2021 Investor Day

December 9, 2021

Nasdaq: IONS

Participating in Today's Presentation

- There will be one Q&A session at the end of today's program
- Submit questions in the "Ask a Question" field and click send
- A replay will be available on the Investors page of the Ionis website later today
- Today's slides may be downloaded from the Investors section of the Ionis website under Events
- For technical assistance, click on the "Help" icon located at the upper right of the page

Forward-Looking Statements

This presentation includes forward-looking statements regarding our business, financial guidance and the therapeutic and commercial potential of SPINRAZA® (nusinersen), eplontersen, olezarsen, donidalorsen, Ionis' technologies, and Ionis' other products in development. Any statement describing Ionis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, including those related to the impact COVID-19 could have on our business, and including but not limited to those related to our commercial products and the medicines in our pipeline, and particularly those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. Ionis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' annual report on Form 10-K for the year ended December 31, 2020 and our most recent Form 10-Q quarterly filing, which are on file with the SEC. Copies of this and other documents are available at www.ionispharma.com.

In this presentation, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries.

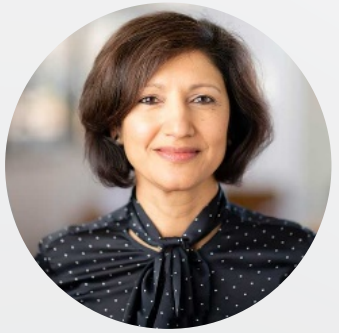
Building a Leading Biotechnology Company

Brett Monia, Ph.D.
Chief Executive Officer

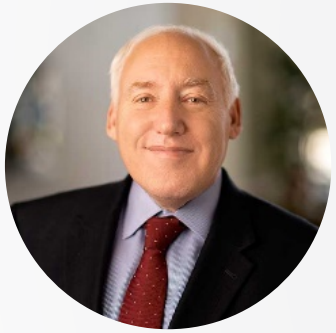
Company Presenters

Brett Monia, Ph.D.
Chief Executive Officer

Sam Tsimikas, M.D.
SVP, Global Cardiovascular Development



Onaiza Cadoret
Chief Corp. Dev. & Commercial Officer



Kenneth Newman, M.D.
VP, Clinical Development

Eric Swayze, Ph.D.
EVP, Research

Beth Hougen
Chief Financial Officer

Agenda

Topic	Speaker
Welcome	Jennifer Capuzelo
Building a Leading Biotechnology Company	Brett Monia, Ph.D.
Advances in Treating Cardiovascular Disease	Sam Tsimikas, M.D.
Delivering Potentially Transformational Medicines to the Market – Eplontersen: offering new hope for patients with ATTR amyloidosis – Olezarsen: delivering a new approach for treating severely elevated triglycerides	Onaiza Cadoret
Donidalorsen: Potential Best-in-Class HAE Prophylactic Treatment – Phase 2 Results	Kenneth Newman, M.D.
Delivering Potentially Transformational Medicines to the Market – Donidalorsen: reimagining the treatment of hereditary angioedema	Onaiza Cadoret
Advances in Antisense Technology	Eric Swayze, Ph.D.
Financial Growth Today and Tomorrow	Beth Hougen
Concluding Remarks	Brett Monia
Q&A	

Key Takeaways

1

Clear vision

Become a **leading** fully-integrated **biotechnology company**

2

Positioned for substantial growth

Rich mid- & late-stage pipeline of potentially transformational medicines advancing towards the market

3

Technology leadership

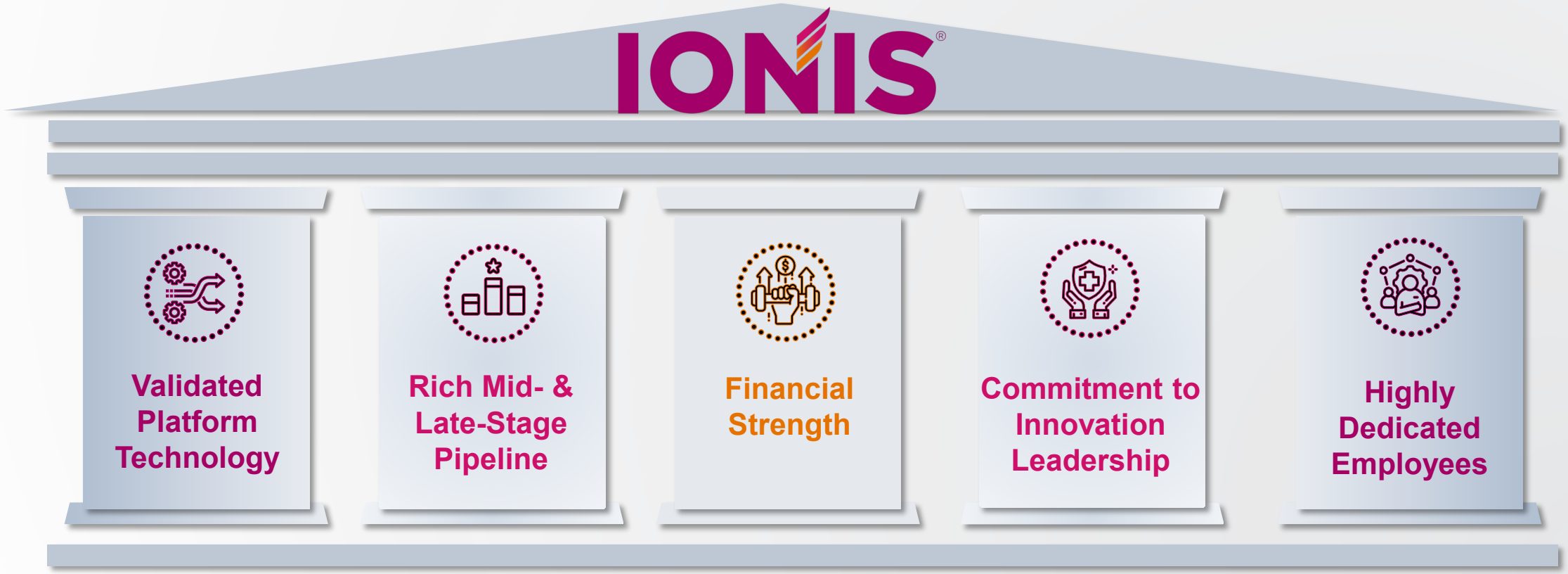
Our technology is advancing at an unprecedented pace, expanding our opportunities and **extending** our **leadership position**

4

Compelling financial profile

Ionis' strong financial position enables all needed investments in support of **substantial growth** and our vision

Established Foundation Enables Accelerated & Substantial Growth



IONIS

GROWTH

Build-Out Pipeline

Commercialize Our Products

Expand & Diversify Technology

Deliver Abundance of New Medicines To Market

Validated Platform Technology

Rich Mid- & Late-Stage Pipeline

Financial Strength

Commitment to Innovation Leadership

Highly Dedicated Employees

Two Leading Therapeutic Franchises

Cardiovascular

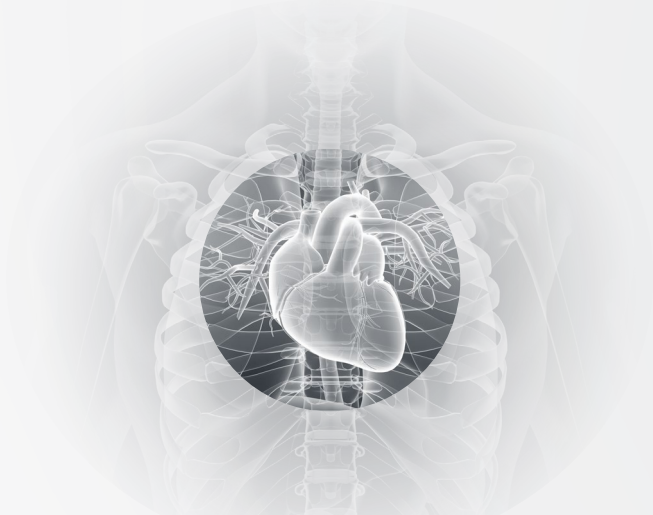
Addressing major cardiovascular disease risk factors

4 Ongoing Phase 3 studies

Eplontersen • Pelacarsen • Olezarsen

9 Medicines in clinical development

- ❑ 4 in Phase 2
- ❑ 2 in Phase 1



Neurological

Addressing major neurological diseases

3 Ongoing Phase 3 studies

Eplontersen • Tofersen • ION363 (FUS-ALS)

10 Medicines in clinical development

- ❑ 7 in Phase 2

Rich Phase 3 Pipeline

6 Medicines for 8 Indications

		Phase 3 Data[1]	Prevalence[2]
Tofersen	SOD1-ALS	2021	**~1.4K patients** in G7 countries
Eplontersen	hATTR polyneuropathy	2022	**>40K patients** worldwide
Olezarsen	FCS	2023	**~3-5K patients** worldwide
Eplontersen	ATTR cardiomyopathy	2024	**~300-500K patients** worldwide
Olezarsen	SHTG	2024	**>3M patients** in US
Donidalorsen	HAE	2024	>**20K patients** in US and EU
ION363	FUS-ALS	2024	**~350 patients** in G7 countries
Pelacarsen	Lp(a) CVD	2025	**>8M patients** worldwide

Cardiovascular Neurology Specialty Rare

1. Timing expectations are based on current assumptions and are subject to change. 2. Market data on file.
ALS, amyotrophic lateral sclerosis; hATTR, hereditary transthyretin amyloidosis; FCS, familial chylomicronemia syndrome; SHTG, severe hypertriglyceridemia; HAE, hereditary angioedema; Lp(a), lipoprotein a; CVD, cardiovascular disease.

