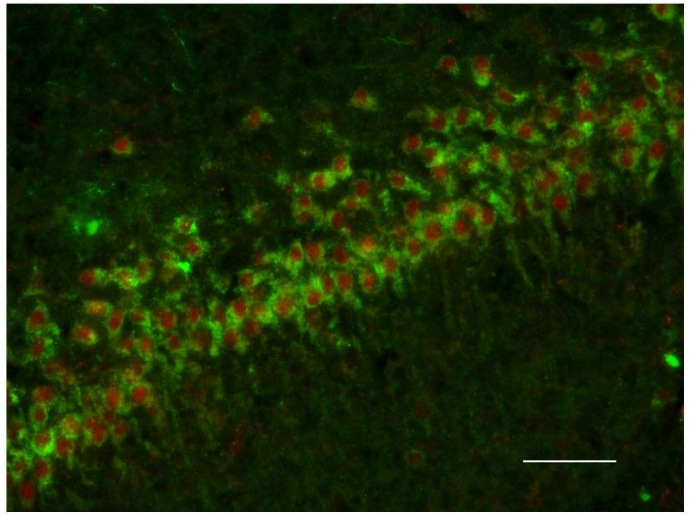
Sporadic CAA: Common cause of ICH that increases with age. Onset typically after age 60

Jäkel L, et al., Alzheimer's Dement (2021); Aguilar MI, et al., Neurohospitalist (2012); Kozberg MG et al., Int J Stroke (2020).
Figure republished with permission of the American College of Cardiology from DeSimone CV, et al., J Am Coll Cardiol (2017)

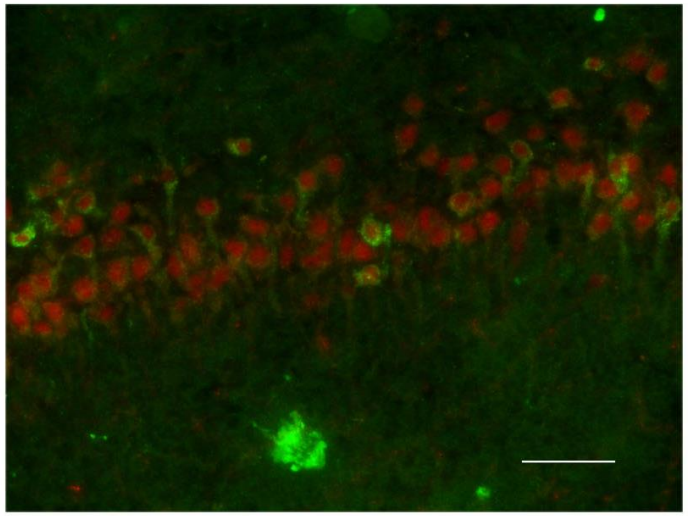
Complete Elimination of Human APP Protein in Rat hCAA Model

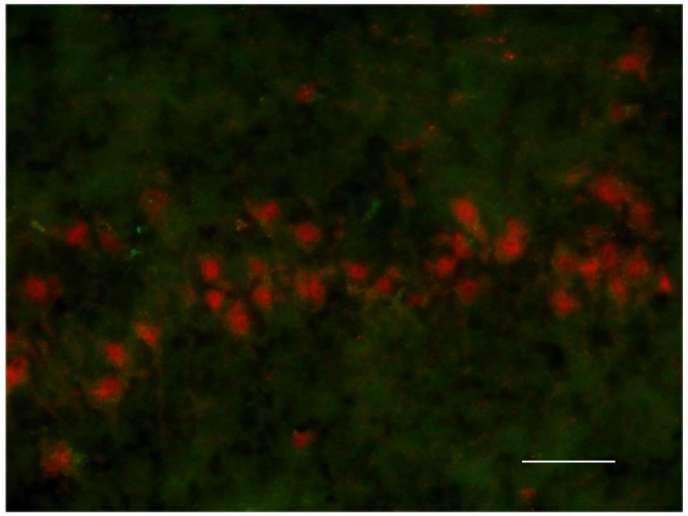
Single IT Dose of 0.9 mg in rTg-DI Rat – Day 28 in Hippocampus

ACSF-CTRL



siRNA Treatment





Antibodies

- NeuN (Red)
- hAPP (Green)

Van Nostrand lab, URI

Pre-Clinical Safety Summary for CNS siRNA Conjugates

No Test Article Related Changes in Rat and NHP Safety Assessments

6-month Platform PD Study in Rat

Single IT LP dose and Multi-IT LP dose

- No TA-related findings in spinal cord, brain, liver, kidney, lung, diaphragm, pituitary, sciatic nerve, skeletal muscle, spleen or thymus
- No TA-related findings on clinical signs, body weight or body weight gain

Platform non-GLP Tox Studies in Rat

15-day systemic tox

- No changes observed in serum chemistry, hematology or histopath

15-day IT LP tox

- No test article findings across all parameters examined: clinical observations, body weight, functional observational battery, clinical pathology parameters, macroscopic findings, and microscopic examinations including expanded neurological assessment with Fluoro-Jade

Platform non-GLP Tox Study in NHP

15-day IT LP tox

- No test article related findings across all parameters examined: clinical observations, body weight, neurological exams, macroscopic findings, and microscopic examinations including neurological assessment including Fluoro-Jade

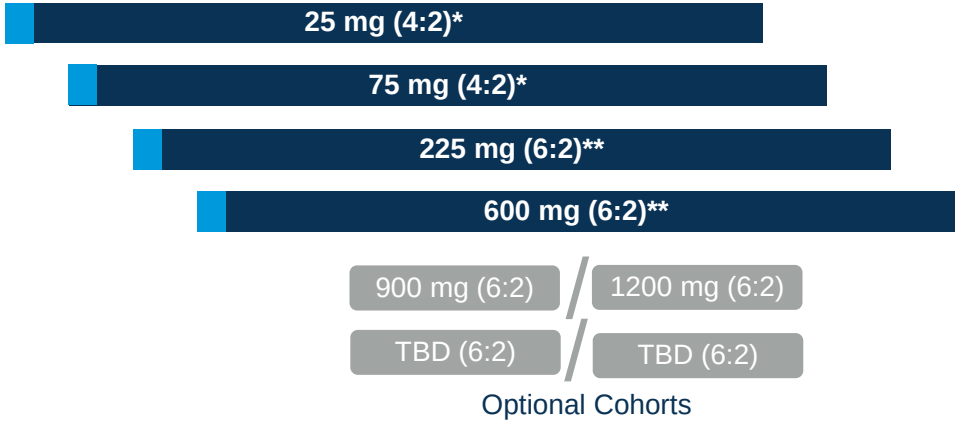
GLP Tox Studies in rat and NHP

Completed for ALN-APP

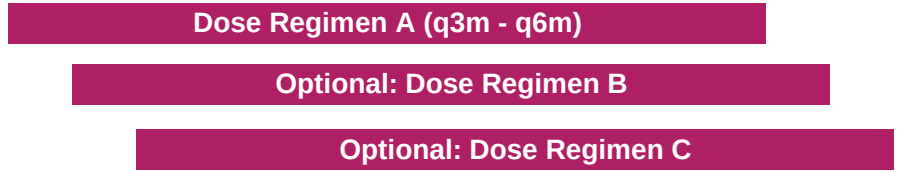
ALN-APP Phase 1 Expected to Start Imminently

- First CNS CTA submission expected in late 2021 with first patient dosed early 2022
  - Ph 1 study design aligned with MHRA
  - Global Study to be conducted in patients with Early Onset Alzheimer's Disease

Part A: Single Ascending Dose (placebo-controlled)



Part B: Multi-Dose (no placebo-control)



Phase 1 Endpoints:

- Primary: Safety / Tolerability
- Secondary: PK/PD (sAPPα/β)
- Exploratory:
  - Imaging – Aβ PET, Tau PET, MRI brain / cord
  - Fluid – Aβ40 / 42, NfL, NfH, APOE, neurogranin, SNAP25, S100B, tTau, and pTau species
  - Clinical – CDR-SB, ADADS-cog, RBANS

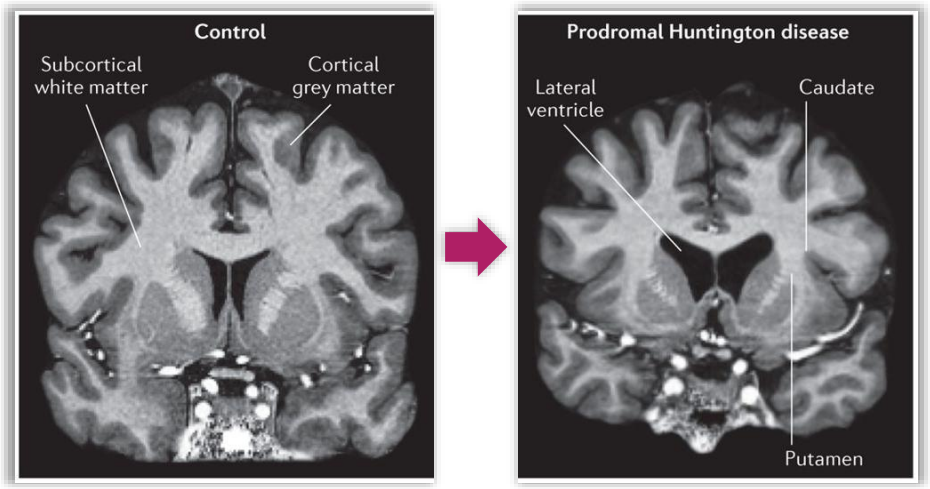
ALN-APP: Summary

- Will be first investigational siRNA therapeutic delivered to the CNS
- First therapeutic targeting APP mRNA
  - The sole precursor of all APP cleavage products, including Aβ
- First therapeutic with potential to prevent synthesis of other potential non-Aβ drivers of Alzheimer's Disease
  - β-CTF (C99), η-CTF
- First therapeutic with potential to comprehensively lower intracellular and extracellular amyloid proteins

HTT Targeting for Early Manifest Huntington's Disease

HTT

Patients present with progressive motor, cognitive and psychiatric decline.



BURDEN

- Affecting ~30,000 in U.S. with disease duration of 15-20 years.

TARGET IDENTIFICATION

- Autosomal dominant, gain-of-function genetic disease.
- 100% age-related penetrance.
- Trinucleotide repeat expansion in exon 1 of the huntington gene (*HTT*).

THERAPEUTIC HYPOTHESIS

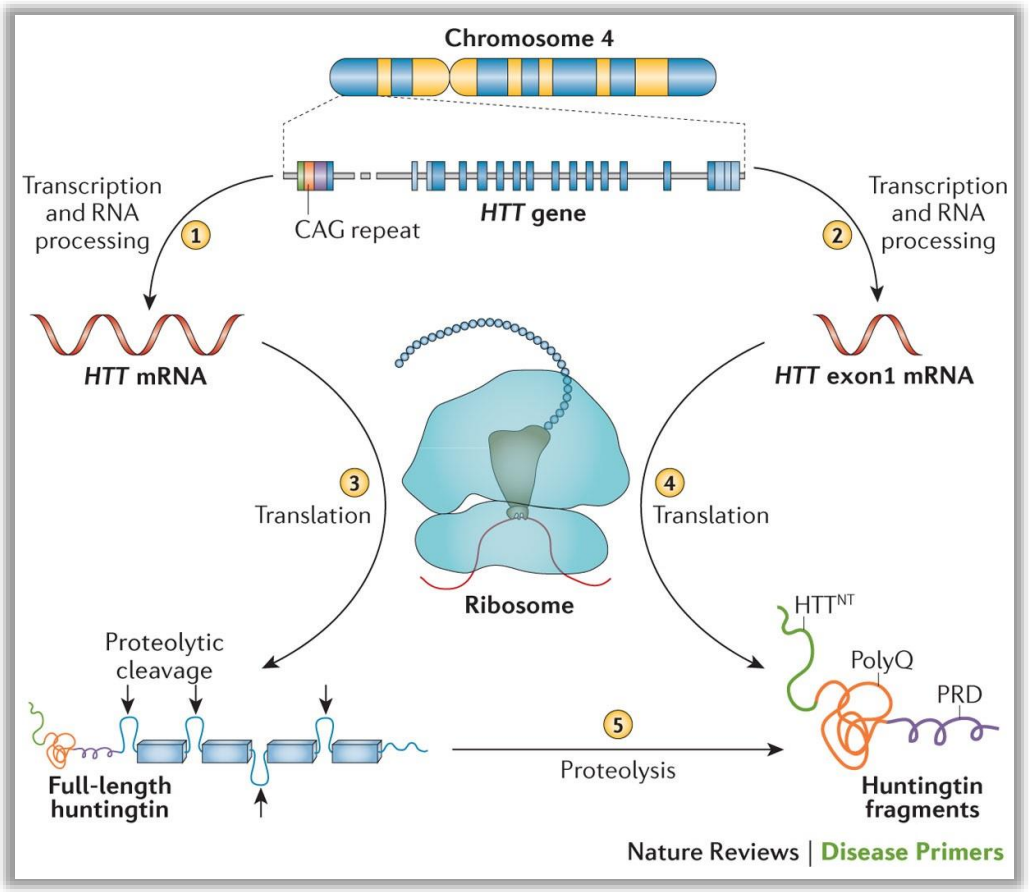
- RNAi-mediated knockdown of *HTT* transcript in neurons will reduce both RNA-induced and protein-induced neuronal toxicity, halting disease progression.

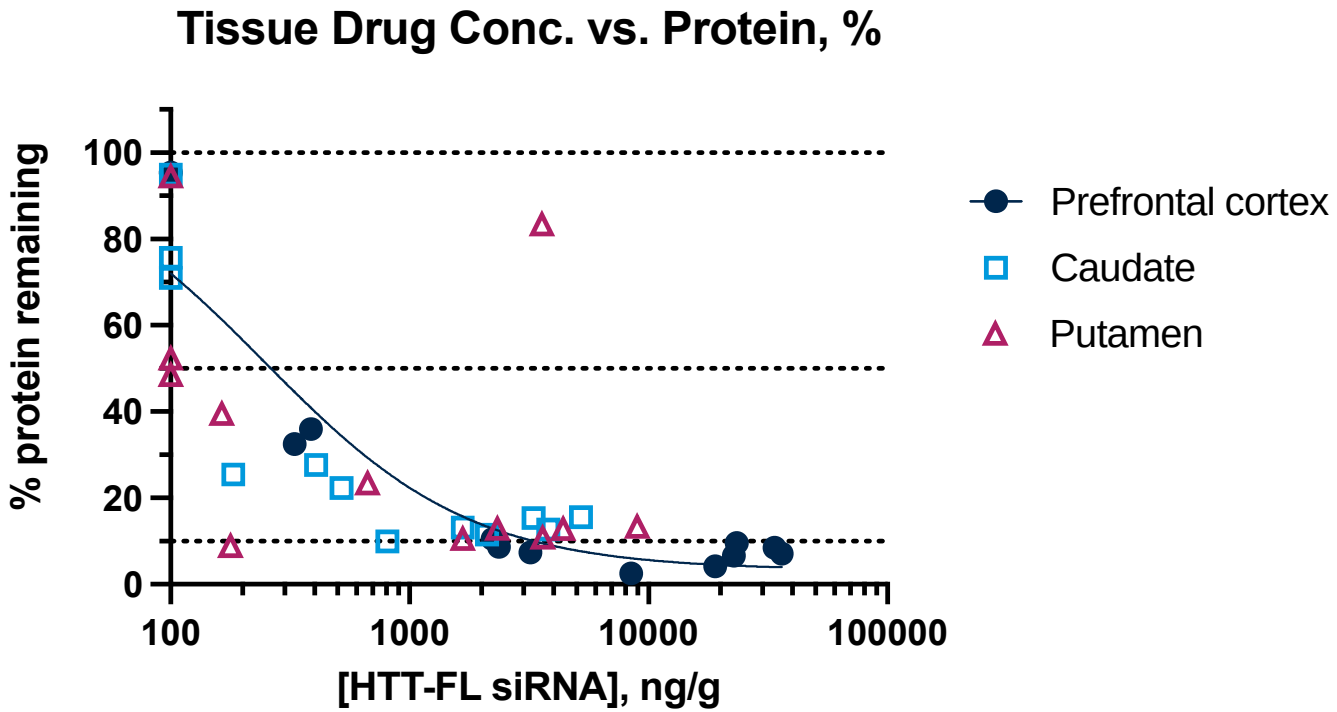
OPPORTUNITY

- Application of Alnylam's CNS platform to develop a therapeutic for a devastating progressive neurodegenerative condition.
- Potential differentiation over competition via exon 1 targeting strategy, targeting a pathogenic isoform that contributes to disease progression.