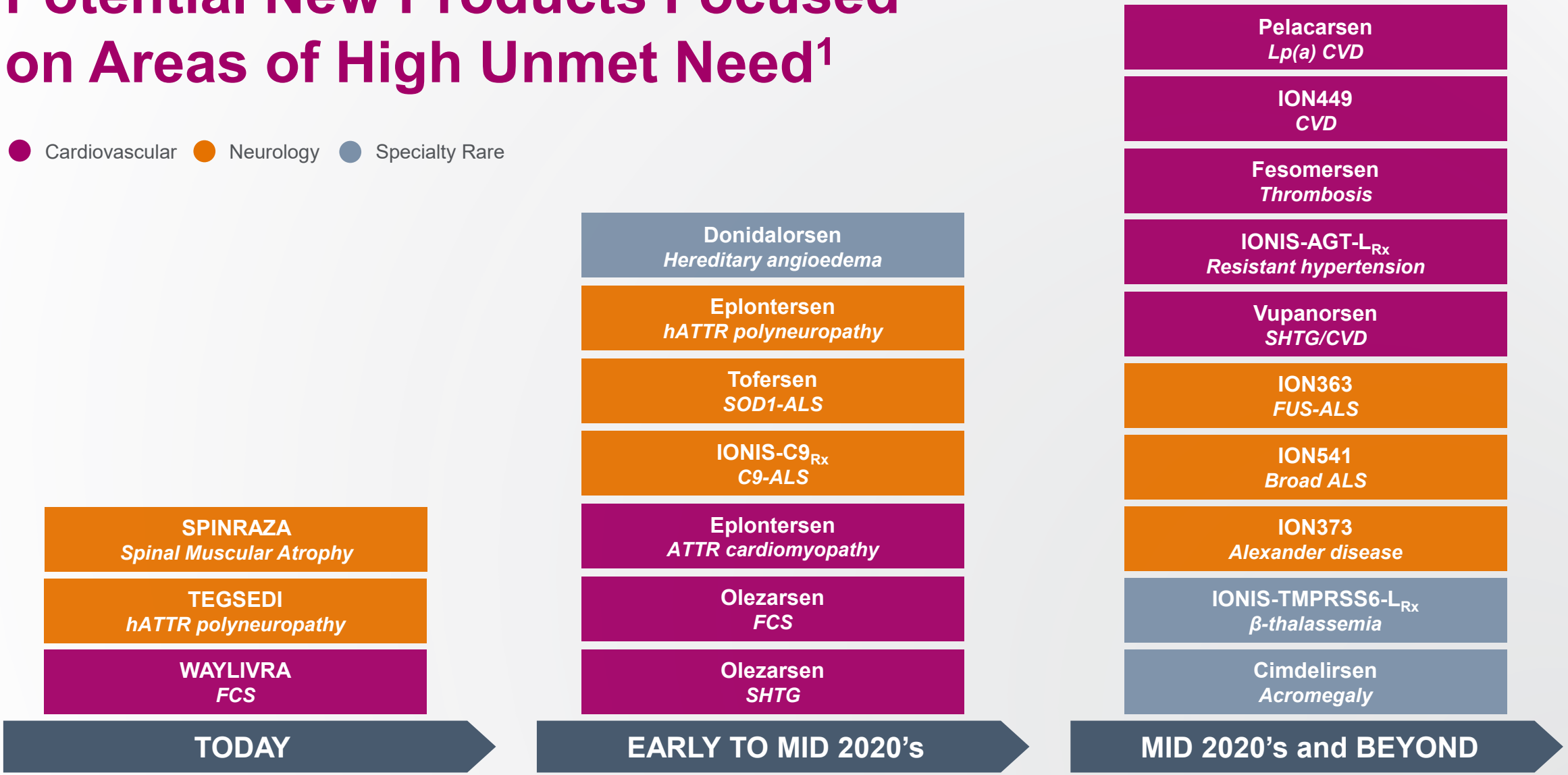
Mid- and Late-Stage Pipeline

		MID-STAGE (Phase 1/2 - Phase 2)	LATE-STAGE (Phase 3)	COMMERCIAL RIGHTS
Eplontersen	hATTR polyneuropathy		●	Cost-sharing & royalty bearing
Olezarsen	FCS		●	Global
Eplontersen	ATTR cardiomyopathy		●	Cost-sharing & royalty bearing
Olezarsen	SHTG		●	Global
Donidalorsen	Hereditary angioedema		●	Global
ION363	FUS/ALS		●	Global
Pelacarsen	Lp(a) CVD		●	Milestones & up to low 20% royalties
Tofersen	SOD1-ALS		●	Milestones & up to mid-teen royalties
Vupanorsen	SHTG/CVD	●		Milestones & up to low 20% royalties
ION449	CVD	●		Milestones & up to low teen royalties
Fesomersen	Clotting disorders	●		Milestones & up to high 20% royalties
IONIS-AGT-L_{Rx}	Treatment-resistant hypertension	●		Global
ION373	Alexander disease	●		Global
IONIS-$MAPT_{Rx}$	Alzheimer's disease	●		Milestones & up to mid-teen royalties
IONIS-$C9_{Rx}$	C9-ALS	●		Milestones & up to mid-teen royalties
ION541	ALS sporadic	●		Milestones & up to mid-teen royalties
ION464	MSA & Parkinson's disease	●		Milestones & up to mid-teen royalties
ION859	Parkinson's disease	●		Milestones & up to mid-teen royalties
IONIS-DNM2-2.5_{Rx}	Centronuclear myopathy	●		Milestones & up to mid-teen royalties
IONIS-TMPRSS6-L_{Rx}	b-thalassemia	●		Global
Cimdelirsen	Acromegaly	●		Global

● Cardiovascular ● Neurology ● Specialty Rare

Potential New Products Focused on Areas of High Unmet Need[1]

Cardiovascular Neurology Specialty Rare



1. Timing expectations are based on current assumptions and are subject to change.

Eplontersen + Olezarsen + Donidalorsen

3 Near-term Opportunities with Aggregate Multibillion-dollar Potential[1,2]

Eplontersen

~300,000-500,000 patients
in 2 indications worldwide

First Phase 3 data readout: 2022

Potential to **change the standard-of-care** for patients with TTR amyloidosis

Estimated peak sales: 

Olezarsen

>3 million patients
in 2 indications in the US

First Phase 3 data readout: 2023

Potential **first-in-class** treatment for patients with elevated triglycerides

Estimated peak sales: 

Donidalorsen

>20,000 patients
in the US and EU

Phase 3 data readout: 2024

Potential **best-in-class** prophylactic treatment for patients with HAE

Estimated peak sales: 

Estimated peak sales:  <1 Billion  >1 Billion  Multibillion

1. Market data on file. 2. Timing expectations and peak sales estimates are based on current assumptions and are subject to change

4 Key Questions To Be Addressed Today

1

Which near-term products will we prioritize for commercialization?

2

What is our go-to-market plan for our prioritized assets?

How will we succeed?

3

How will we extend our technology leadership?

How will this drive continued success versus competition?

4

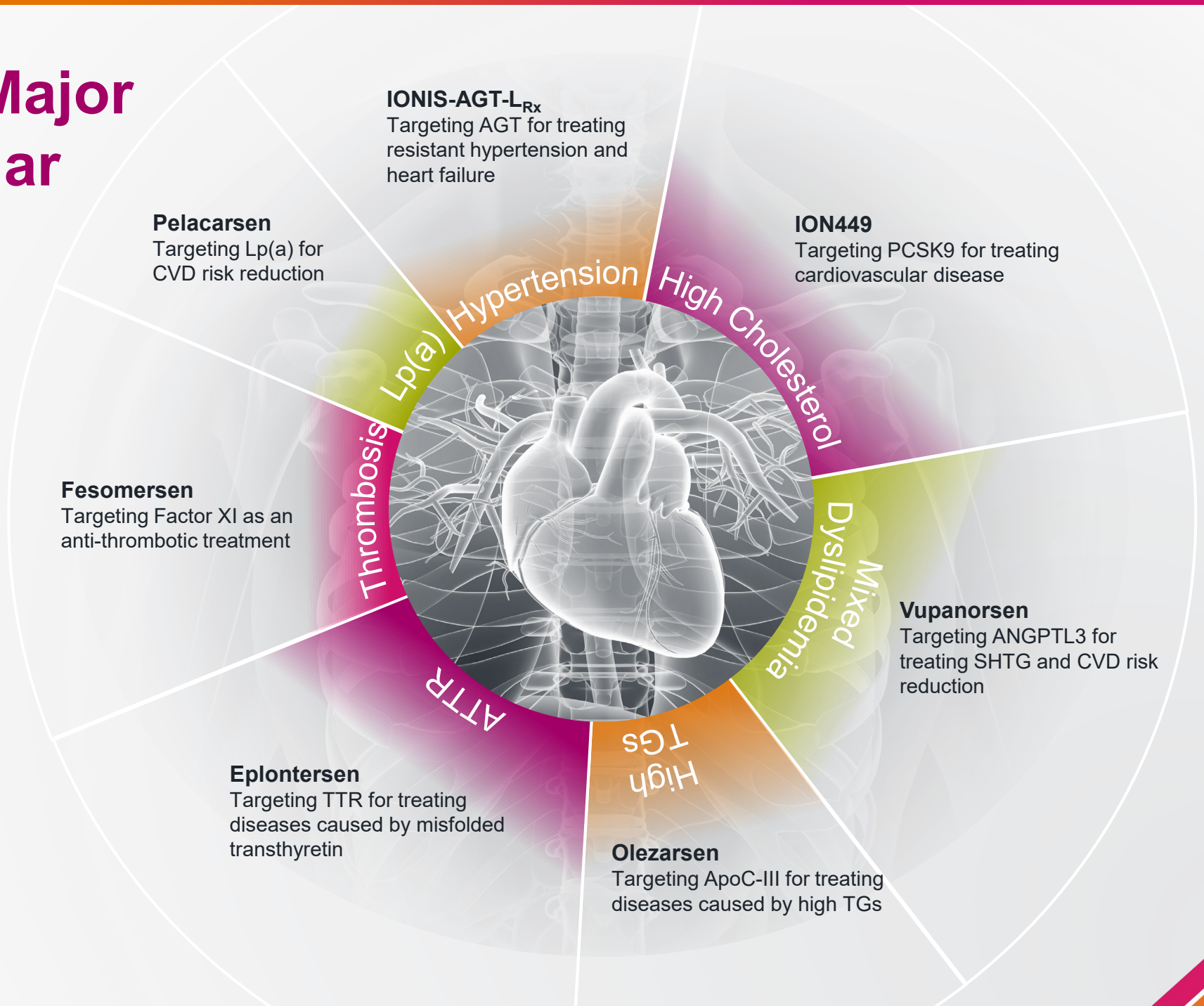
Do we have the resources to achieve our vision?

What are our growth expectations?

Advances in Treating Cardiovascular Disease

Sam Tsimikas, M.D.
SVP, Global Cardiovascular Development

Addressing Major Cardiovascular Disease Risk Factors



IONIS-AGT-L_{Rx}
Targeting AGT for treating resistant hypertension and heart failure

Pelacarsen
Targeting Lp(a) for CVD risk reduction

ION449
Targeting PCSK9 for treating cardiovascular disease

Fesomersen
Targeting Factor XI as an anti-thrombotic treatment

Vupanorsen
Targeting ANGPTL3 for treating SHTG and CVD risk reduction

Eplontersen
Targeting TTR for treating diseases caused by misfolded transthyretin

Olezarsen
Targeting ApoC-III for treating diseases caused by high TGs

Major Ionis CV Publications since 2010

The NEW ENGLAND JOURNAL of MEDICINE

2014 *WAYLIVRA*

Targeting APOC3 in the Familial Chylomicronemia Syndrome

2015 *WAYLIVRA*

Antisense Inhibition of Apolipoprotein C-III in Patients with Hypertriglyceridemia

2015 *Fesomersen*

Factor XI Antisense Oligonucleotide for Prevention of Venous Thrombosis

2017 *Vupanorsen*

Cardiovascular and Metabolic Effects of *ANGPTL3* Antisense Oligonucleotides

2018 *TEGSEDI*

Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis

2019 *WAYLIVRA*

Volanesorsen and Triglyceride Levels in Familial Chylomicronemia Syndrome

2020 *Pelacarsen*

Lipoprotein(a) Reduction in Persons with Cardiovascular Disease

THE LANCET

2010 *KYNAMRO*

Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolaemia: a randomised, double-blind, placebo-controlled trial

2015 *Pelacarsen*

Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study

2016 *Pelacarsen*

Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials

European Heart Journal

2019 *Olezarsen*

N-acetyl galactosamine-conjugated antisense drug to APOC3 mRNA, triglycerides and atherogenic lipoprotein levels

2020 *Vupanorsen*

Vupanorsen, an N-acetyl galactosamine-conjugated antisense drug to ANGPTL3 mRNA, lowers triglycerides and atherogenic lipoproteins in patients with diabetes, hepatic steatosis, and hypertriglyceridaemia

JACC Basic to Translational Science An Open Access Journal

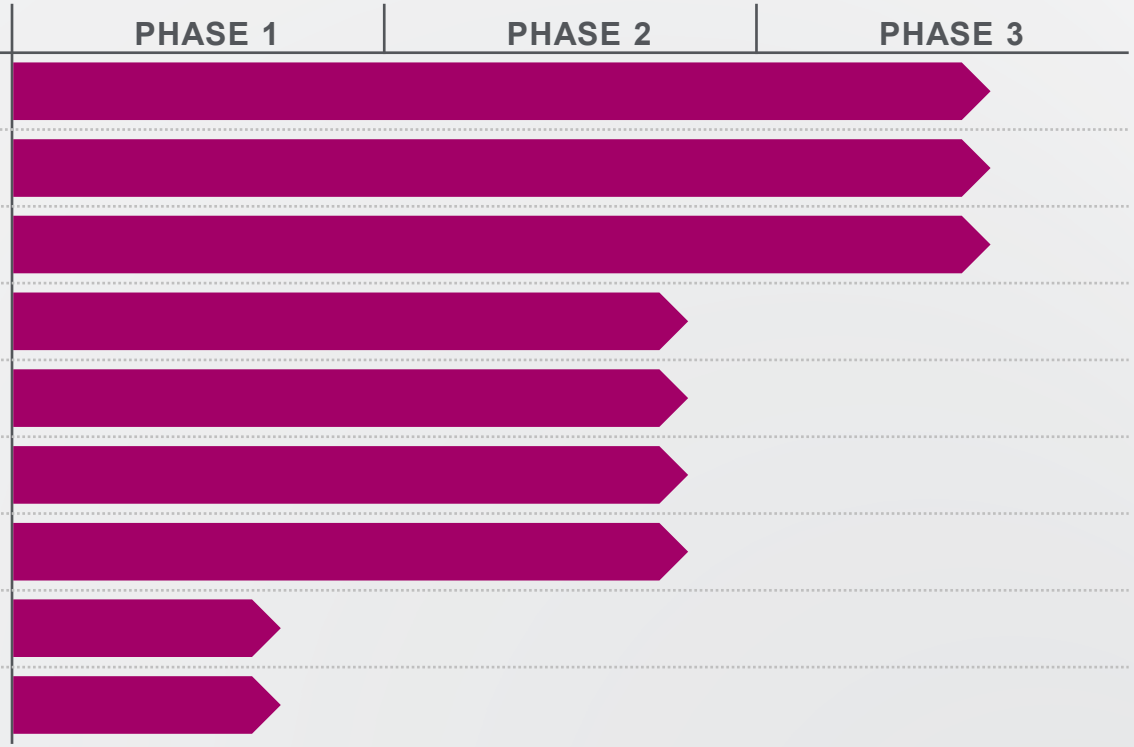
2021 *AGT-L_{Rx}*

Antisense Inhibition of Angiotensinogen With IONIS-AGT-L Rx: Results of Phase 1 and Phase 2 Studies