HTT Program Status

ALN-HTT: Advanced Preclinical Program





Continued work is ongoing on full length, exon 1, and intron 1 strategies

Tabrizi, S. J. et al. (2015) Huntington disease. Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.5

SOD1 Targeting for Amyotrophic Lateral Sclerosis (ALS)

SOD1-Specific ALS

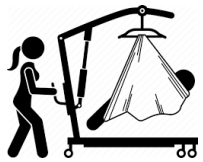
Fatal neurodegenerative disease characterized by motor neuron loss in the spinal cord and brain.

Healthy Motor Neuron

Atrophied ALS Motor Neuron

BURDEN

Slurred Speech



Progressive Loss of Functional Capabilities

TARGET IDENTIFICATION

- Over 180 different SOD1 mutations have been described including single point mutations, deletions, insertions, and truncation mutations.
- Mutant SOD1 produces toxic, gain of function and/or mis-localization.
- Multidose clinical study with Tofersen (ASO targeting SOD1) showed dose dependent reduction of CSF SOD1.

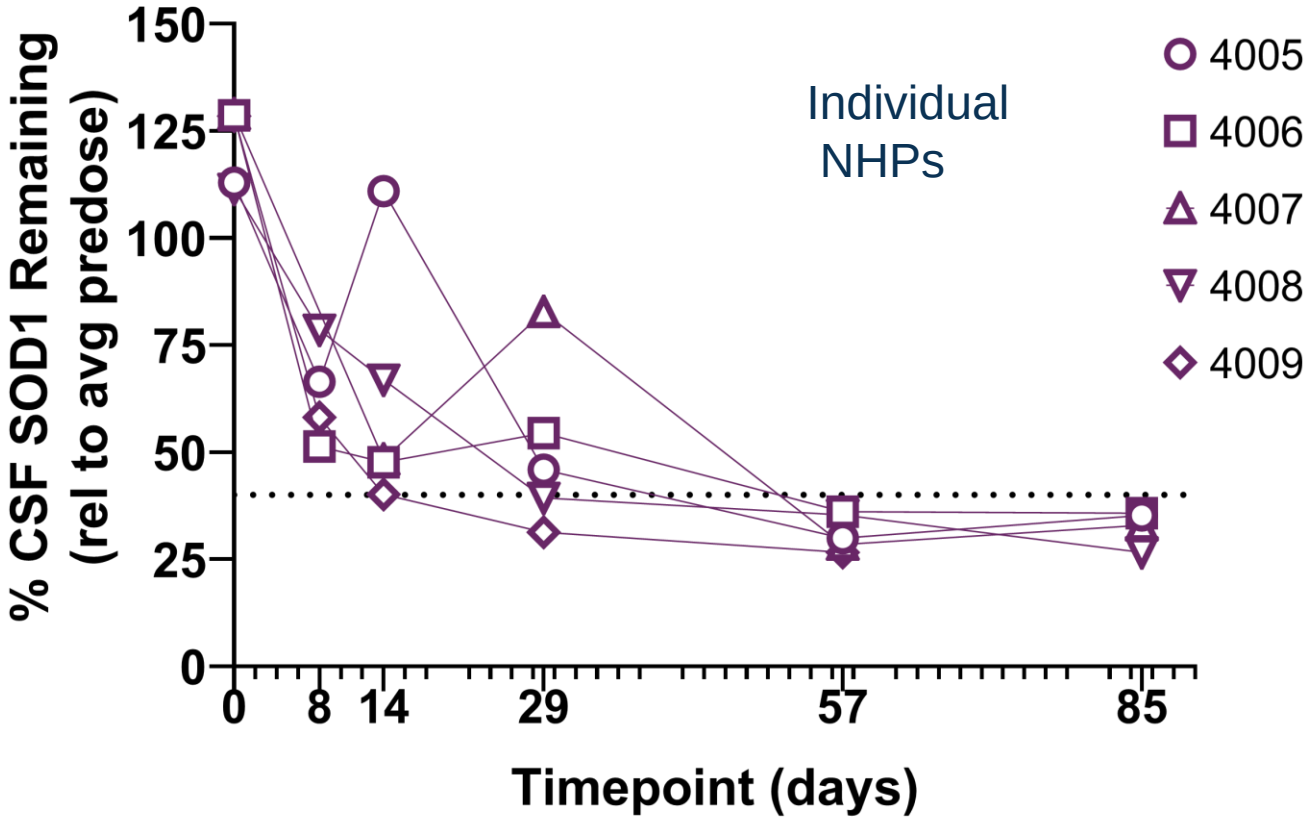
THERAPEUTIC HYPOTHESIS

- RNAi-mediated knockdown of *SOD1* transcript in CNS will reduce neuronal toxicity, halting disease progression.

OPPORTUNITY

- RNAi could provide more robust and durable knockdown of SOD1 relative to other modalities, with the potential for improved clinical outcomes.
    - Infrequent dosing profile enabled by durable RNAi-mediated knockdown could ease treatment burden.

ALN-SOD Silencing via Single IT Injection (70mg) NHP Pharmacodynamics

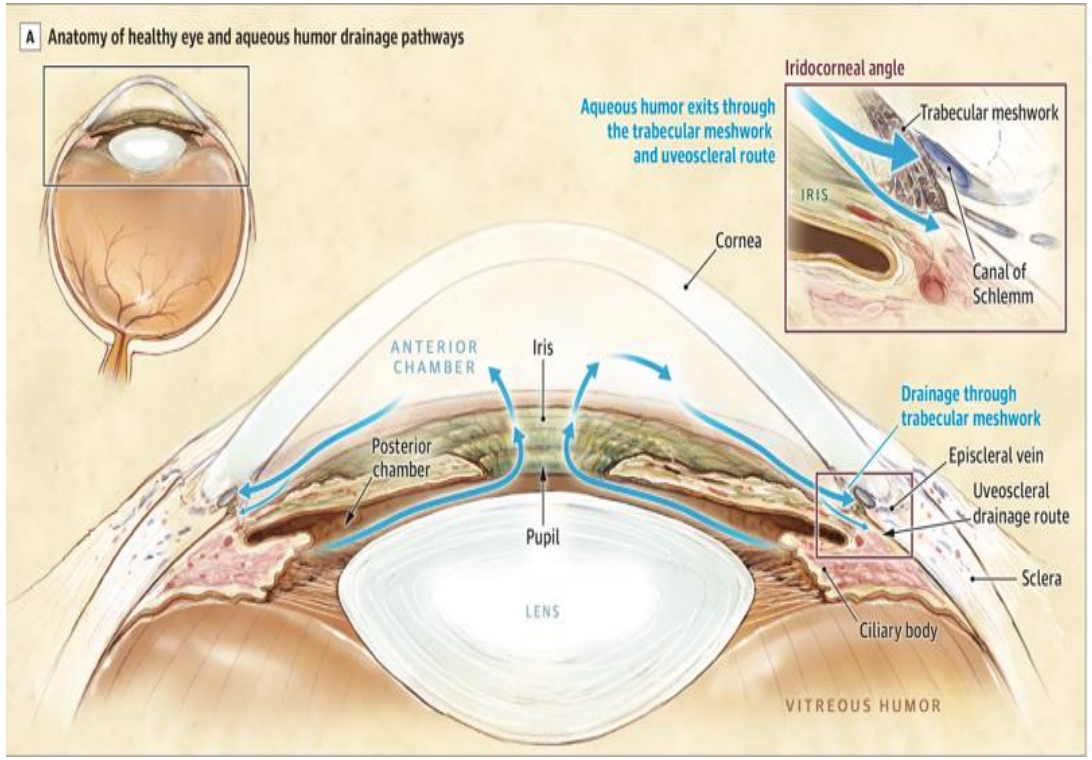


ALN-SOD

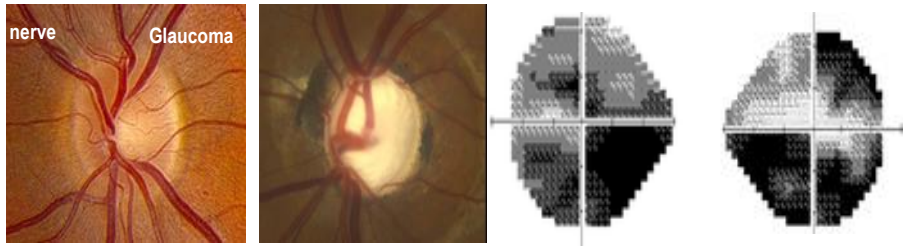
Ongoing Work

- **Development candidate declared**
- **Advancing toward IND**

Glaucoma is Leading Cause of Irreversible Vision Loss Worldwide: Elevated Intraocular Pressure (IOP) Leads to Progressive Optic Nerve Damage



Severe visual field loss



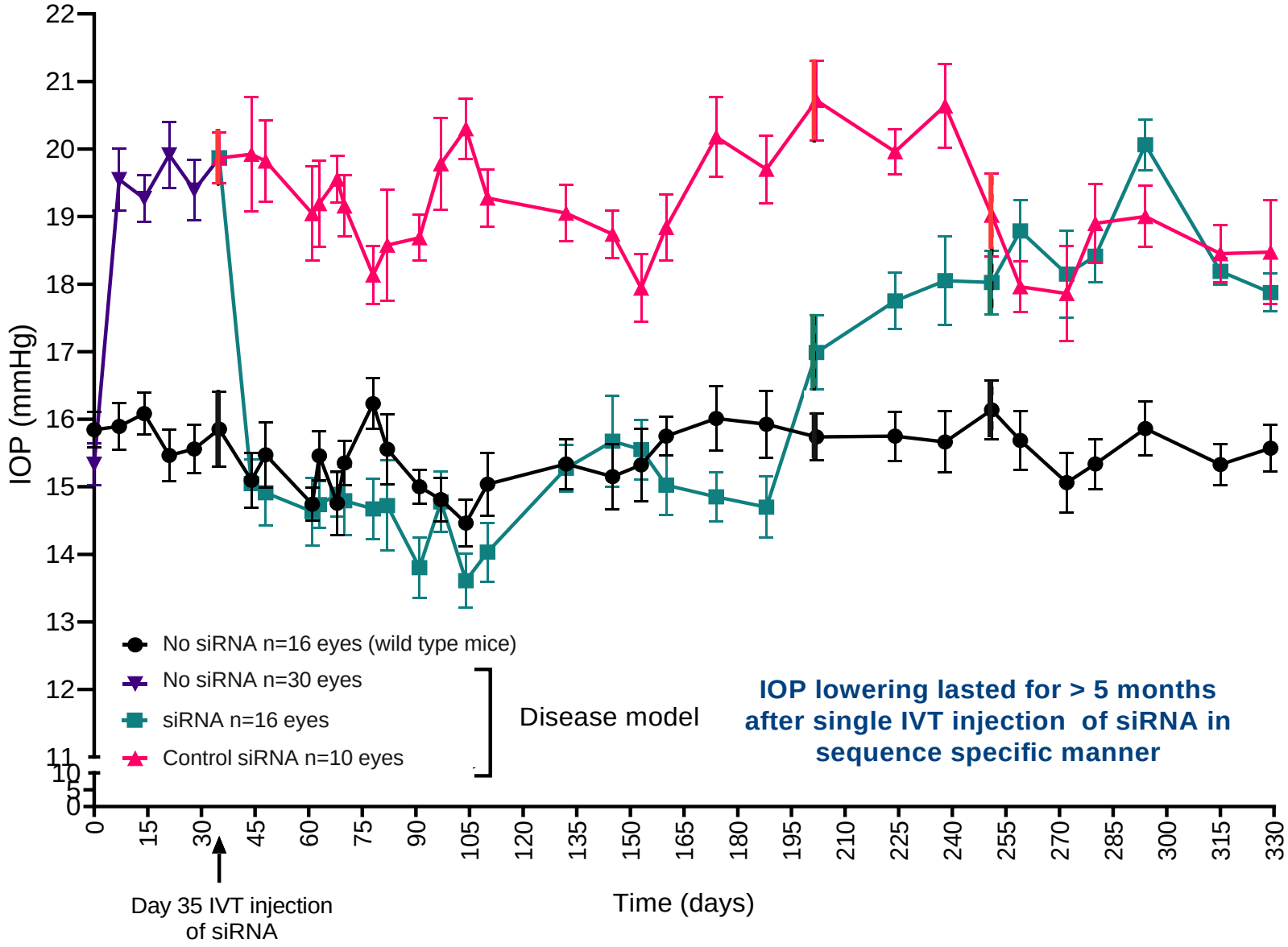
- Glaucoma: 76 million cases worldwide, 3.2 million in the US
- Many different subtypes, all lead to progressive optic nerve damage and vision loss
- Risk Factors include
  - older age
  - nonwhite race
  - family history
  - elevated intraocular pressure (IOP)

Intraocular Pressure (IOP)

Not a diagnostic criterion for glaucoma, however:
- Only modifiable risk factor
- Lowering IOP slows progression of disease
- Measured non-invasively in the clinic

[1]Tham et al, Ophthalmology 2014; [2]Stein et al JAMA 2021

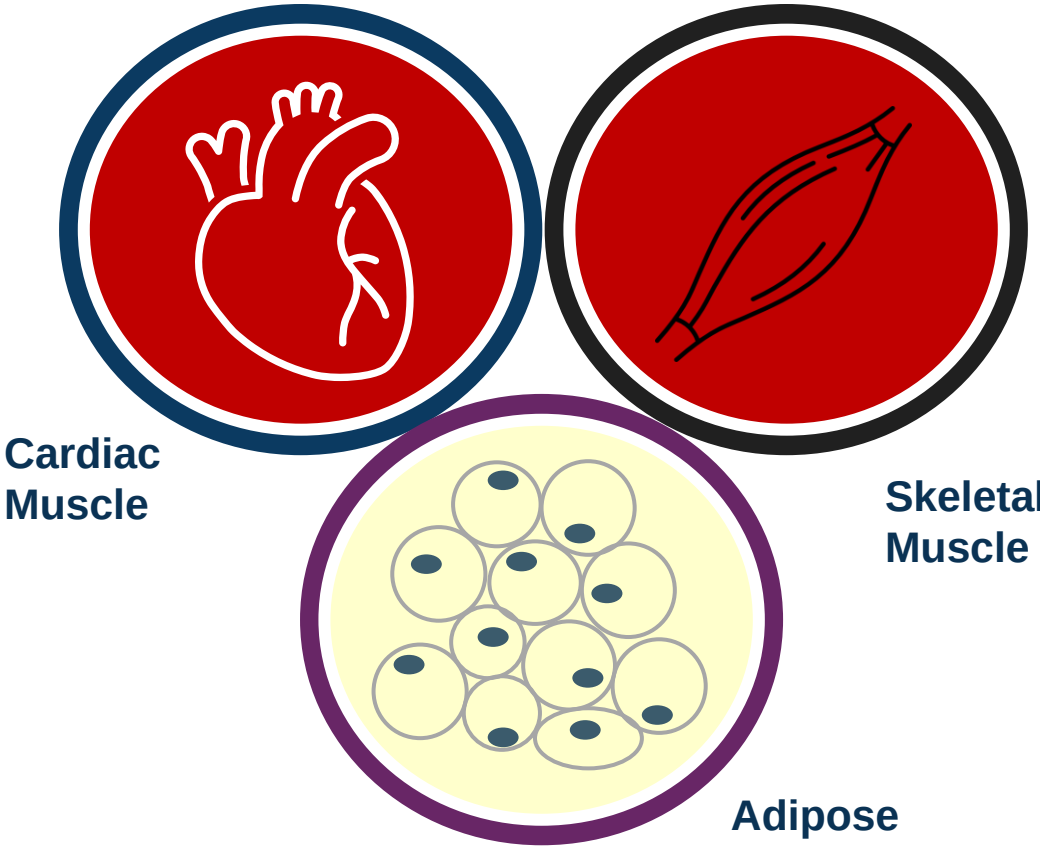
Efficacy in High IOP Disease Mouse Model via Intravitreal Dosing of siRNA Conjugate