Current Cardiovascular Disease Pipeline

Promising Programs to Drive Mid-term Growth

MEDICINES	INDICATION	TARGET	PARTNER
Eplontersen	ATTR cardiomyopathy	TTR	AstraZeneca
Olezarsen	FCS/SHTG	APOCIII	Ionis
Pelacarsen	Lp(a) CVD	Lp(a)	Novartis
Vupanorsen	SHTG/CVD	ANGPTL3	Pfizer
Fesomersen	Clotting disorders	FXI	Bayer
ION449	LDL-C/CVD	PCSK9	AstraZeneca
IONIS-AGT-L_{Rx}	Resistant hypertension	AGT	Ionis
ION904	Resistant hypertension	AGT	Ionis
ION547	Thrombotic disorders	FXII	Ionis



Cardiovascular disease pipeline programs benefit from LICA platform advantages

CVD, cardiovascular disease

Current Cardiovascular Disease Pipeline

Promising Programs to Drive Mid-term Growth

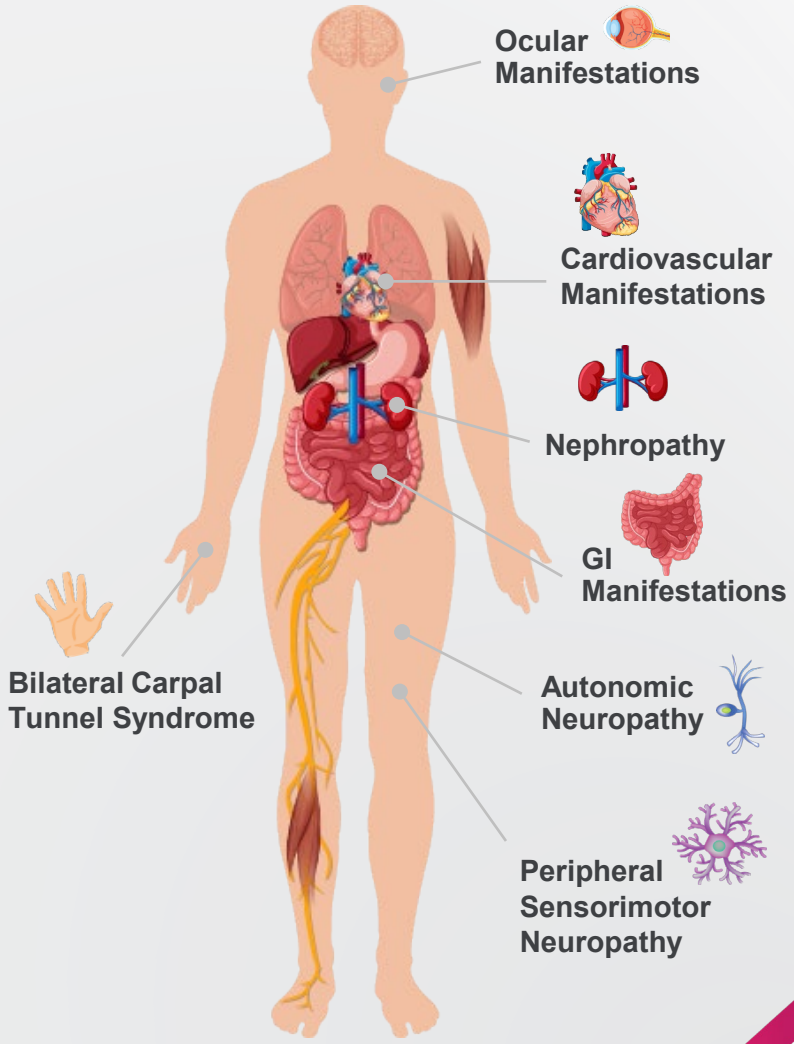
MEDICINES	INDICATION	TARGET	PARTNER	PHASE 1	PHASE 2	PHASE 3
Eplontersen	ATTR cardiomyopathy	TTR	AstraZeneca			
Olezarsen	FCS/SHTG	APOCIII	Ionis			
Pelacarsen	Lp(a) CVD	Lp(a)	Novartis			
Vupanorsen	SHTG CVD	ANGPTL3	Pfizer			
Fesomersen	Clotting disorders	FXI	Bayer			
ION449	LDL-C/CVD	PCSK9	AstraZeneca			
IONIS-AGT-L_{Rx}	Resistant hypertension	AGT	Ionis			
ION904	Resistant hypertension	AGT	Ionis			
ION547	Thrombotic disorders	FXII	Ionis			

TTR Amyloidosis: a Progressively Debilitating and Fatal Disease

- Patients suffer from neuropathy, cardiac disease, nephropathy and gastrointestinal symptoms
- Progressive disease resulting in a rapid decline in quality of life
  - 3-15 year life expectancy for polyneuropathy[3] patients
  - 2-5 year life expectancy for cardiomyopathy[4] patients

~300K-500K
patients worldwide[1,2]

~40K hATTR polyneuropathy
>300K ATTR cardiomyopathy



GI, gastrointestinal. 1. Conceição I et al. *J Peripher Nerv Syst*. 2016;21:5-9. 2. Ando Y et al. *Orphanet J Rare Dis*. 2013;8:31. 3. Gertz MA. *Am J Manag Care*. 2017;23:S107-S112. 4. Maurer MS et al. *Circulation*. 2017;135:1357-1377.

Eplontersen Phase 1 Results

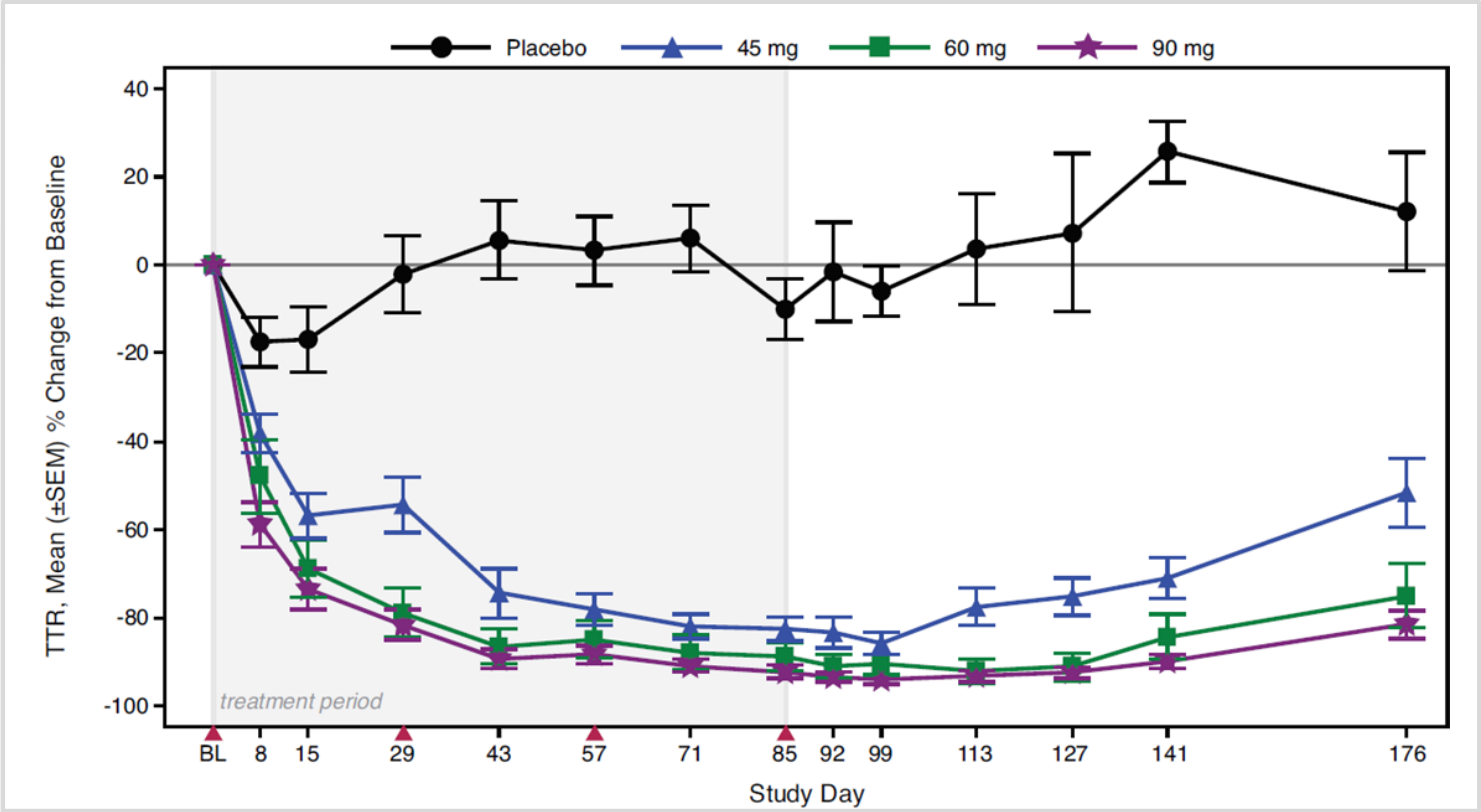
Robust TTR Reductions with Favorable Safety and Tolerability