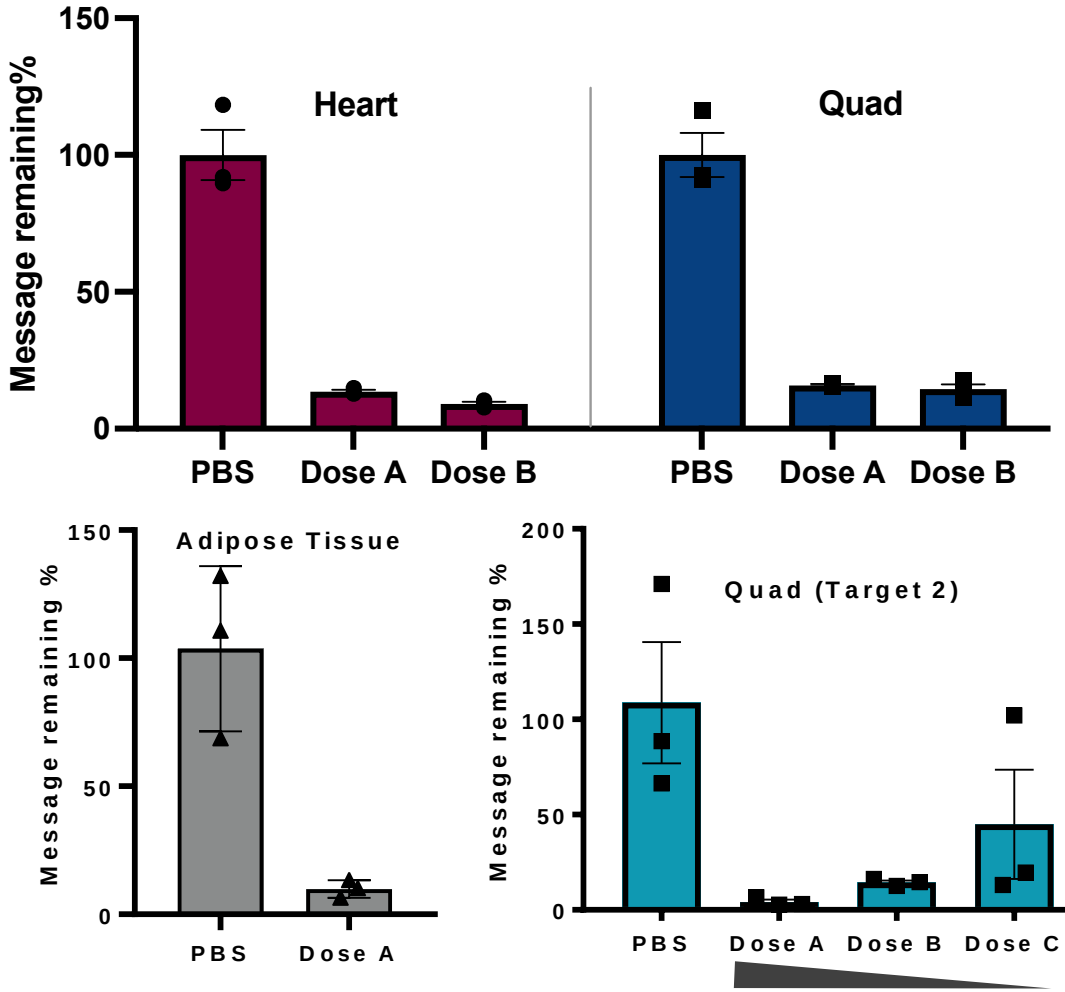
RNAi Therapeutics for Muscle/Adipose Disorders

Expanding Alnylam Opportunities Beyond Liver

Devastating diseases with enormous burden and unmet need



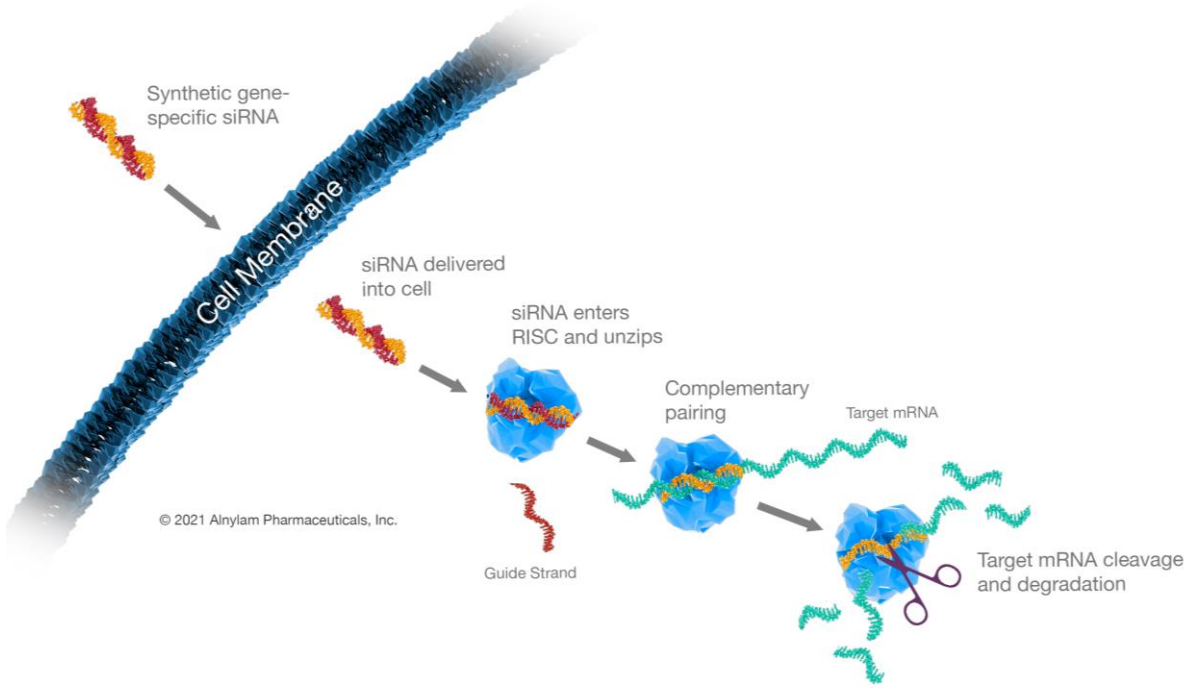
Robust Activity of RNAi in Muscle



RNAi's Potential to Expand the Medical Armamentarium for Oncology

Harness Power of RNAi, Through Modular and Reproducible Platform, to Uniquely Address Biological Challenges in Oncology

- ✓ Natural, catalytic mechanism for gene regulation—operative in cancer cells
- ✓ Ability to regulate both intracellular and extracellular targets, including difficult-to-drug targets
- ✓ Mechanism applicable to variety of anticancer strategies
- ✓ Rapid and reliable generation of molecules to interrogate targets and pathways preclinically
- ✓ Potent and durable mechanism of action



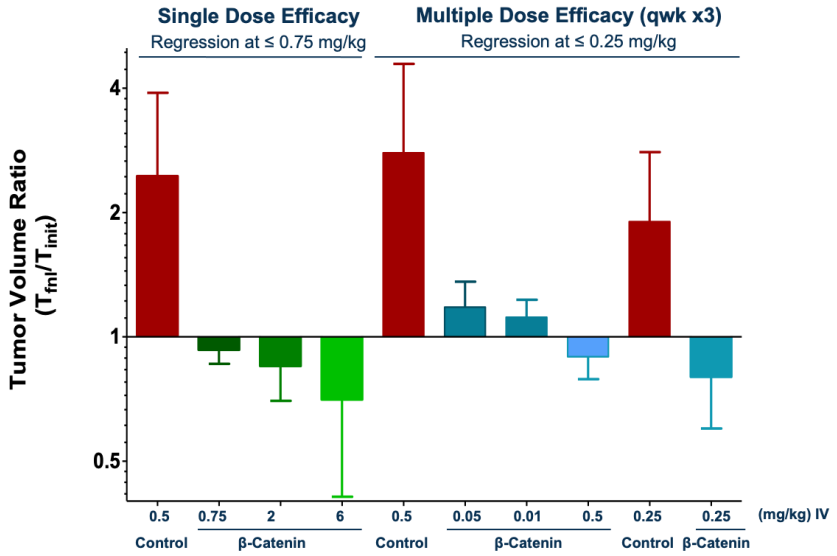
Harnessing the Power of RNAi for Oncology

Current Liver Delivery Platform Could Enable Important Applications in Oncology

Targeting difficult to drug pathways: Ex. Wnt/β-catenin for hepatocellular carcinoma (HCC)

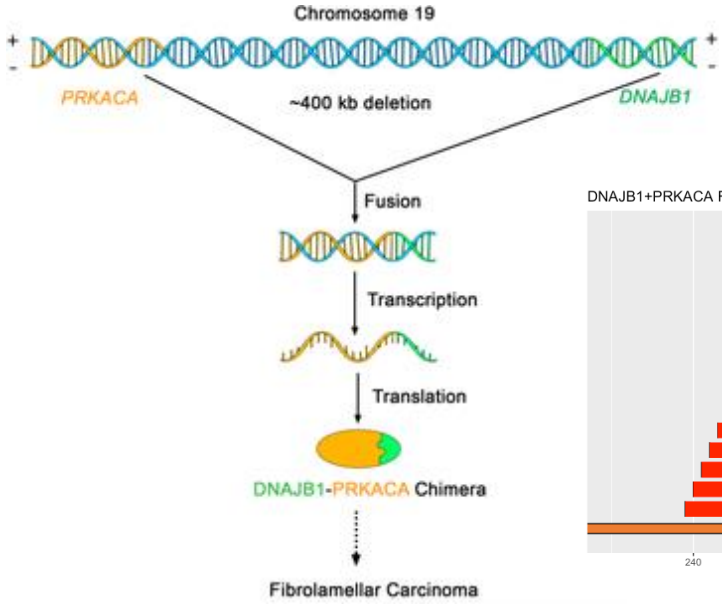
- The Wnt/β-catenin pathway is implicated in many human cancers, including HCC
- Activation drives up-regulation of genes involved in proliferation, angiogenesis, survival, metabolism, and immune evasion

Tumor regression in mouse model of HCC with LNP-β-catenin

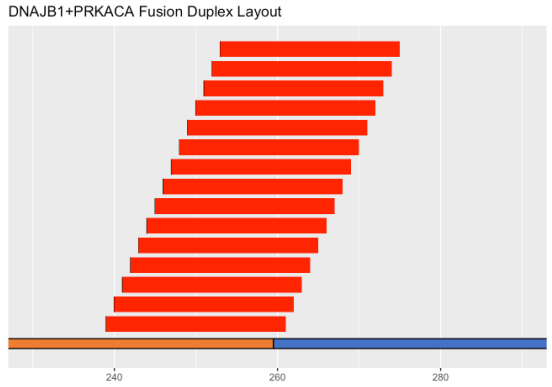


Targeting genetically defined cancers: fibrolamellar carcinoma (FLC)

- FLC is a rare primary liver cancer (~1% of liver cancer)
- ~100% of FLC patients have DNAJB1-PRKACA gene fusion



Potential to target fusion transcript



Summary

- siRNA/AGO2 mechanism is well conserved in all tissue studied to date
- PK/PD relationships with RNAi therapeutics are also conserved across tissues
  - Similar duration of effect in CNS, ocular as in liver
- ALN-APP CTA filing expected late 2021; first dose in early 2022 for AD
- ALN-SOD1 development candidate identified
- Continued pre-clinical progress in ocular (IOP target data)
- Specific ligand-receptor pairs identified in other tissues
  - Muscle, heart, adipose, tumors

Glaucienne
Diagnosed with AHP (Brazil)

Early and Mid-Stage Liver-Directed RNAi Programs to Drive Future Growth

Pushkal Garg, M.D.
Chief Medical Officer

Alnylam® PHARMACEUTICALS

Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

- Genetic Medicines
- Cardio-Metabolic Diseases
- Infectious Diseases
- CNS/Ocular Diseases

		EARLY/MID-STAGE *(IND/CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION/ COMMERCIAL[1] (OLE/Phase 4/IIS/registries)	COMMERCIAL RIGHTS
onpattro (patisiran)	*hATTR Amyloidosis-PN*[2]			●	Global
GIVLAARI (givosiran)	*Acute Hepatic Porphyria*[3]			●	Global
OXLUMO (lumasiran)	*Primary Hyperoxaluria Type 1*[4]			●	Global
Leqvio® (inclisiran)	*Hypercholesterolemia*			●	Milestones & up to 20% Royalties[5]
Vutrisiran*	*hATTR Amyloidosis-PN*			●	Global
Patisiran	*ATTR Amyloidosis*		●		Global
Vutrisiran*	*ATTR Amyloidosis*		●		Global
Fitusiran*	*Hemophilia*		●		15-30% Royalties
Lumasiran	*Severe PH1* *Recurrent Renal Stones*	●	●		Global
Cemdisiran (+/- Pozelimab)[6]*	*Complement-Mediated Diseases*	●			50-50; Milestone/Royalty
Belcesiran[7]*	*Alpha-1 Liver Disease*	●			Ex-U.S. option post-Phase 3
ALN-HBV02 (VIR-2218)[8]*	*Hepatitis B Virus Infection*	●			50-50 option post-Phase 2
Zilebesiran (ALN-AGT)*	*Hypertension*	●			Global
ALN-HSD*	*NASH*	●			50-50
ALN-APP*	*Alzheimer's Disease;* *Cerebral Amyloid Angiopathy*	○			50-50
ALN-XDH*	*Gout*	○			Global

[1] Includes marketing application submissions; [2] Approved in the U.S. and Canada for the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy; [3] Approved in the U.S., Brazil and Canada for the treatment of adults with acute hepatic porphyria (AHP), and in the EU and Japan for the treatment of AHP in adults and adolescents aged 12 years and older; [4] Approved in the U.S., EU and Brazil for the treatment of primary hyperoxaluria type 1 in all age groups; [5] Novartis has obtained global rights to develop, manufacture and commercialize inclisiran; 50% of inclisiran royalty revenue from Novartis will be payable to Blackstone by Alnylam; [6] Cemdisiran and pozelimab are each currently in Phase 2 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics; [7] Dicerna is leading and funding development of Belcesiran; [8] Vir is leading and funding development of ALN-HBV02; * Not approved for any indication and conclusions regarding the safety or efficacy of the drug have not been established.

As of October 2021

Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

- Genetic Medicines
- Cardio-Metabolic Diseases
- Infectious Diseases
- CNS/Ocular Diseases

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As of October 2021

Cemdisiran for Complement-Mediated Diseases

Alnylam PHARMACEUTICALS

Complement C5 and Cemdisiran Program

Complement C5 is *genetically* validated target

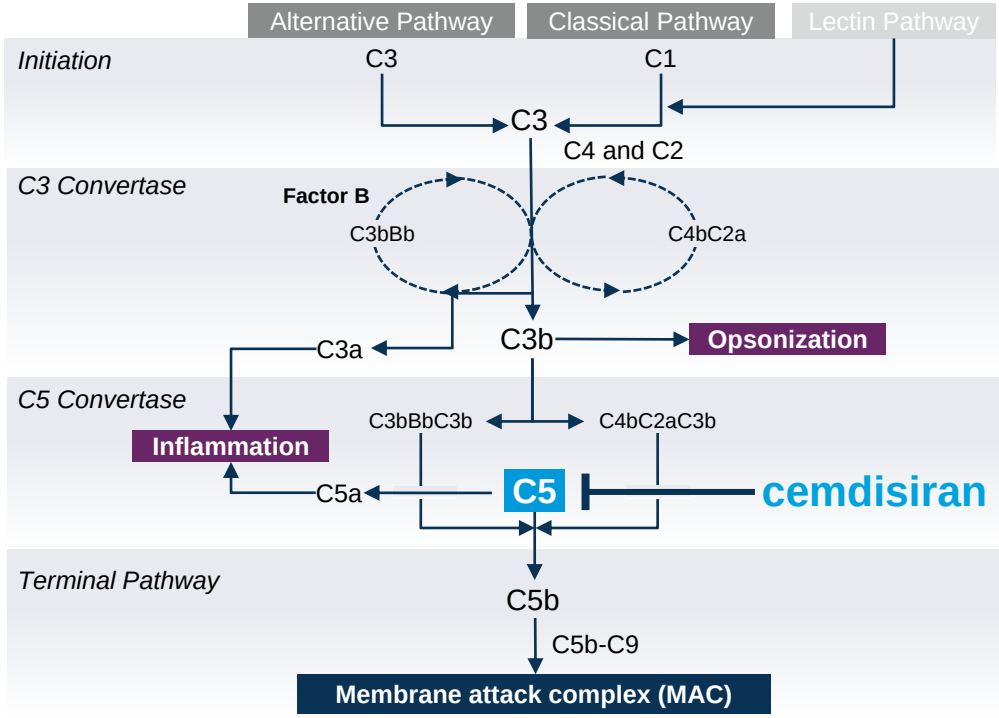
- Key component of terminal pathway
- Human C5 deficiency associated with minimal complications
- Majority expressed in liver; circulates in plasma