Phase 1 Study

- Dose-escalation, placebo-controlled study in 47 healthy volunteers
- Objectives: Safety and pharmacokinetics, pharmacodynamics and change in TTR levels

Results

- Achieved a mean reduction in TTR levels of 94%
- Favorable safety and tolerability profile



CARDIO-TTRansform

Phase 3 Study in Patients with ATTR-cardiomyopathy

cardio TTRansform

DESIGN

A global, randomized, double-blind, placebo-controlled study in up to 750 patients with hereditary or wild-type TTR amyloid cardiomyopathy

MRI sub-study to understand eplontersen impact on cardiac structure and function

PRIMARY ENDPOINT

Cardiovascular death & frequency of cardiovascular clinical events at Week 120

On track for data in 2024[1]

1. Timing expectations are based on current assumptions and are subject to change

APOCIII: A New Approach to Treating Diseases Caused by Severely Elevated Triglycerides (TGs)

ApoCIII

- Protein produced in the liver that regulates triglyceride metabolism in the blood
- Independent cardiovascular risk factor
- Validated target for FCS, SHTG & CVD

Elevated triglycerides associated with major medical issues

- Acute pancreatitis, with attendant significant morbidity and mortality
- Higher risk of cardiovascular disease

FCS

~ 3,000-5,000

patients in the US[1]

SHTG

(≥500mg/dL)

> 3 million

patients in the US[1]

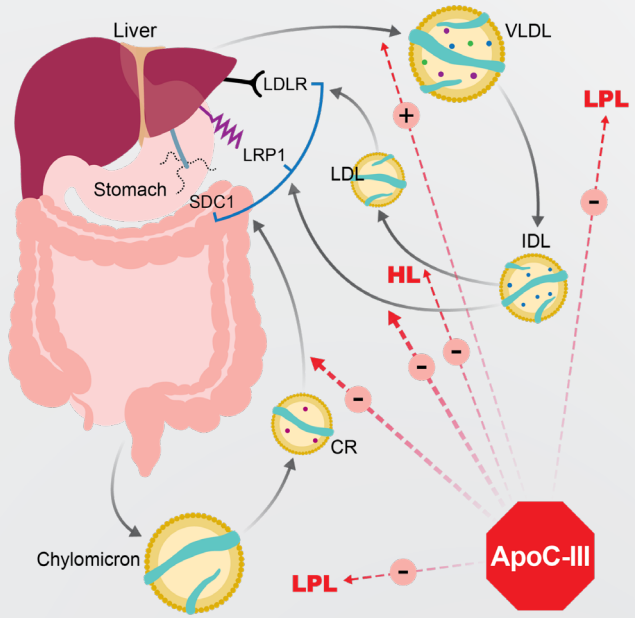
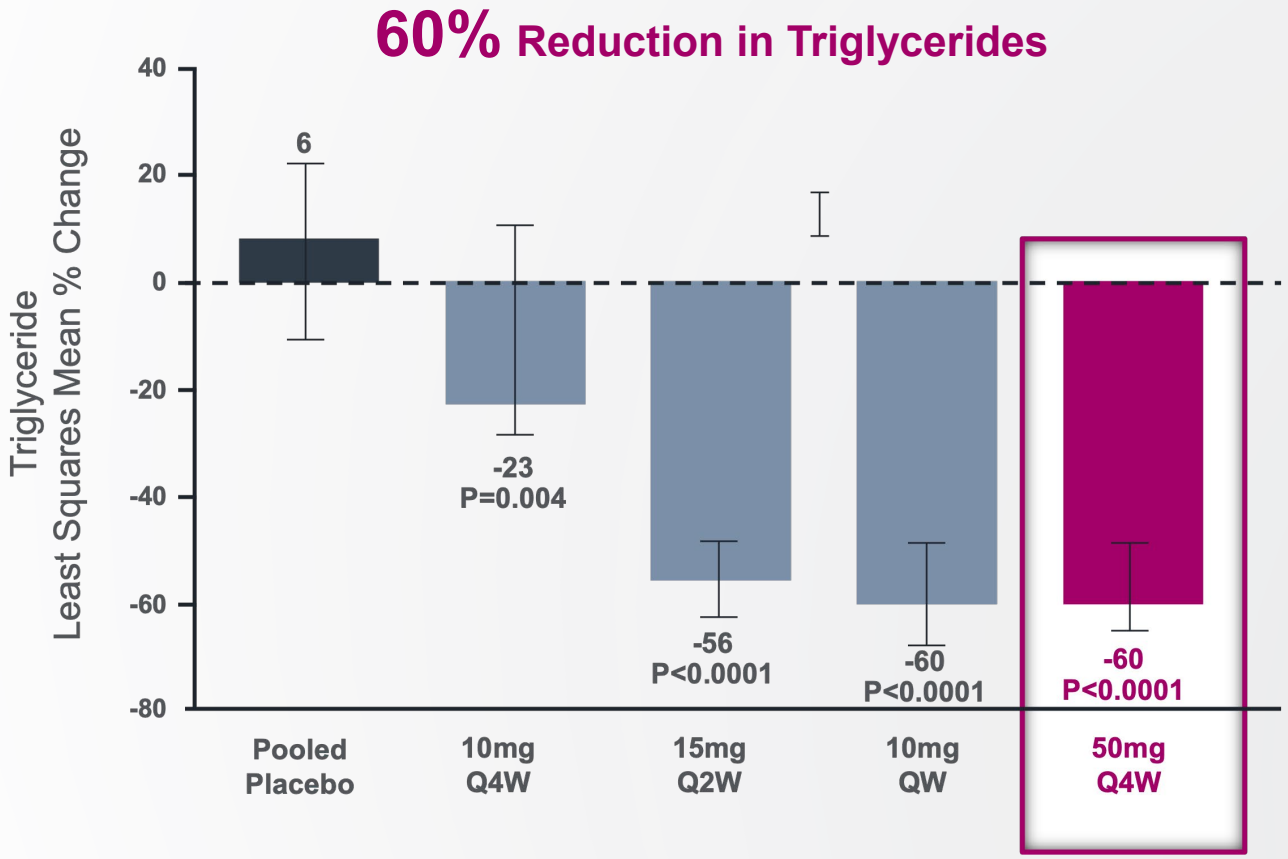


Image adapted from: Gordts PL, et al J Clin Invest. 2016;126:2855

1. Market data on file.

Olezarsen Phase 2 Results

Setting a New Standard for Triglyceride Management



Phase 2 Study

- Dose-ranging, placebo-controlled study in 114 patients with CVD and TGs 200-500mg/dL
- Primary endpoint: percentage change in fasting triglycerides at 6 months

Results

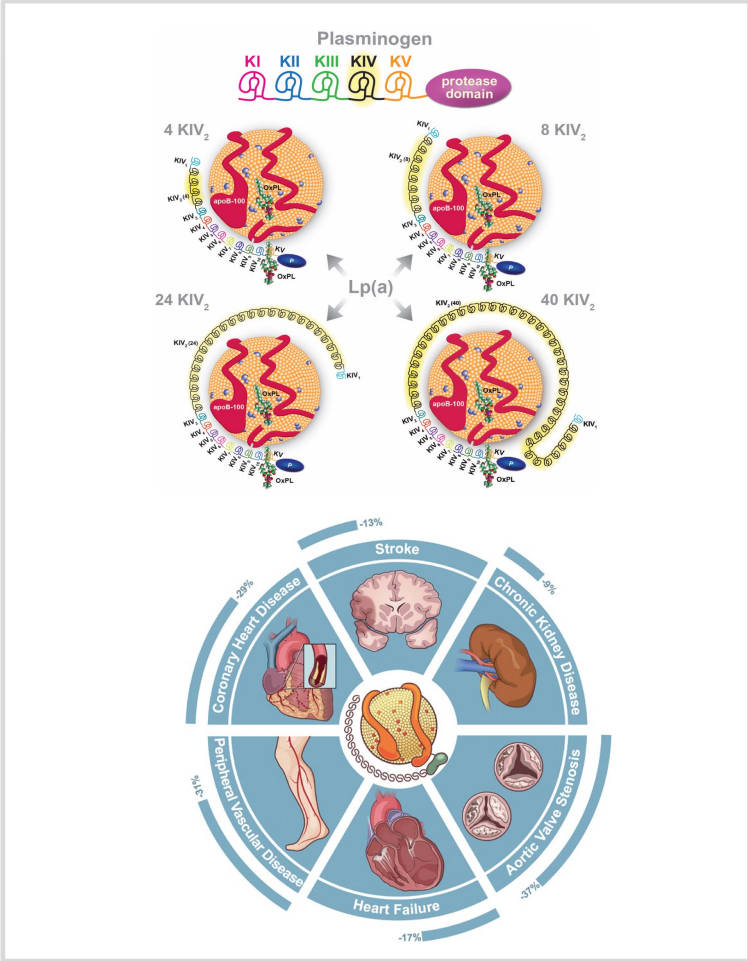
- Met primary endpoint of significant triglyceride lowering
- Favorable safety and tolerability profile

Next Steps

- Phase 3 studies in FCS and SHTG with 50mg and 80mg monthly dose underway

Lp(a) is an Independent Risk Factor for CVD and Aortic Stenosis

- Lp(a) is an independent, genetic and causal risk factor for CVD, mediating MI, stroke and peripheral artery disease
- Lp(a) levels genetically determined, not influenced by diet or exercise
- 1 in 5 people worldwide have elevated Lp(a)
- Currently no approved therapies to treat elevated Lp(a)



>8 million

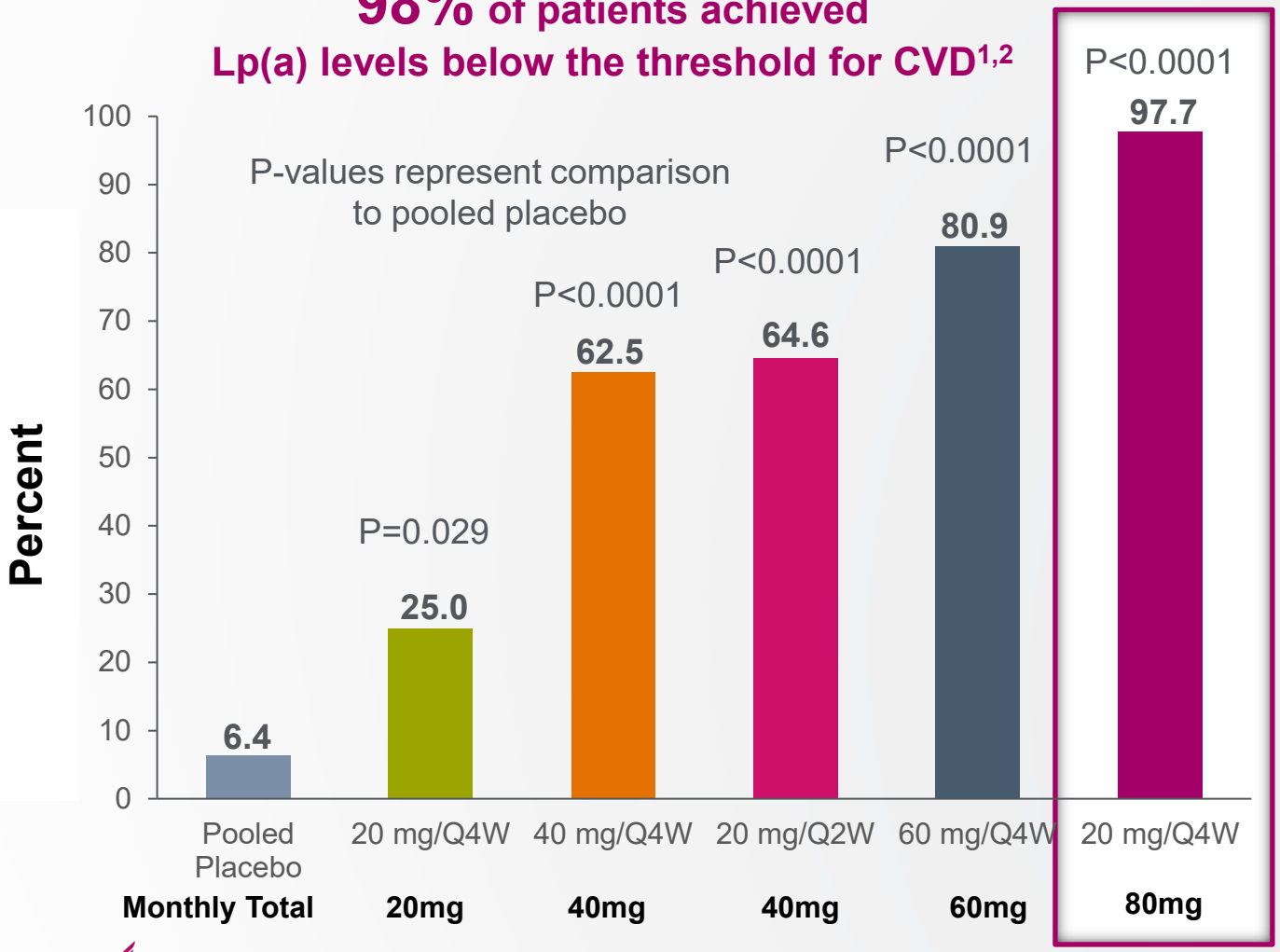
patients with CVD & elevated Lp(a) worldwide[1]

ASCVD, atherosclerotic cardiovascular disease;
1. Market data on file. *Images: Tsimikas JACC 2017;69:692-711. 2. Emdin et al JACC 2016;68:2761-72*

Pelacarsen Phase 2b Study

Significant Lp(a) Reductions in Patients with Established CVD

98% of patients achieved Lp(a) levels below the threshold for CVD[1,2]



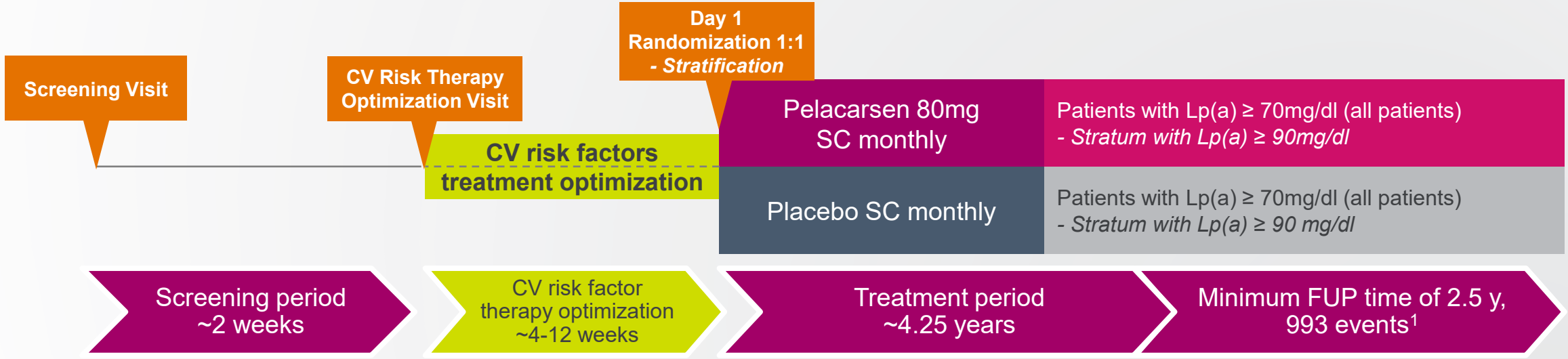
Results

- Lp(a) levels were reduced to ≤50mg/dL in 98% of CVD patients on 80mg Q4W equivalent dose
- Dose-dependent Lp(a) reductions up to 80%
- Durable Lp(a) reductions in patients treated for up to 1 year
- Favorable safety and tolerability
- 80mg Q4W dose under evaluation in Phase 3

1. Patients on 80mg equivalent monthly dose. 2. 50mg/dL is the Lp(a) threshold for CVD event risk

Pelacarsen Phase 3 Lp(a) HORIZON Study

- Multicenter, randomized, double-blind, placebo-controlled study
- **Study population:** Up to 7,680 patients with elevated Lp(a) levels (≥ 70mg/dL) and established CVD (prior MI, stroke, PAD)
- **Co-primary endpoints:** 1) time to first major adverse cardiovascular event in patients with Lp(a) levels of ≥ 70mg/dL, or 2) patients with Lp(a) levels of ≥ 90mg/dL; significance of either endpoint will be considered a positive trial