Complement C5 is *clinically* validated target

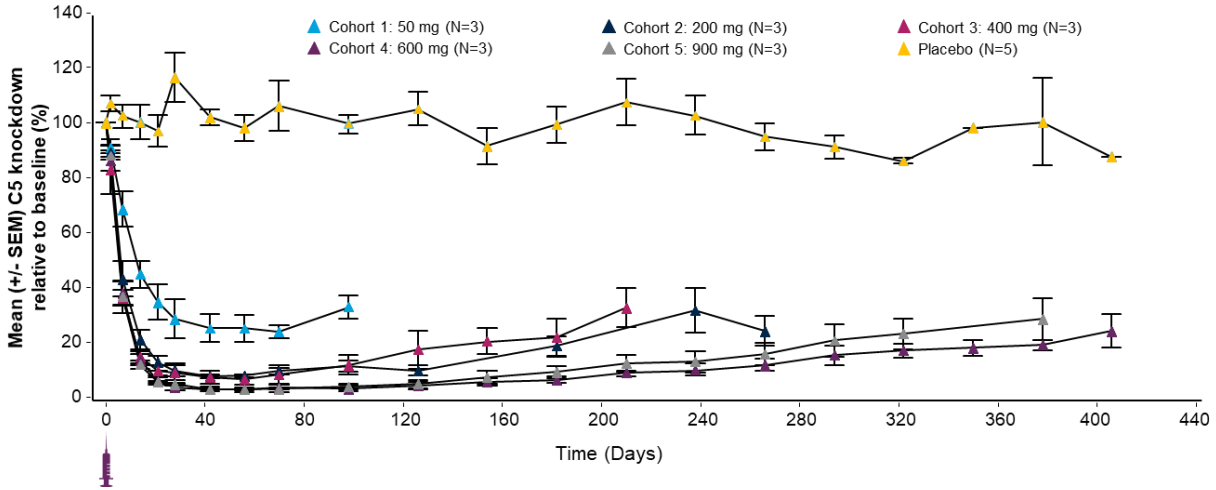
- Eculizumab is anti-C5 Mab approved in PNH and aHUS
  - In PNH, >80% inhibition of hemolytic activity associated with clinical benefit[1]
- Potential advantages of synthesis inhibition vs. protein binding approach

Deep and durable C5 inhibition observed with single doses of cemdisiran in healthy volunteers

- Maximum C5 knockdown relative to baseline up to 99%
- Mean maximum (± SEM) C5 knockdown: 98 ± 0.9% (600mg)



Healthy Volunteer Study



[1]Hillmen *et al., NEJM*; 350:552-9 (2004)

Complement-Mediated Disorders

Numerous Debilitating Diseases

REGENERON

IgA Nephropathy
Prevalence ~300-450K
Reduce proteinuria, and improve kidney function

Myasthenia Gravis
Prevalence ~175K
Improve Motor Function & Activities of Daily Living

PNH
Prevalence ~25K
Reduce RBC hemolysis

Evaluating Role for Cemdisiran Monotherapy

- Sub-maximal levels of complement inhibition may be effective
- Phase 2 study underway
- Opportunity to expand to other renal diseases involving complement (e.g., membranoproliferative glomerulonephritis)

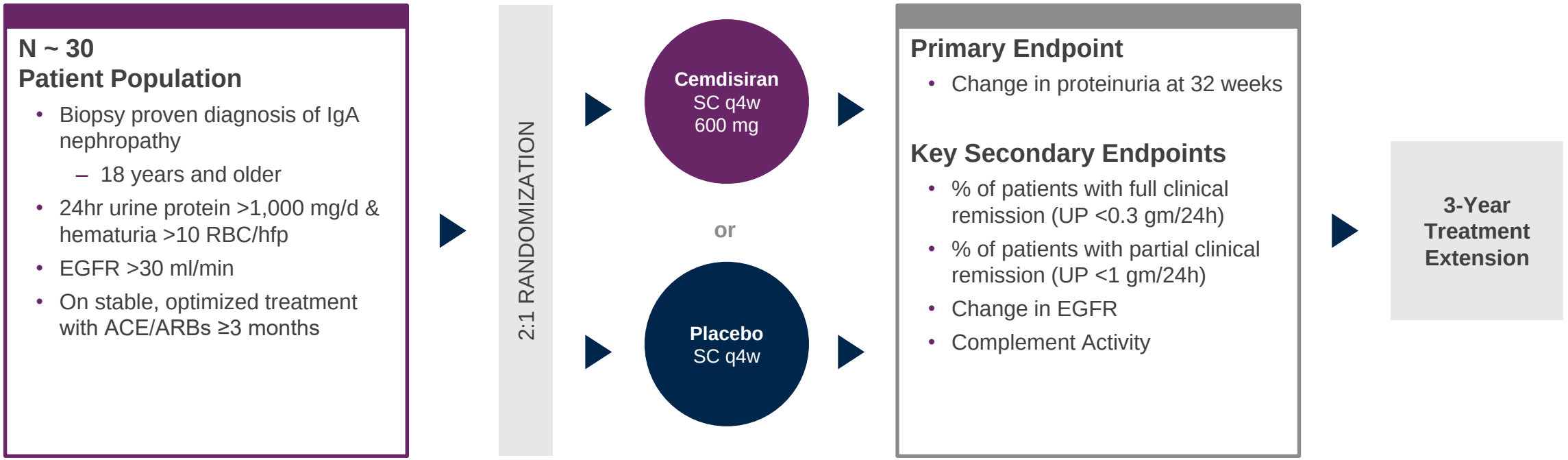
Evaluating Role for Combination Therapy with Cemdisiran + Pozelimab*

- Potent inhibition of C5 required
- Phase 2 studies for PNH underway
- Opportunity to expand to other complement-driven diseases

* Pozelimab is an investigational anti-C5 monoclonal antibody in development by Regeneron

Cemdisiran Phase 2 Study*

Randomized, Double-Blind Study in Patients with IgA Nephropathy



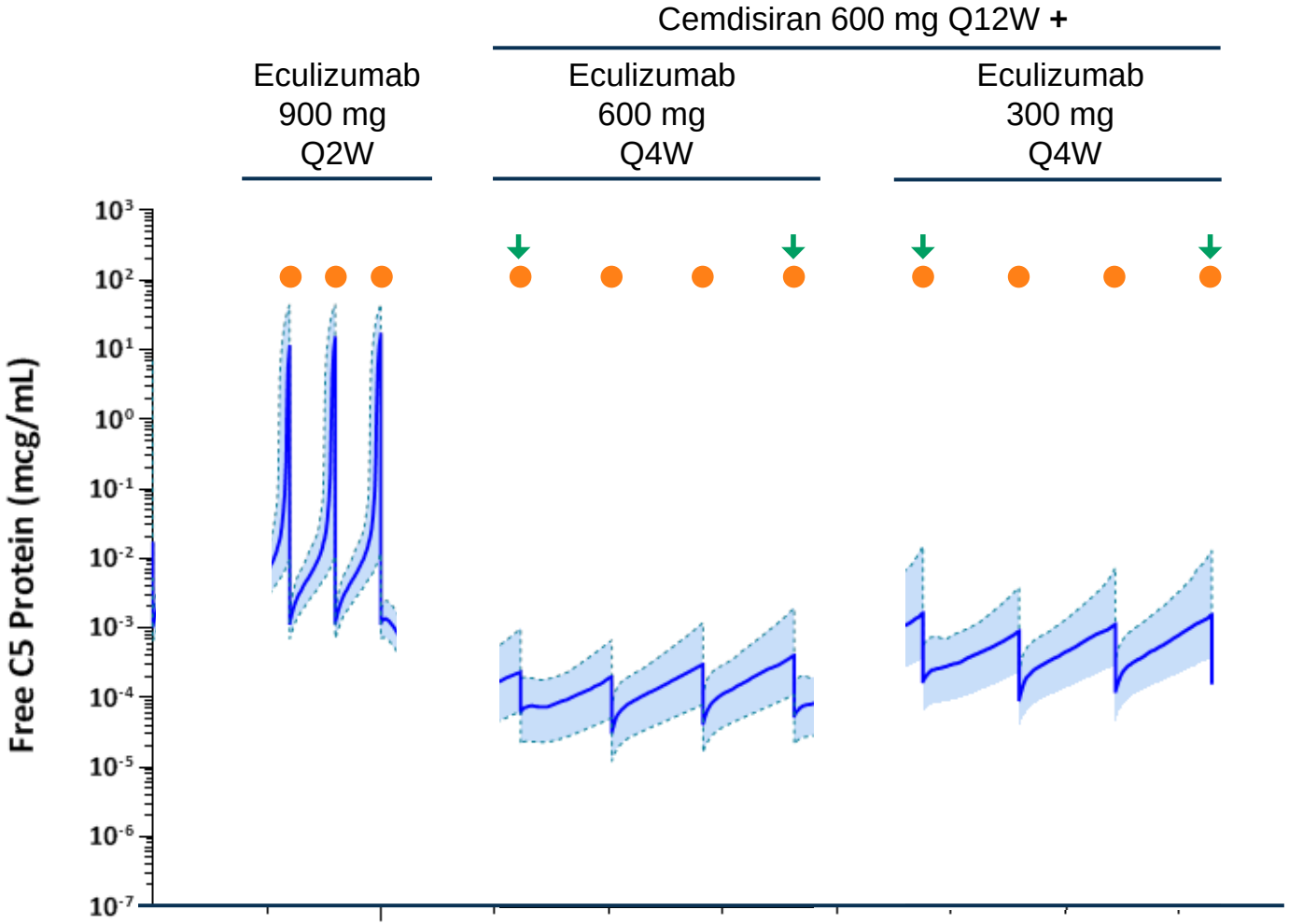
Enrollment **completed**

Initial data expected **early 2022**

* NCT03841448

Combination of Cemdisiran and Anti-C5 Mab Offers Potential for Highly Potent C5 Inhibition with Monthly SC Dosing

Results of PK/PD Modeling with Eculizumab*



Prior Experience in PNH

- Co-treatment with cemdisiran + eculizumab studied in PNH patients in prior Phase 1/2 study**
- Combination resulted in lower free C5 levels than either therapy alone
- Enabled monthly dosing of Mab with quarterly cemdisiran

Potential Role in Diseases Requiring Potent C5 Inhibition

- PNH
- Myasthenia Gravis
- aHUS
- Others

* 100 subjects were simulated to obtain 95th percentiles. Figure depicts three independent simulations and does not represent actual clinical results. X-axis tick marks indicate Q4W intervals.

** NCT02352493

Clinical Plan with Cemdisiran/Pozelimab Combination

REGENERON

Clinical Activities Led by Regeneron

NORMAL HEALTHY VOLUNTEERS

Phase 1 study[1]

Study in healthy adult volunteers evaluating safety, tolerability, PK, and PD of pozelimab in combination with cemdisiran administered on either same day or 28 days apart

Study underway

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

Phase 2 study[2]

Study in adult patients with PNH evaluating safety and tolerability of two dosing regimens of combination therapy

Phase 2 study[3]

Study of pozelimab and cemdisiran combination therapy in adult patients with PNH who switch from eculizumab therapy

Studies underway

MYASTHENIA GRAVIS

Phase 3 study[4]

Study in adult patients with Myasthenia Gravis

Study initiated

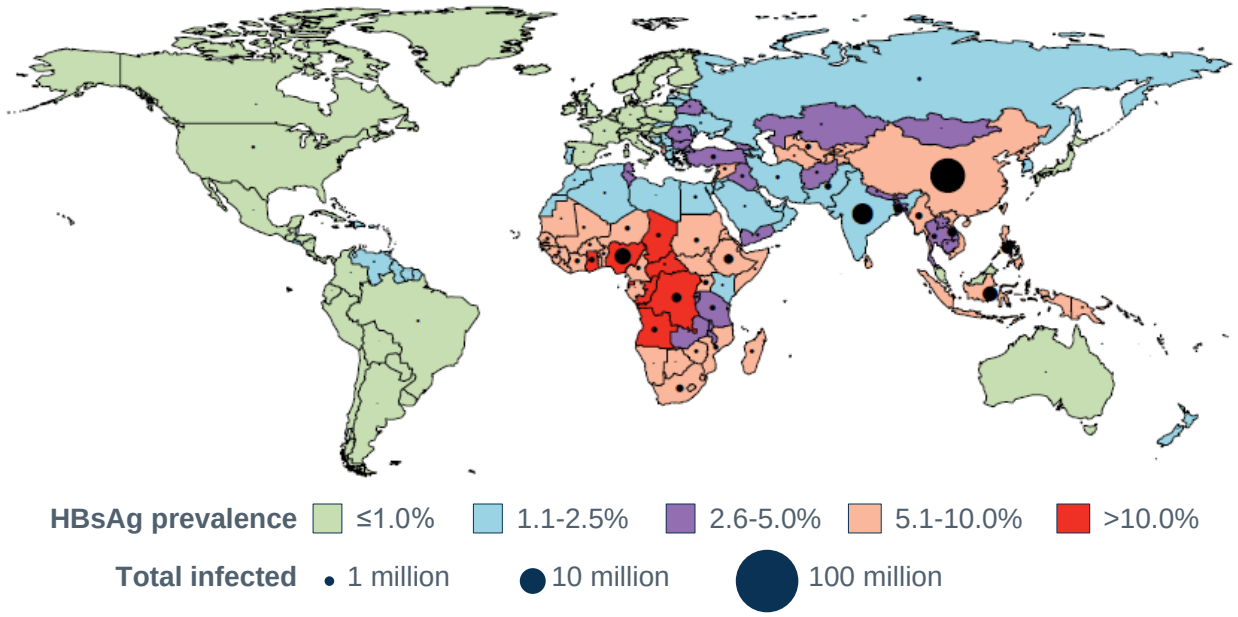
[1]NCT04601844; [2]NCT04811716; [3]NCT04888507; [4]NCT05070858

ALN-HBV02 (VIR-2218) for HBV Infection

Alnylam PHARMACEUTICALS

HBV: Global Health Problem Impacting Developed and Developing Countries

HBV Prevalence Estimate: ~290 M
(diagnosed + undiagnosed)



~24M diagnosed patients
in top high-/middle-income countries*

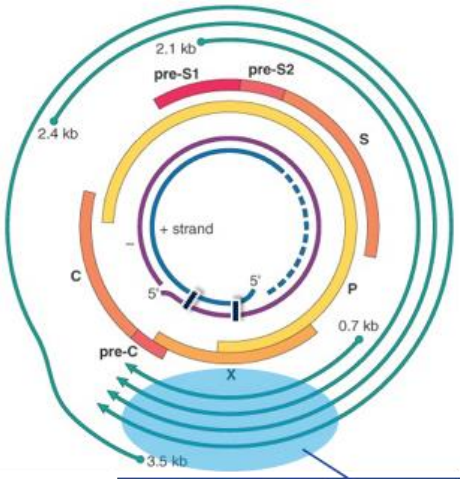
ALN-HBV02 (VIR-2218)
Investigational RNAi Therapeutic for Treatment of Chronic HBV Infection

Targets conserved region in X gene, upstream of integration hotspot, allowing for

- Single siRNA to suppress HBsAg from both intDNA and cccDNA
- Suppression of all HBV mRNAs, which overlap in this region

GalNAc-conjugated ESC+ siRNA

- Subcutaneous administration with GalNAc ligand for targeted delivery to liver and prolonged pharmacodynamic effect
- ESC+ technology: improved specificity of RNAi activity



siRNA targeting an overlapping region can silence all transcripts

*Main high-income countries (HICs) outside US/EU with high prevalence are S Korea, Taiwan, Canada, and Australia; HIC is defined per World Bank designations.