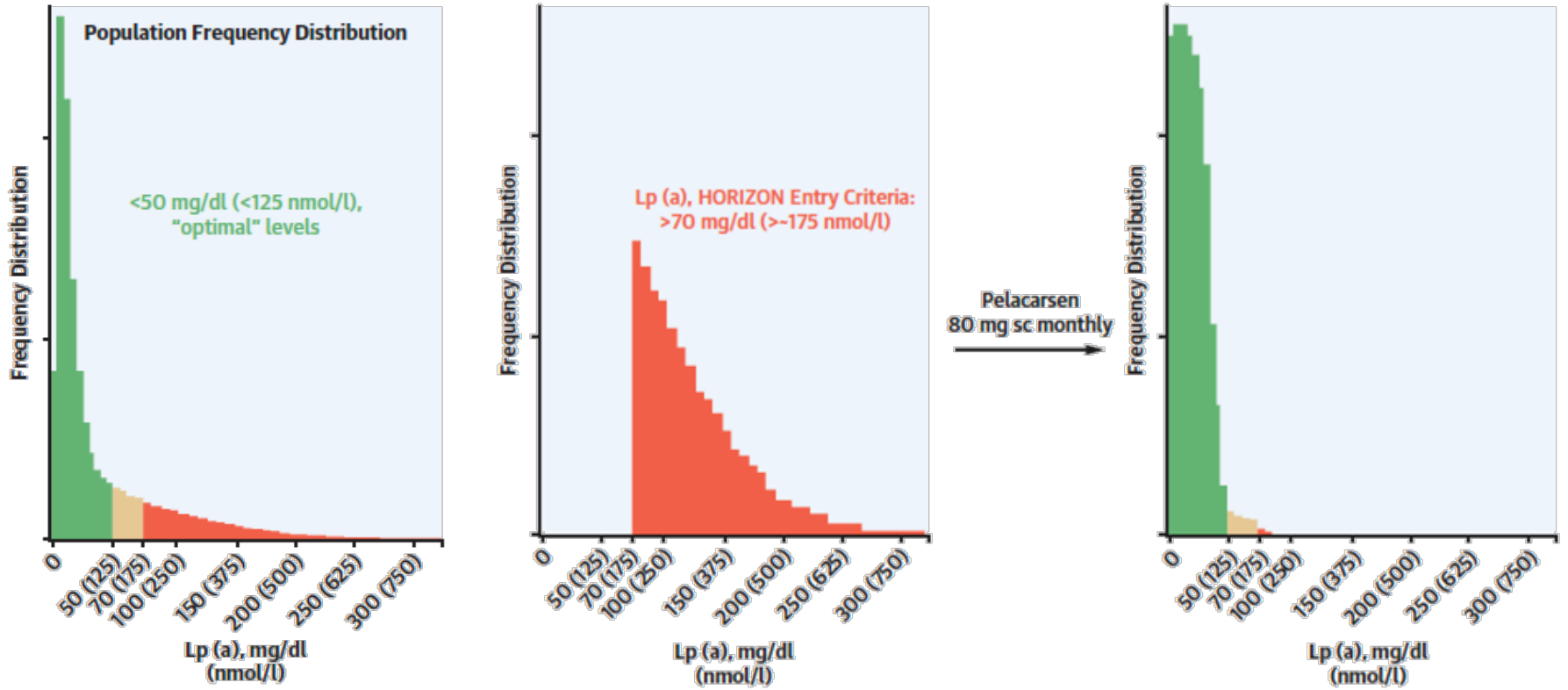
Achieved 50% Enrollment August 2021 • Data expected in 2025[2]

1. A total sample size of 7,680 subjects is required to obtain 993 primary endpoint MACE events.
2. Timing expectations are based on current assumptions and are subject to change.

Robust Efficacy Anticipated with Pelacarsen in Phase 3 Lp(a) HORIZON Study

Pelacarsen Phase 3 Lp(a) HORIZON Study

Anticipated change in frequency distribution of Lp(a) levels



Tsimikas S, Moriarty PM, Stroes ES. Emerging RNA therapeutics to lower blood levels of Lp(a): JACC Focus Seminar 2/4. J Am Coll Cardiol. 2021;77:1576-1589

ANGPTL3: Key Regulator of Triglycerides and Cholesterol

- ANGPTL3 is a genetically validated target, secreted by the liver as an inhibitor of lipoprotein lipase & endothelial lipase
- Loss of function mutations in ANGPTL3 are associated with familial combined hypolipidemia, type 2, FHBL2
- People with loss-of-function mutations and/or decreased ANGPTL3 levels have reduced risk for CVD

CVD

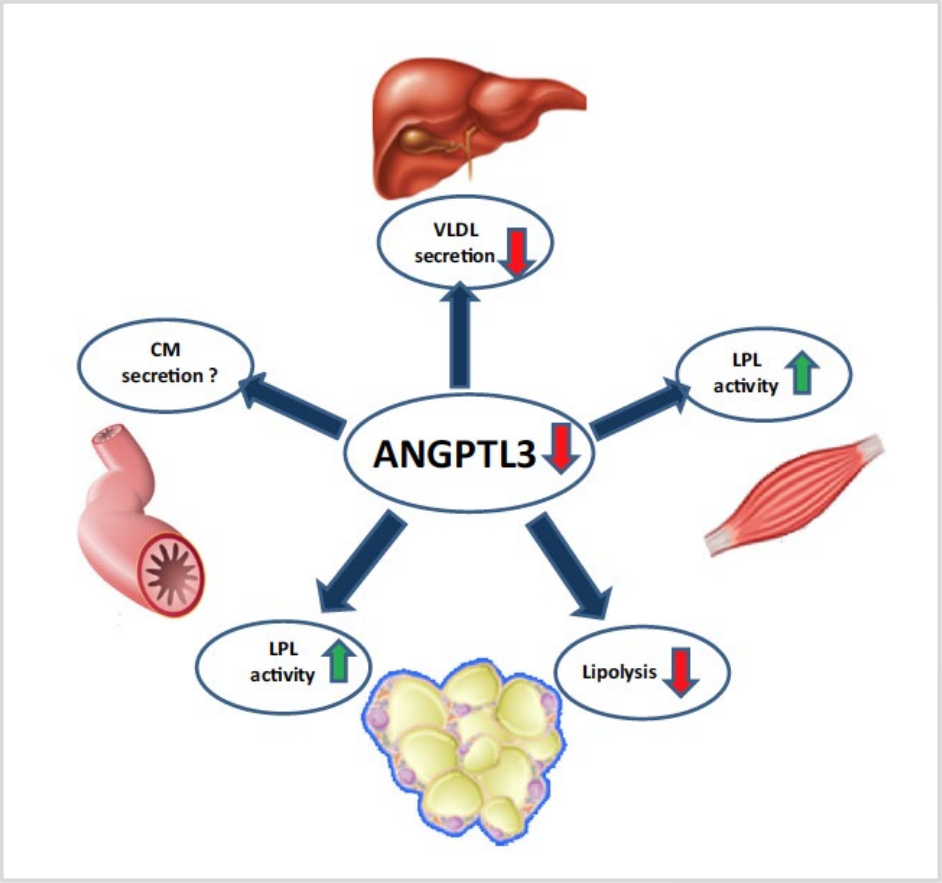
>6 million

patients in the US[1]

SHTG (≥500mg/dL)

>3 million

patients in the US[1]



Tikka et al Endocrine (2016) 52:187–193

1. Market data on file.

Vupanorsen Phase 2b Study

Met the Primary and Key Secondary Endpoints in Patients with Mixed Dyslipidemia

Phase 2b Study

- Phase 2b dose-ranging study in patients with non-HDL-C (≥ 100mg/dL) and TG (150-500mg/dL)
- Explored a wide range of doses as high as 320mg per month

Results

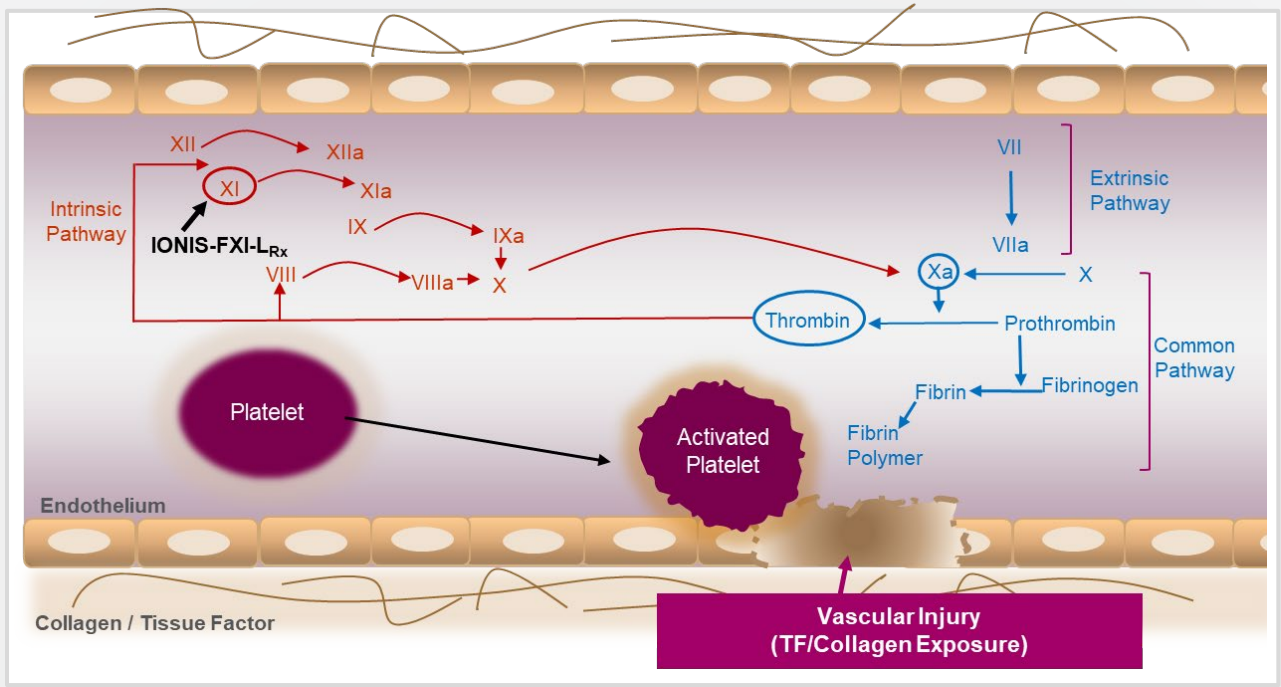
- Significantly reduced non-HDL-C, TGs and ANGPTL3 at all doses
- No treatment-related SAEs, similar rate of SAEs between vupanorsen placebo
- Lab abnormalities associated with certain doses