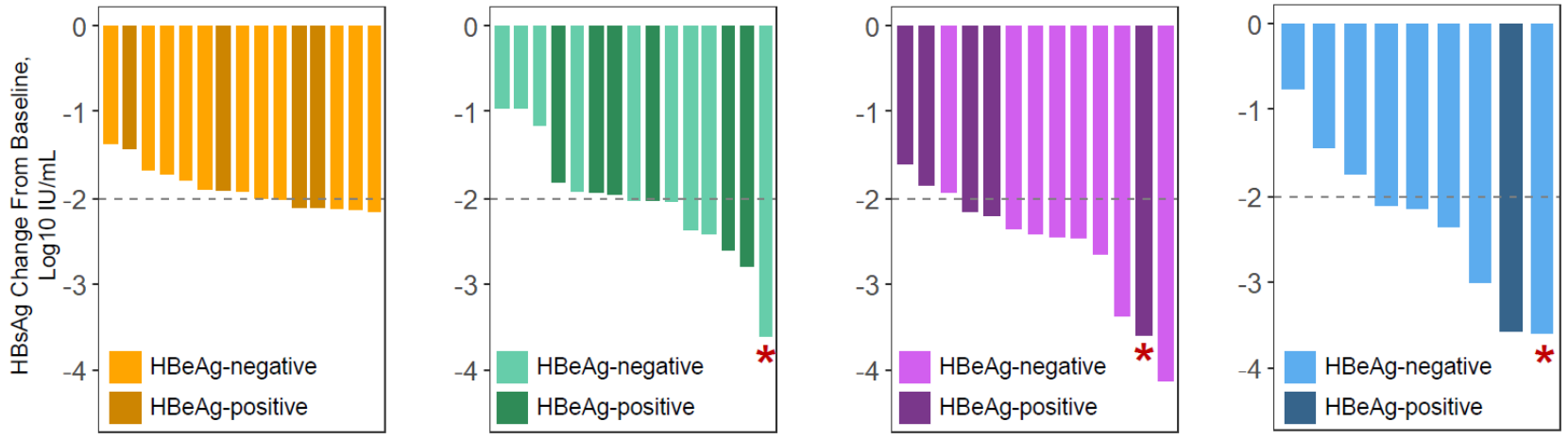
The Polaris Observatory Collaborators. Lancet Gastroenterol Hepatol 2018

Ongoing VIR-2218 Phase 2 Study Evaluating Impact of Concomitant PEG-IFNα

Multilog Reductions in HbSAg Levels

	Cohort 1	Cohort 2	Cohort 3	Cohort 4
	VIR-2218 only	**VIR-2218 lead-in + PEG-IFNα (12 wk)**	**VIR-2218 + PEG-IFNα (24 wk)**	**VIR-2218 + PEG-IFNα (≤ 48 wk)**
Week 4, n	15	15	17	13
Mean Change in HBsAg (log_{10} IU/mL)	-0.51	-0.51	-0.92	-1.01
Week 12, n	14	15	16	11
Mean Change in HBsAg (log_{10} IU/mL)	-1.39	-1.42	-1.98	-2.05
At Week 24, n	15	15	13	9
Mean Change in HBsAg (log_{10} IU/mL)	-1.89	-2.03	-2.55	-2.30

Change in HBsAg (log_{10} IU/mL) from baseline at Week 24



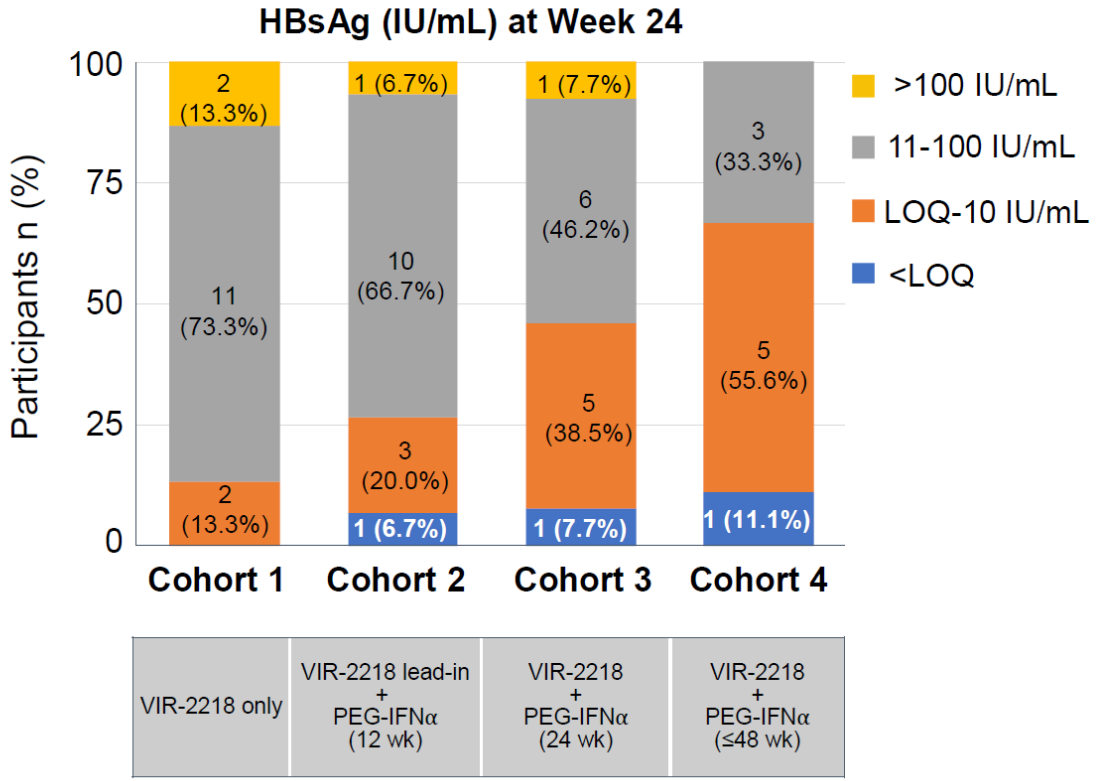
*Participant achieved HBsAg < LLOQ (0.05 IU/mL)

EOT, end of treatment; HBeAg-negative, Hepatitis B e antigen negative; HBeAg-positive, Hepatitis B e antigen positive

Yuen et al., *AASLD,* November 2021

Ongoing VIR-2218 Phase 2 Study Evaluating Impact of Concomitant PEG-IFNα

Significant Proportion Achieve HbSAg <10 IU/mL, Including <LOQ



- VIR-2218 alone or in combination with PEG-IFNα has been generally well tolerated
- All VIR-2218 plus PEG-IFNα regimens were associated with clinically meaningful HBsAg reductions (> 2 log10IU/mL on average) by Week 24
- Three participants receiving VIR-2218 and PEG-IFNα achieved HBsAg loss by Week 24; 2 of 3 achieved anti-HBs seroconversion

Alnylam Opt-in Right to VIR-2218 Prior to Phase 3

Yuen et al., *AASLD,* November 2021

ALN-HSD and ALN-PNP for NASH

Alnylam

Nonalcoholic Fatty Liver Disease (NAFLD)

Disorder of Over-Nutrition Leading to Accumulation of Hepatic Fat

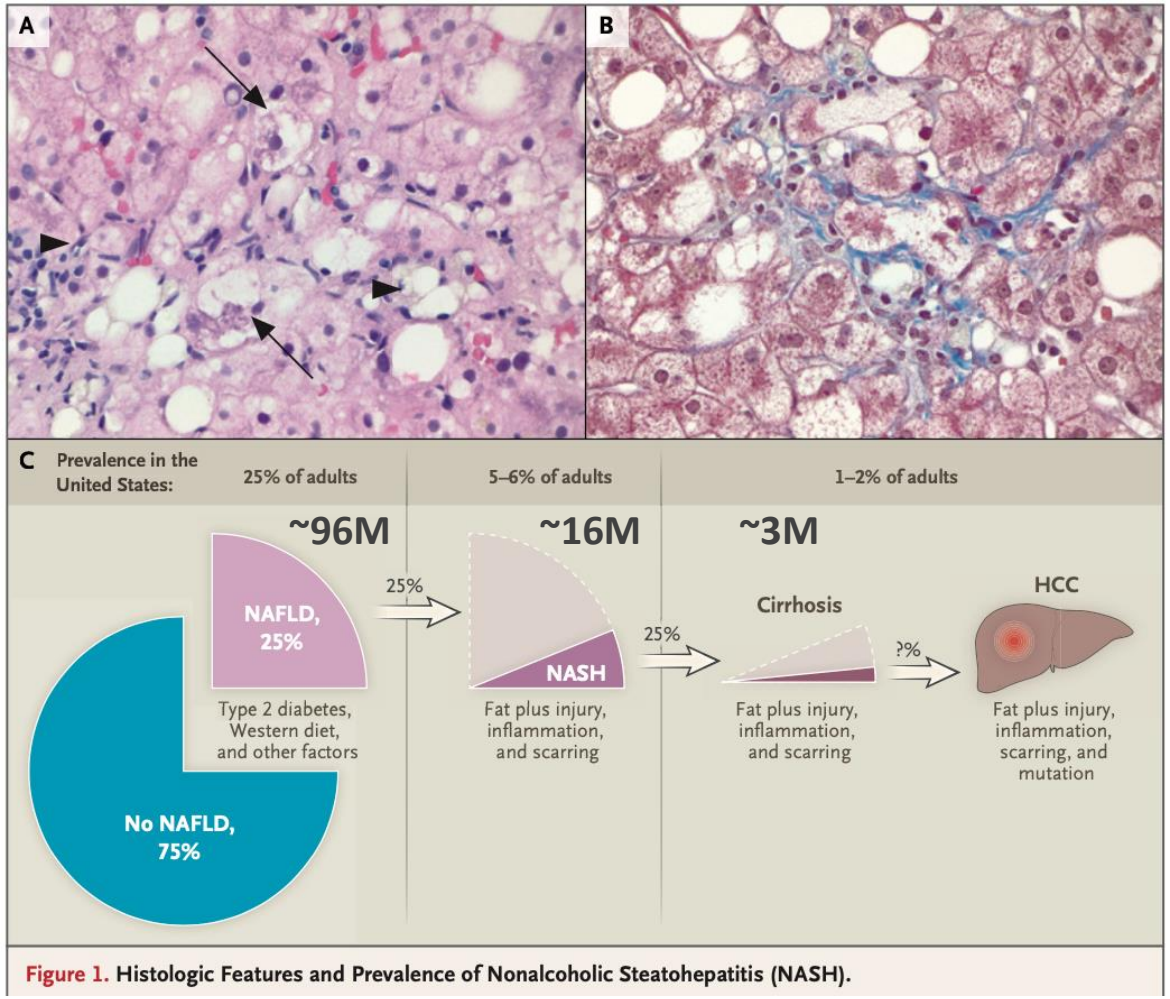


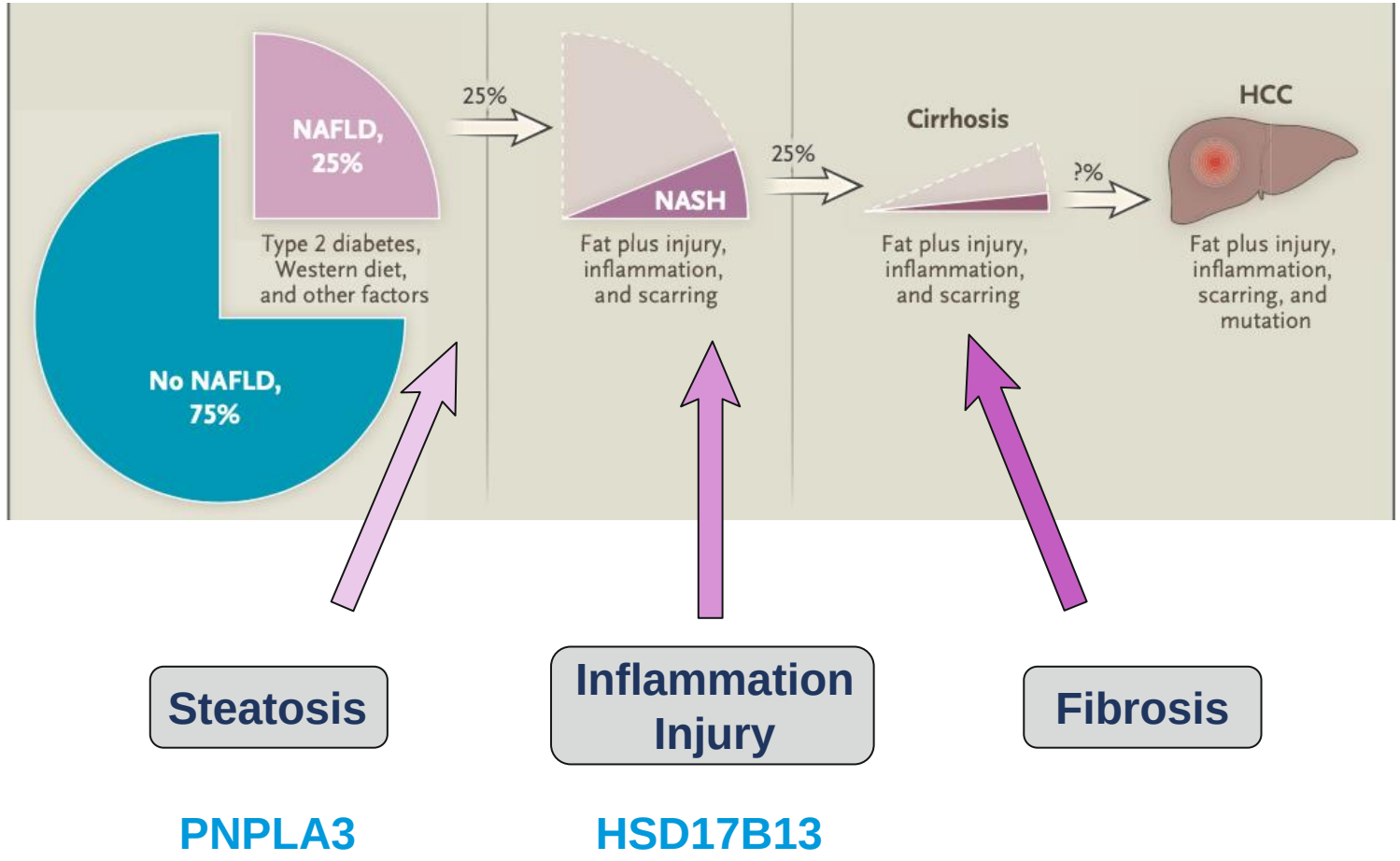
Figure 1. Histologic Features and Prevalence of Nonalcoholic Steatohepatitis (NASH).

- **Nonalcoholic steatohepatitis (NASH)**
  - Subset of NAFLD defined by presence of liver cell injury and inflammation
  - Associated with progressive fibrosis, cirrhosis, and hepatocellular carcinoma
  - Co-morbidities include obesity, metabolic syndrome, and type 2 diabetes
- **NASH treatment**
  - No approved medical therapies
  - Weight loss is effective but difficult to achieve and generally not durable

Adapted from *Diehl, A., Day, C.* (2017). NEJM 377(21), 2063-2072.

Therapeutic Strategies for Nonalcoholic Fatty Liver Disease (NAFLD)

Each Stage of NASH Pathogenesis is Candidate for Intervention



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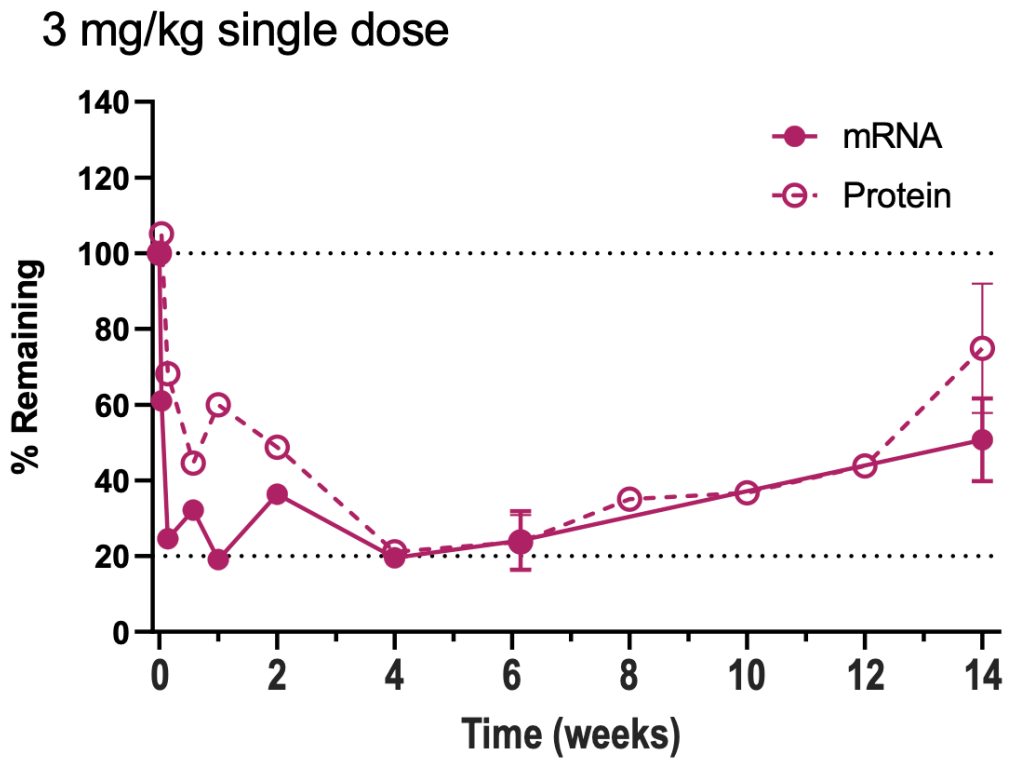
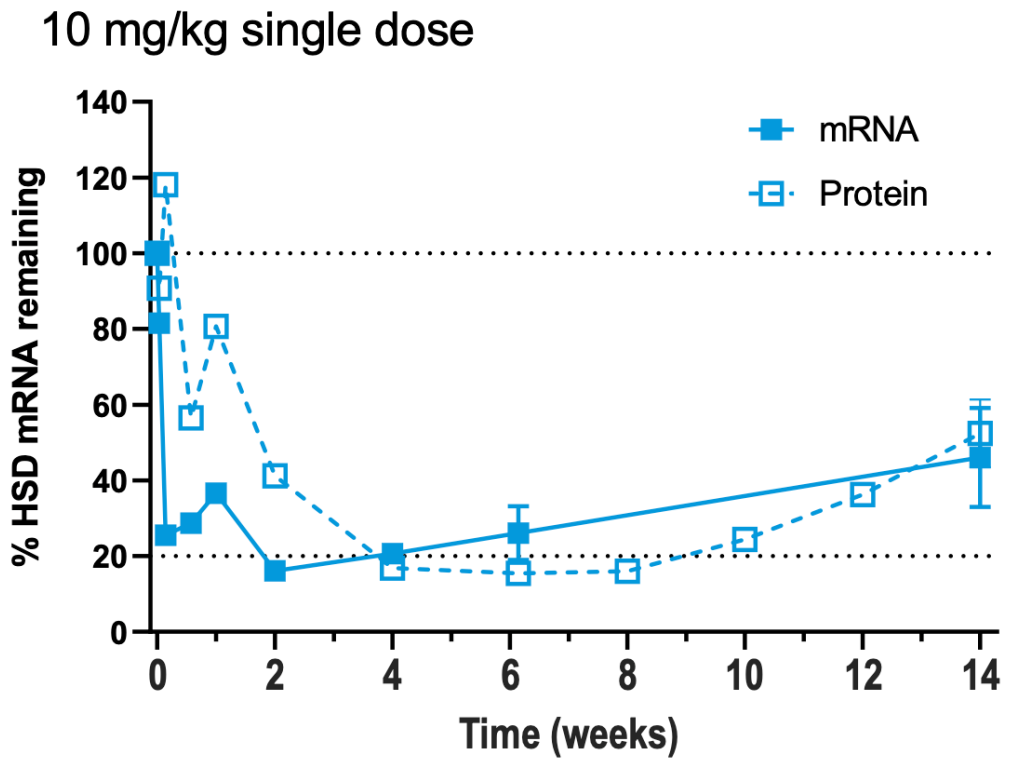
ALN-HSD Results in Potent mRNA and Protein HSD17B13 Knockdown in NHP Liver





- ALN-HSD suppresses HSD17B13 with high specificity *in vitro* and *in vivo* (rodents and healthy and obese NHPs)
- Preliminary evidence suggesting highly durable pharmacodynamic profile
- No pre-clinical toxicity of concern observed, with high safety margins demonstrated

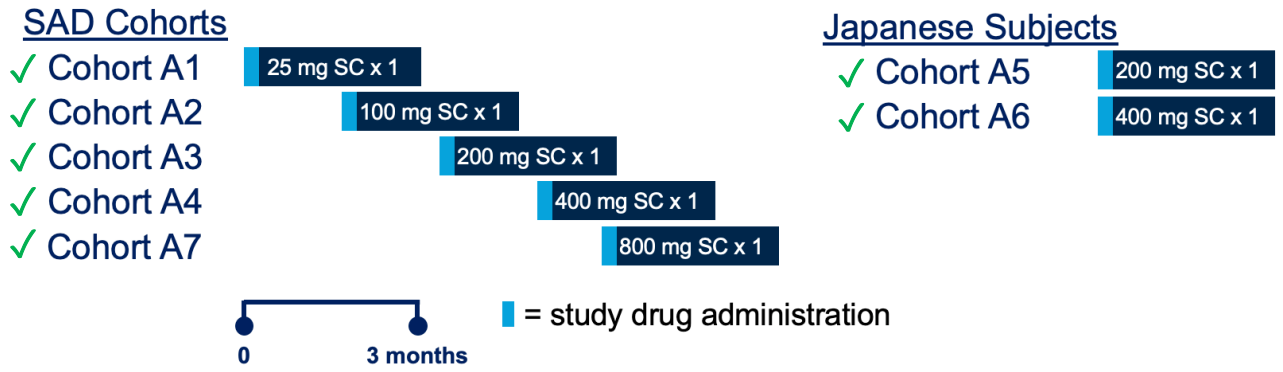
ALN-HSD Phase 1 Design Highlights

Part A: Healthy Volunteers

Primary Endpoint: Safety and tolerability of ALN-HSD

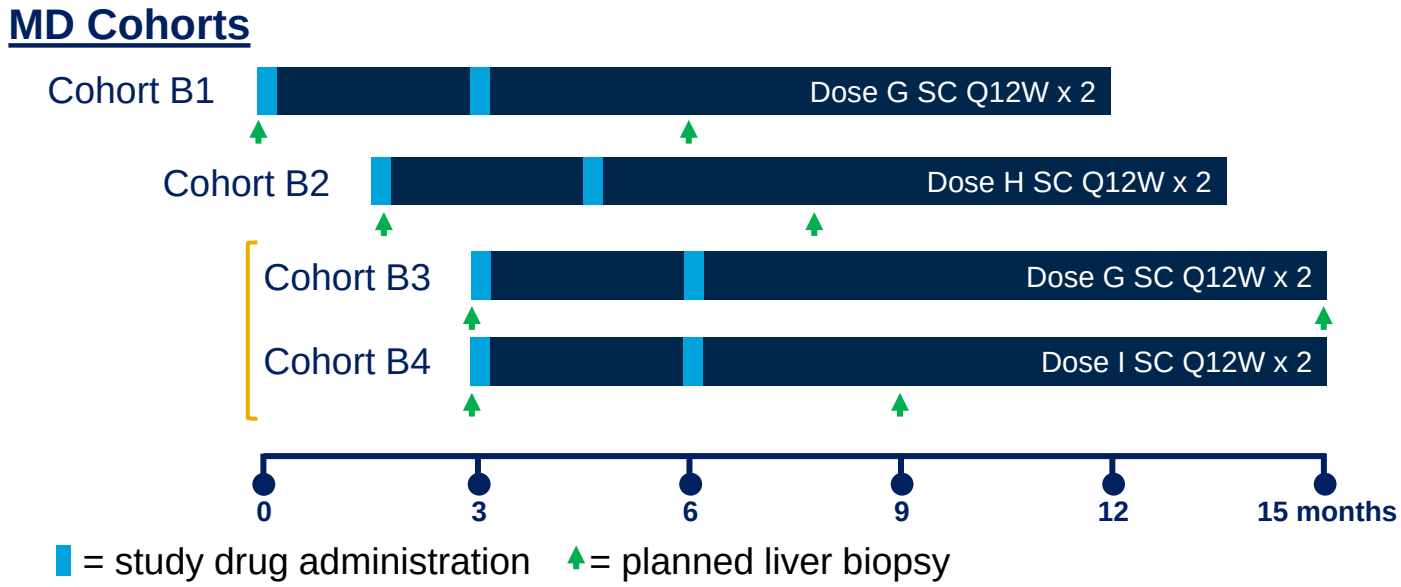
Key Secondary Endpoints: ALN-HSD PK/PD

Exploratory Endpoints: Identify potential biomarkers of HSD; Assess effects of ALN-HSD on histologic and circulating biomarkers of NASH



Part B: NASH Patients

- Multiple-dose (2 doses)
- Baseline and post-dose liver biopsies
- Designed to:
  - Test doses predicted to result in 50, 80, and 90% maximal KD
  - Assess kinetics of recovery from maximal KD
  - Assess safety and tolerability



NCT04565717

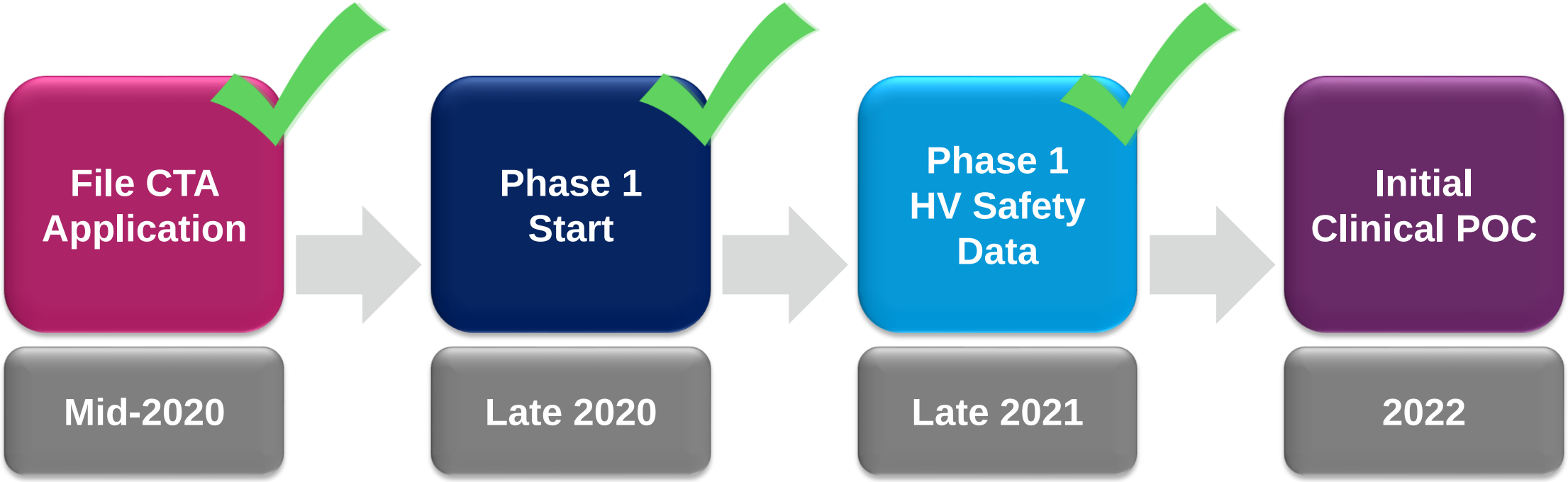
Primary Endpoint: Safety & Tolerability in Healthy Volunteers

ALN-HSD Well Tolerated in Healthy Subjects

At Least One TEAE, n	ALN-HSD Part A Dose Cohort						
	A1 PBO/25 mg N=4	A2 PBO/100 mg N=9	A3 PBO/200 mg N=9	A4 PBO/400 mg N=9	A5 PBO/200 mg N=9 (Japanese)	A6 PBO/400 mg N=9 (Japanese)	A7 PBO/800 mg N=9
Adverse Event	1	3	3	4	3	1	3
Serious Adverse Event	0	0	1	0	0	0	0
Severe Adverse Event	0	0	0	0	0	0	0

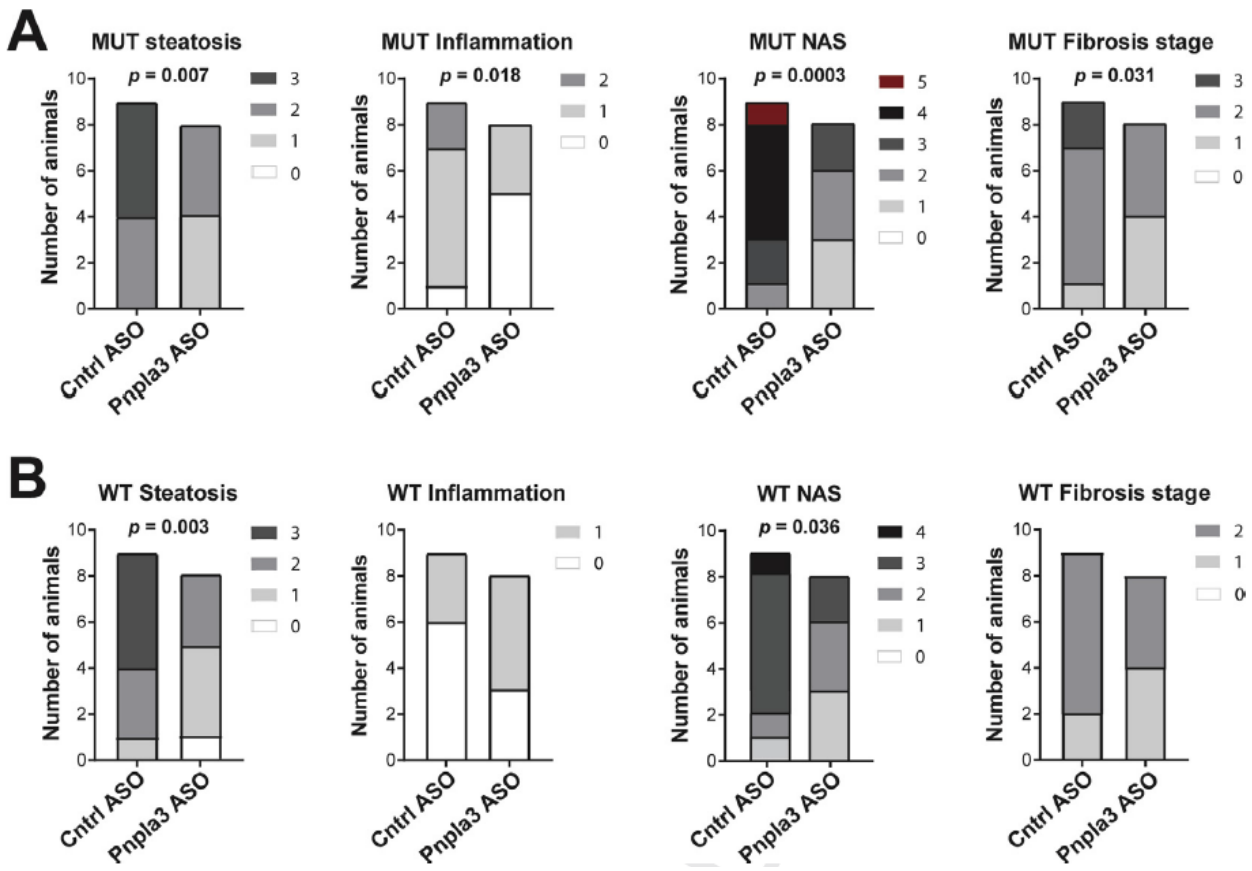
- No AEs related to study drug
- All AEs mild in severity
- No deaths or AEs leading to study withdrawal
- One treatment-emergent SAE (unrelated to study drug) in Cohort A3
  - Tonsillitis requiring hospitalization; resolved
- No clinically significant elevations in serum ALT or other laboratory abnormalities
- 4 patients with injection site reactions, all mild and transient
- No ECG findings of clinical significance

Planned Next Steps for ALN-HSD



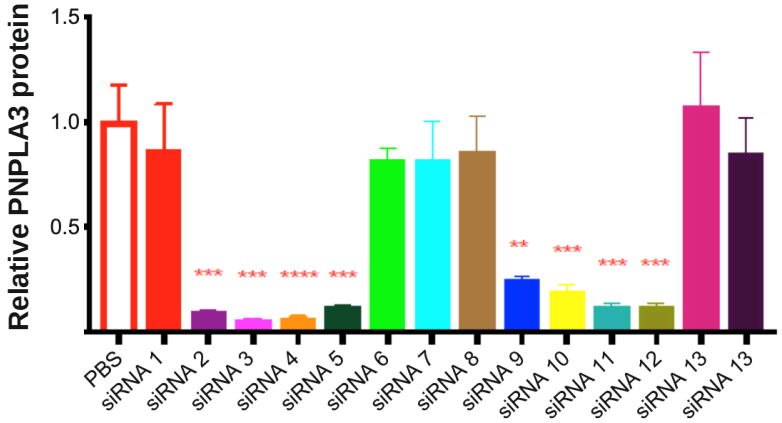
Silencing Hepatic PNPLA3 as Potential Mechanism to Treat NASH

ASO-mediated lowering of PNPLA3 reduces steatosis and NASH activity in mouse model



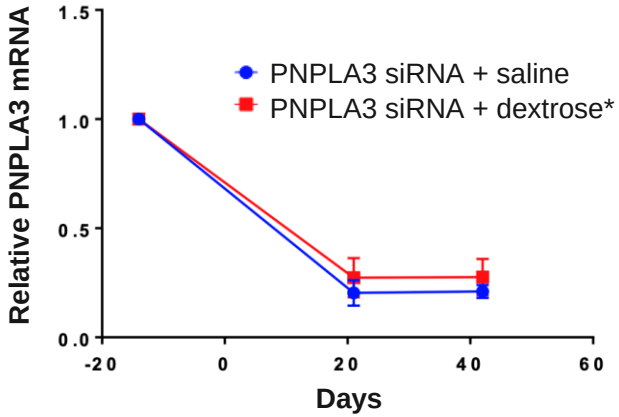
Efficient KD of PNPLA3 protein by candidate siRNAs

Human PNPLA3 I148M knock-in mice



Durable RNAi-mediated silencing of PNPLA3 in NHPs

Following single SC injection



*PNPLA3 is induced by elevated blood glucose

Lindén, D., et al. (2019). Molecular Metabolism 22(), 49-61. https://dx.doi.org/10.1016/j.molmet.2019.01.013

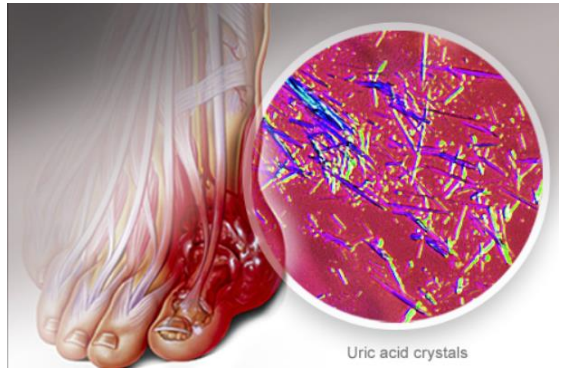
ALN-XDH for Gout

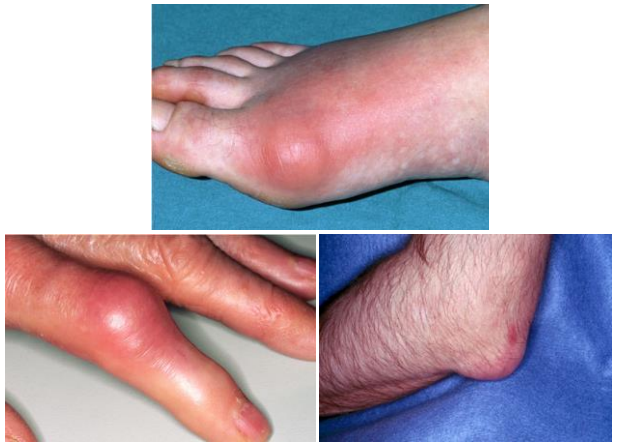
Alnylam PHARMACEUTICALS

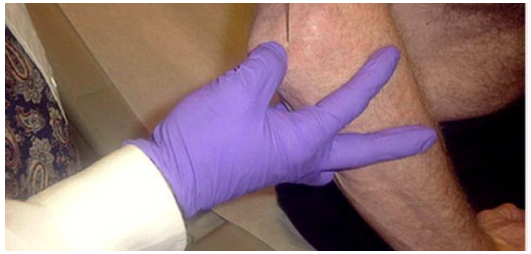
Gout

Arthritis Caused by Uric Acid Crystal Accumulation in Joints

- Most common inflammatory arthritis globally
  - Adult prevalence <1% - 6.8%
  - 14-18M individuals in US, EU5 and Japan
  - Risk factors include, increasing age, obesity, poor diet and comorbid metabolic conditions (CKD, HTN, CVD, etc.)
- Debilitating symptoms
  - Pain, edema, inflammatory arthropathy
  - Tophi, joint destruction
  - Accompanied by chronic urate nephropathy in some patients
- Diagnosis by detection of monosodium urate crystals (MSU) in aspirated joint fluid
- Urate lowering therapy essential to prevent attacks
- Targeting hepatic XDH may offer potent urate-lowering and disease control



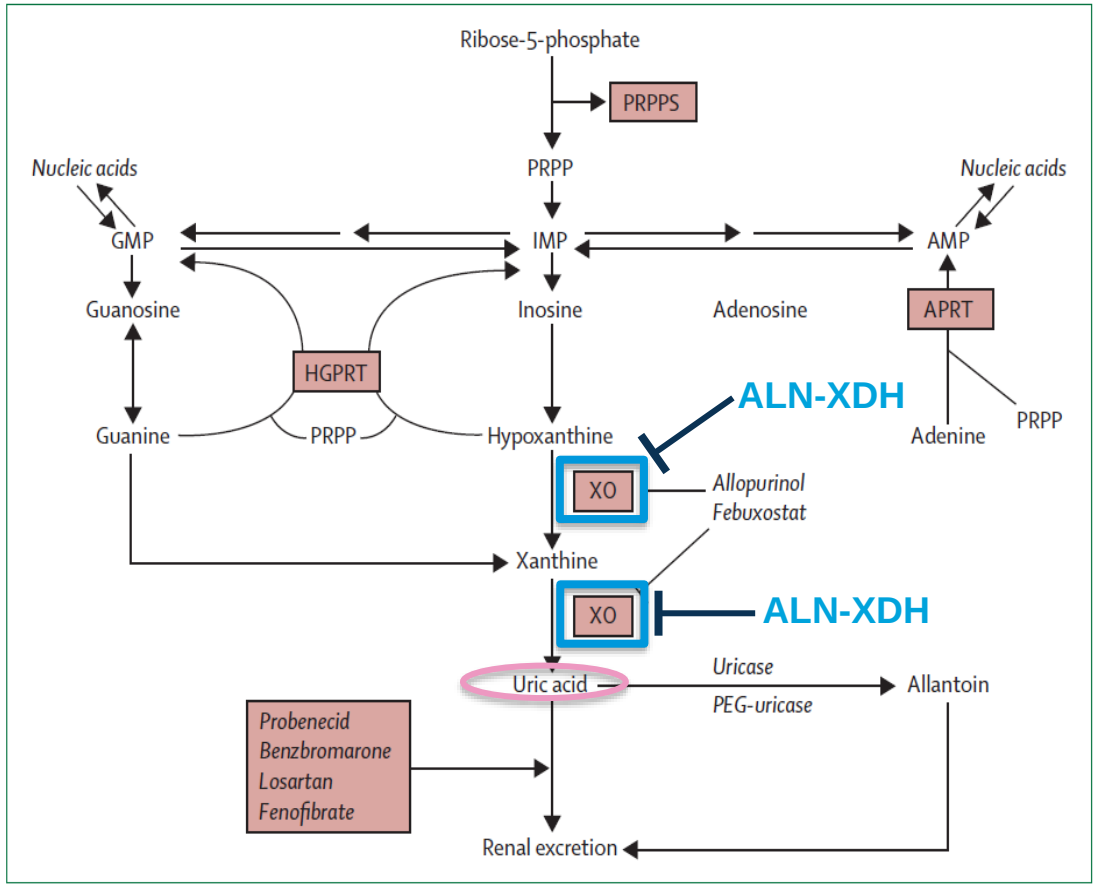




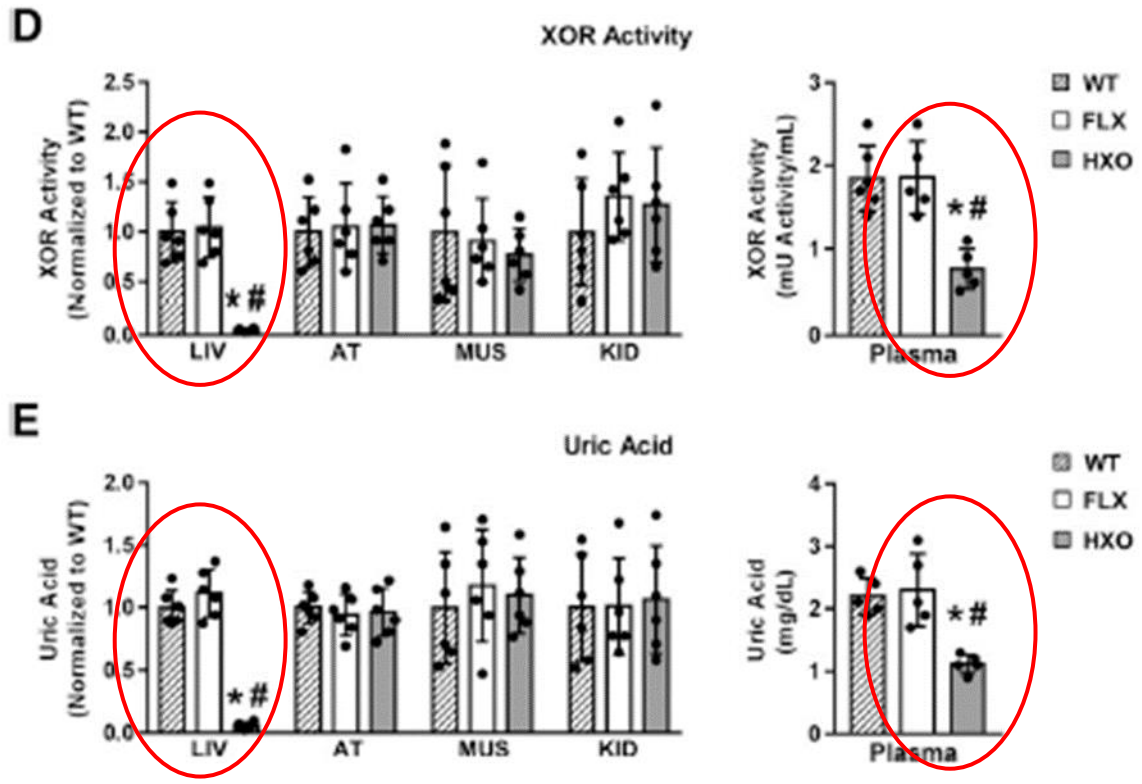
Dehlin et al. *Nature Reviews Rheumatology* 16(7):380-390 (2020); Chen-Xu et al. *Arthritis & Rheumatology* 71(6): 991-999 (2019); Koto et al. *Modern Rheumatology* 20:1-9 (2020); Kuo et al. *Nature Reviews Rheumatology 11*(11):649-662 (2015); GlobalData Disease Analysis

Targeting Xanthine Dehydrogenase (XDH)

Enzyme in Purine Metabolism Pathway*



Liver-specific Knockout of XDH in Mice Lowered Circulating Uric Acid*



*Xanthine dehydrogenase (XDH) and xanthine oxidase (XO) are enzymatic forms of the protein xanthine oxidoreductase (XOR); the target gene is XDH

Harmon DB, et al Diabetes, 68:1221–1229 (2019); Schumacher HR, et. al, Arth Care Res, 59:1540-48 (2008)

ALN-XDH Phase 1/2 Study Design

Proposed Seamless Study in Healthy Volunteers and Gout Patients

Part A: Healthy Volunteers

- Single-ascending doses
- Objectives:
  - Safety & tolerability
  - Uric acid lowering
  - PK
  - XO activity

Part B: Gout Patients

- Multiple doses
- Objectives:
  - Safety & tolerability
  - Uric acid lowering
  - Occurrence of gout flares
  - XO activity

Potential to Improve Gout Control with ALN-XDH

- Current gout therapies have substantial limitations
  - Allopurinol most commonly prescribed; however, side effects limit ability to achieve target uric acid levels in majority of patients
  - Uricosuric agents (e.g., probenecid) dosed multiple times per day and can promote stone formation
  - Newer agents (e.g., febuxostat, pegloticase) associated with other challenges (e.g., potential cardiovascular risk, immunogenicity)

- As a result, majority of patients are untreated, cannot adhere to prescribed therapy, or do not reach target uric acid levels

- ALN-XDH is an investigational RNAi therapeutic that may address key unmet needs for gout patients:
  - Potent urate-lowering effects
  - Infrequent dosing with tonic control between doses
  - Reduction in gout flares
  - Acceptable safety and tolerability

CTA filing planned **late 2021**
Phase 1/2 study start expected **early 2022**

Chen-Xu et al. Arthritis & Rheumatology 71(6): 991-999 (2019); Kim et al. *Arthritis Care & Research* 65(4): 578-584 (2013); Reinders et al. *Ann Rhuem Dis* 68: 51-56 (2009); UpToDate
July 2020 US KOL & PCP Market Research

Additional Opportunities from Liver-Directed Investigational RNAi Therapeutics

Summary

- Multiple attractive programs addressing areas of high unmet need
  - Cemdisiran for complement-mediated diseases
  - ALN-HBV02 (VIR-2218) for HBV infection
  - ALN-HSD and ALN-PNP for NASH
  - ALN-XDH for gout
  - ALN-KHK for metabolic syndrome and type 2 diabetes
- Reliance on genetically validated targets increases probability of success
- Increasing focus on specialty and large market opportunities, supported by platform safety profile and potential for tonic control of target gene expression with infrequent dosing

Progress Towards P^{5}x25

Yvonne Greenstreet, MBChB, MBA
President and COO

Alnylam PHARMACEUTICALS

Alnylam 2022 Goals

			Early	Mid	Late
onpattro (patisiran) / GIVLAARI (givosiran) / OXLUMO (lumasiran)		*Combined Net Product Revenue Guidance to be Provided at Q4'21 Earnings*			●
PATISIRAN	hATTR/ATTR Amyloidosis	APOLLO-B Phase 3 Topline Results		●	
		File sNDA for ATTR-CM			●
VUTRISIRAN*	hATTR/ATTR Amyloidosis	FDA Approval (4/14/22 PDUFA)	●		
		U.S. Launch	●		
		EMA Approval		●	
		Biannual Dose Regimen Data			●
	Stargardt Disease	Initiate Phase 3 in Stargardt Disease			●
ALN-TTRsc04*	ATTR Amyloidosis	File IND			●
		Initiate Phase 1 Study			●
LUMASIRAN	PH1, Recurrent Renal Stones	Complete Enrollment in Phase 2 Study in Recurrent Renal Stones			●
INCLISIRAN	Hypercholesterolemia	FDA Approval (1/1/22 PDUFA)	●		
CEMDISIRAN* (+/- POZELIMAB)	Complement-Mediated Diseases	Phase 2 Monotherapy Results in IgA Nephropathy	●		
		Initiate Phase 3 Combination Study in PNH			
ZILEBESIRAN*	Hypertension	Complete KARDIA-1 Enrollment		●	
		Complete KARDIA-2 Enrollment			●
		KARDIA-1 Phase 2 Topline Results			●
ALN-HBV02 (VIR-2218)*	Chronic HBV Infection	Phase 2 Combination Results	●		●
ALN-HSD*	NASH	Phase 1 Part B Topline Results		●	
ALN-APP*	Alzheimer's Disease	Initiate Phase 1 Study	●		
		Phase 1 Topline Results			●
ALN-XDH*	Gout	Initiate Phase 1 Study	●		
		Phase 1 Topline Results			●
ADDITIONAL PROGRAMS		File 2-4 new INDs	●	●	●

* Not approved for any indication and conclusions regarding the safety or effectiveness of these drugs have not been established

Early is Q1-Q2, Mid is Q2-Q3, and Late is Q3-Q4

Alnylam 2022 Goals

			Early	Mid	Late
onpattro (patisiran) / GIVLAARI (givosiran) / OXLUMO (lumasiran)		*Combined Net Product Revenue Guidance to be Provided at Q4'21 Earnings*			●
PATISIRAN	hATTR/ATTR Amyloidosis	APOLLO-B Phase 3 Topline Results		●	
		File sNDA for ATTR-CM			●
VUTRISIRA		FDA Approval (4/14/22 PDUFA)	●		
					●
					●
ALN-TTRsc					●
					●
LUMASIRA					●
INCLISIRA					
CEMDISIRA (+/- POZELIM					
ZILEBESIRA					●
					●
ALN-HBV02 (VIR-2218)	Chronic HBV Infection	Phase 2 Combination Results	●		●
ALN-HSD*	NASH	Phase 1 Part B Topline Results		●	
ALN-APP*	Alzheimer's Disease	Initiate Phase 1 Study	●		
		Phase 1 Topline Results			●
ALN-XDH*	Gout	Initiate Phase 1 Study	●		
		Phase 1 Topline Results			●
ADDITIONAL PROGRAMS		File 2-4 new INDs	●	●	●

- 5 commercial products
- 1 product launch
- 1 Phase 3 readout
- 1 sNDA filing
- 5 Phase 3 programs
- 5 Phase 2 programs
- 2-4 new INDs

* Not approved for any indication and conclusions regarding the safety or effectiveness of these drugs have not been established

Early is Q1-Q2, Mid is Q2-Q3, and Late is Q3-Q4

2022: Catalyst-Rich Year

Full 18-Month HELIOS-A Phase 3 Results with Vutrisiran	Early 2022
FDA Approval of Vutrisiran	Early 2022 *(PDUFA date = 4/14/22)*
APOLLO-B Phase 3 Results with Patisiran	Mid-2022
ALN-HSD Phase 1 Part B Topline Results in NASH Patients	Mid-2022
Vutrisiran Biannual Dose Regimen Data	Late 2022
ALN-APP Phase 1 Topline Results	Late 2022
KARDIA-1 Phase 2 Topline Results with Zilebesiran	Late 2022
ALN-XDH Phase 1 Topline Results	Late 2022

Patients: Over 0.5 million on Alnylam RNAi therapeutics globally

Products: 6+ marketed products in rare and prevalent diseases

Pipeline: Over 20 clinical programs, with 10+ in late stages and 4+ INDs per year

Performance: ≥40% revenue CAGR through YE 2025

Profitability: Achieve sustainable non-GAAP profitability within period

Alnylam P5x25

1. Patients

World-First Innovative Agreement for Leqvio

NOVARTIS

NHS

NICE National Institute for Health and Care Excellence

Office for Life Sciences

ATTR-CM

SPECIALTY

Patisiran: ATTR-CM[1]
Vutrisiran: ATTR-CM[2]
Cemdisiran

[1] Patisiran has not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in this population; [2] Vutrisiran is an investigational agent and has not been approved by the FDA, EMA, or any other regulatory agency and no conclusions can or should be drawn regarding its safety or effectiveness; NDA accepted seeking approval of vutrisiran for the treatment of the polyneuropathy of hATTR amyloidosis in adults based on positive 9-Month results in HELIOS-A study; HELIOS-B study of vutrisiran in ATTR patients with cardiomyopathy is ongoing.

Alnylam P[5]x25

2. Products

onpattro® (patisiran) lipid complex injection 10 mg/5 mL

Hereditary ATTR Amyloidosis with Polyneuropathy

GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

Acute Hepatic Porphyria

OXLUMO® (lumasiran) for injection 94.5 mg/0.5 mL

Primary Hyperoxaluria Type 1

Leqvio® (inclisiran)

Hypercholesterolemia

NOVARTIS

Vutrisiran – April 2022 PDUFA

(Hereditary ATTR Amyloidosis with Polyneuropathy)

HELIOS·A

Fitusiran[1]

(Hemophilia A or B, with or without inhibitors)

ATLAS

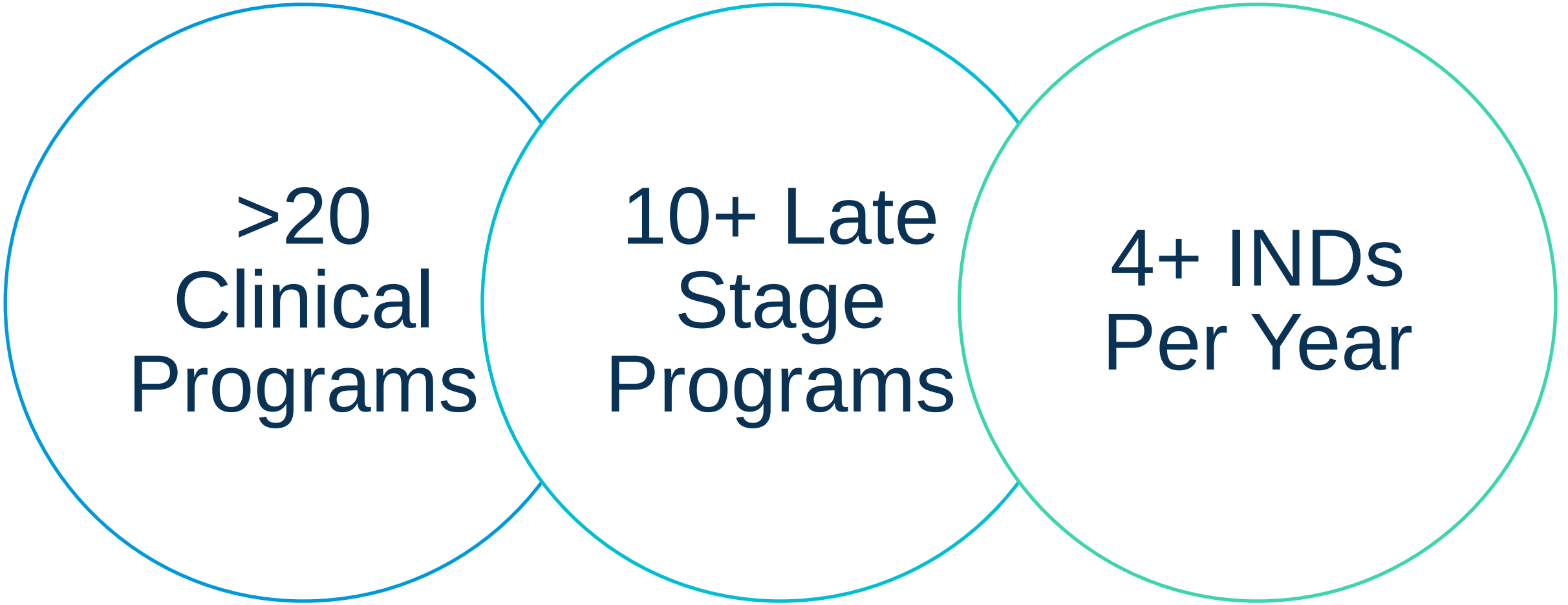
Cemdisiran[2]

(Myasthenia Gravis)

[1] Sanofi is leading and funding development of investigational fitusiran; [2] Alnylam and Regeneron are evaluating potential combinations of cemdisiran and pozelimab, both of which are investigational therapeutics.

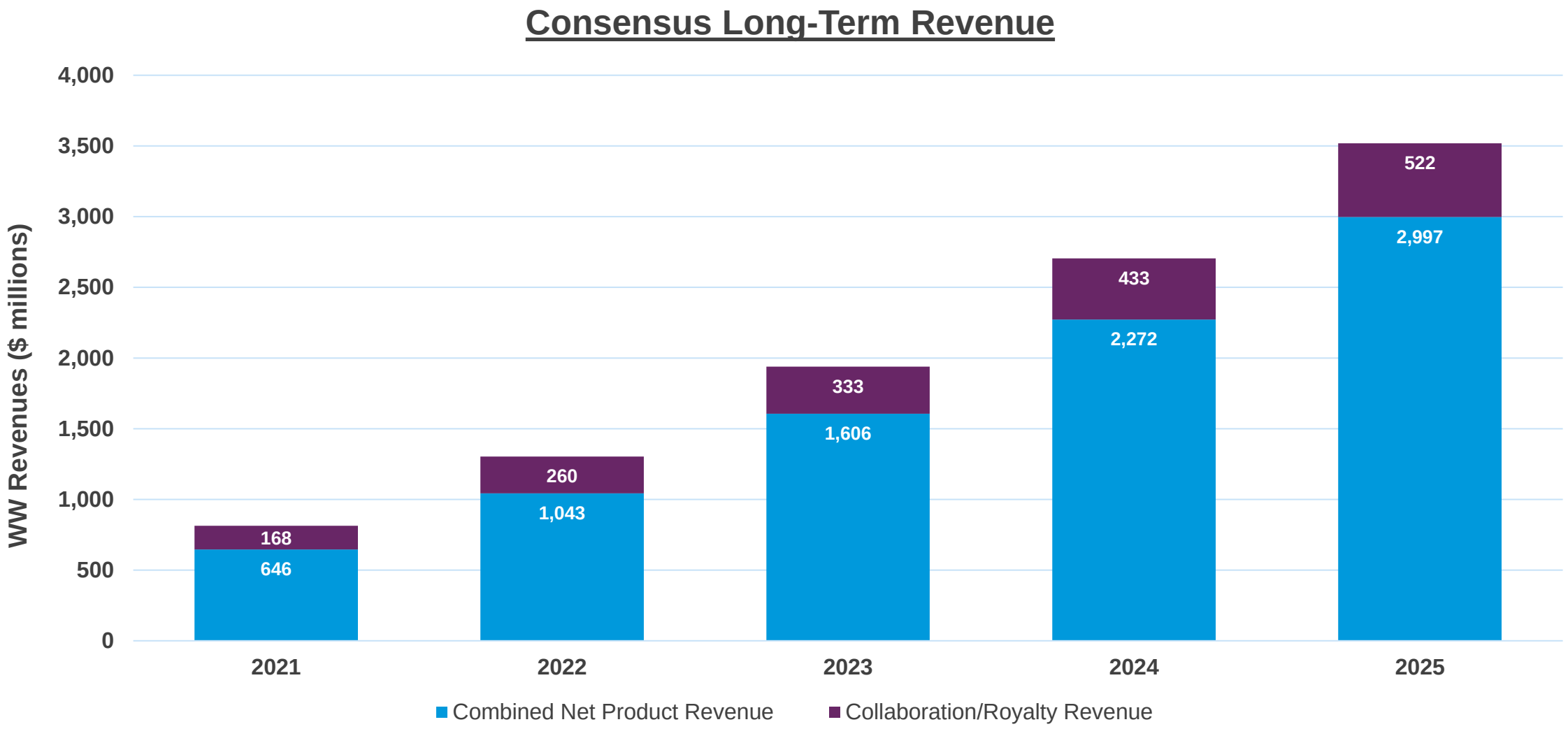
Alnylam P5x25

3. Pipeline



Alnylam P5x25

4. Performance



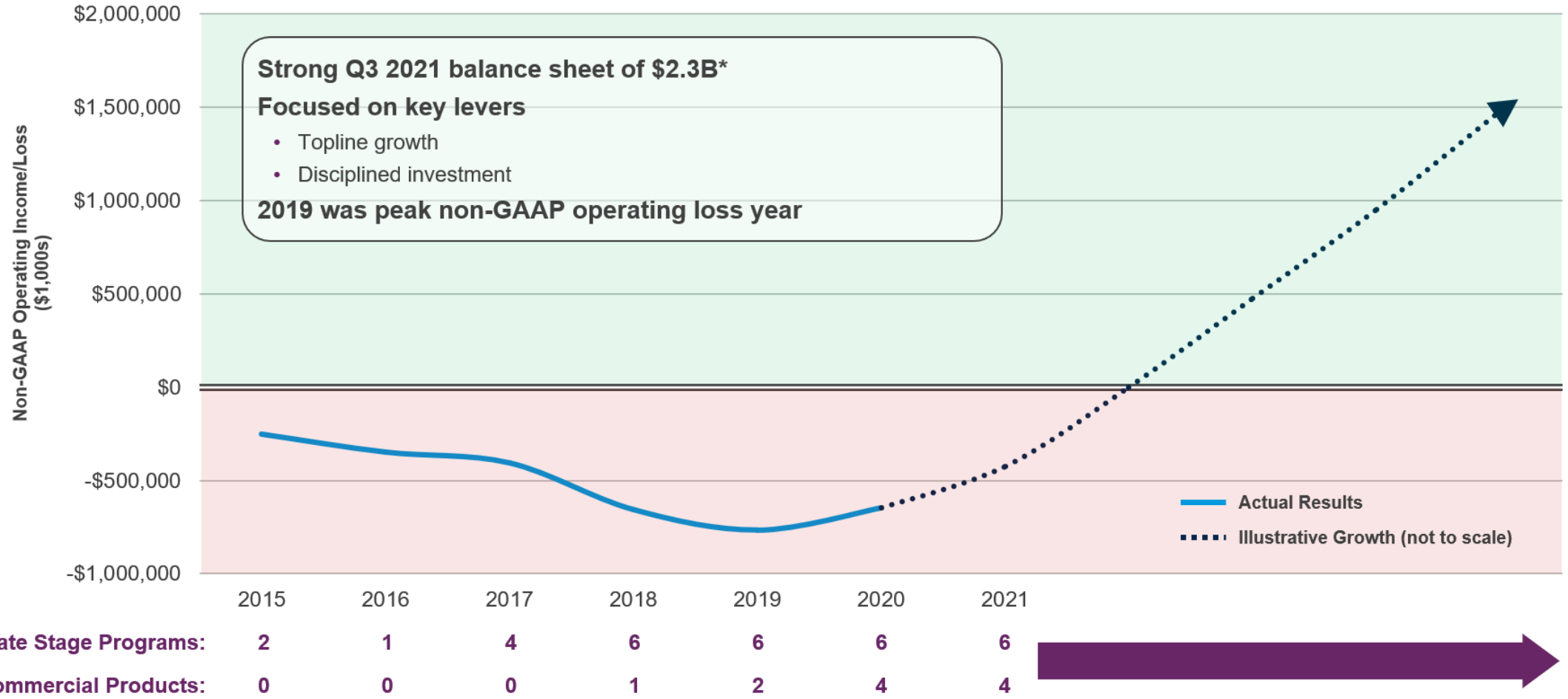
As of November 8, 2021

Disclaimer: Analyst consensus estimates are calculated by Alnylam Pharmaceuticals, Inc. based on the projections made by sell-side analysts who cover Alnylam as of November 8, 2021. The opinions, estimates or forecasts regarding Alnylam's performance made by these analysts (and therefore the consensus estimate numbers) are theirs and do not represent opinions, estimates, forecasts or predictions of Alnylam or its management. Alnylam does not by its reference above or distribution imply its endorsement of or concurrence with such opinions, estimates, forecasts or predictions. Alnylam does not assume any duty to update or revise the consensus estimate numbers, even if they differ from Alnylam's own estimates, forecasts or projections.

Alnylam P5x25

5. Profitability

Alnylam entering period of projected growth on path to profitability



* Including cash, cash equivalents, and marketable securities

Alnylam P5x25

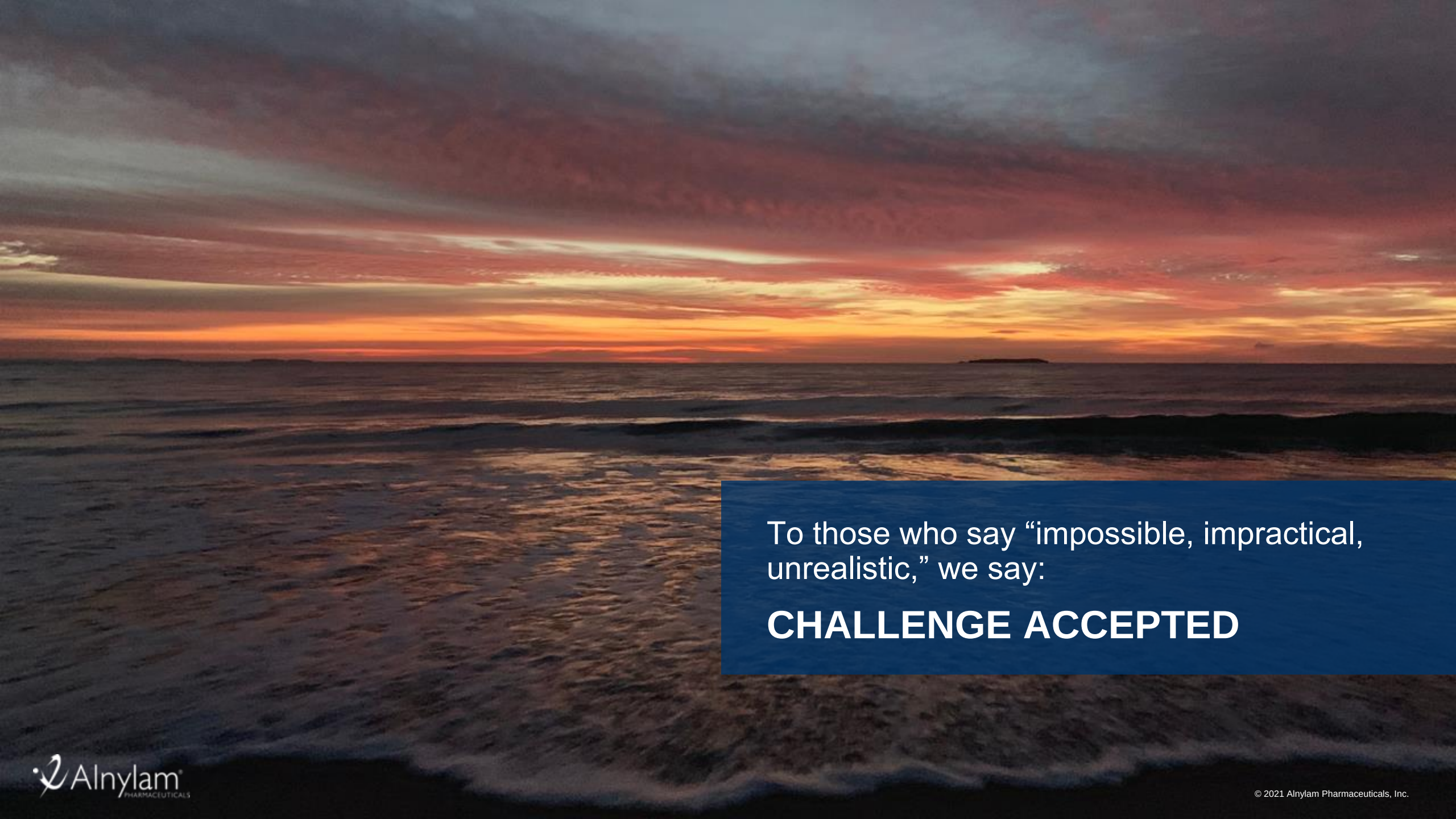
People = Priceless

Science 2021 TOP EMPLOYER

BEST WORKPLACES FOR INNOVATORS
FAST COMPANY

Great Place To Work®

The Boston Globe TOP PLACES TO WORK



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