Next Steps

- Pfizer continuing to evaluate the data
- Full results to be presented at future medical conference

FXI Has Potential to Change the Standard-of-Care for Patients with End-Stage Renal Disease

- Thrombosis is associated with increased risk for heart attack, stroke and pulmonary embolism
- Current therapies are effective but associated with increased bleeding risk
- Reduced FXI levels associated with a reduced incidence of venous thrombosis[1]
- ESRD patients suffer from numerous thrombotic and bleeding events
  - 10x higher risk of stroke[3]
  - 1 out of every 7 patients will be hospitalized for bleeding within 3 years of starting dialysis[4]



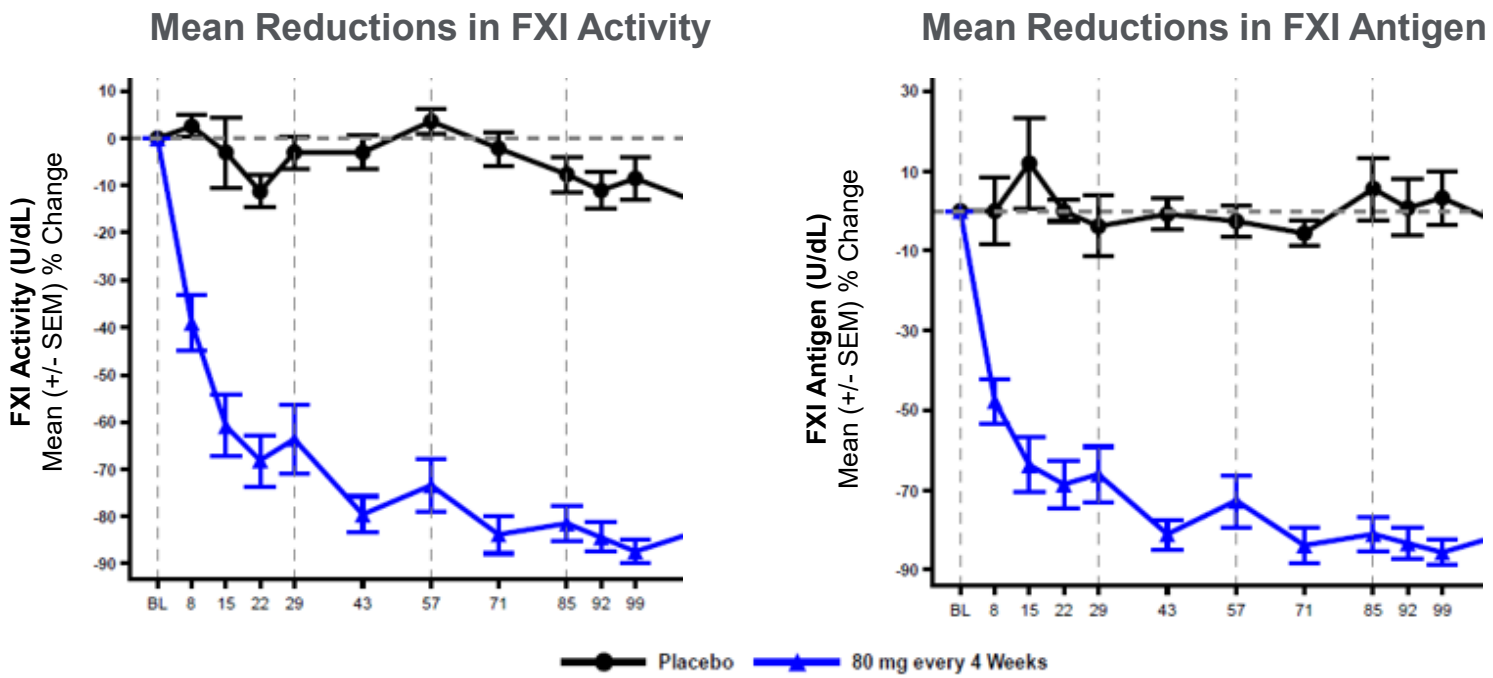
~2 million

patients receive dialysis for end stage renal disease (ESRD) globally[2]

1. Salomon et al. (2011) J Thromb Haemost. 105, 269-273. 2. National Kidney Foundation. 3. Power, Blood Purif 2013;36:179–183.
4. Sood, et al. Can J Kidney Health Dis. 2014;

Fesomersen Reduced FXI by >80% without Increased Bleeding Risk in Phase 1 Study

Phase 1: >80% Reduction in FXI Sustained Through 4-Month Treatment Period



Results

- Robust and sustained reductions in FXI activity and FXI antigen with no spontaneous bleeding
- >80% FXI reductions at 80mg Q4W dose
- Well tolerated at all doses/dose regimens
  - No SAEs reported
  - All AEs mild or moderate

Next Steps

- Phase 2b ESRD study fully enrolled
- Data expected 1H:22[1]

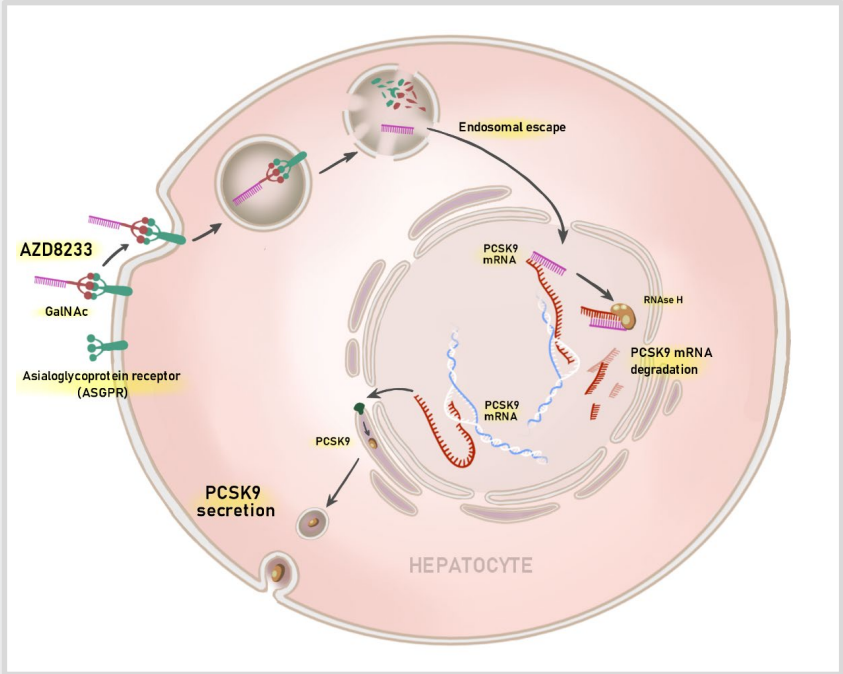
1. Timing expectations are based on current assumptions and are subject to change.

Potential Best-in-Class LDL-C Therapy Targeting PCSK9

~ 60 million

patients with atherosclerotic cardiovascular disease in the US and EU[2]

- PCSK9 inhibition is associated with reduced LDL-C, a key risk factor for CVD
- Among patients on high-intensity statins, 80% do not achieve target LDL-C levels
- CVD accounts for 1 out of every 3 deaths in the US



GalNAc-conjugation gives selective delivery to hepatocytes via the asialoglycoprotein receptor[1]

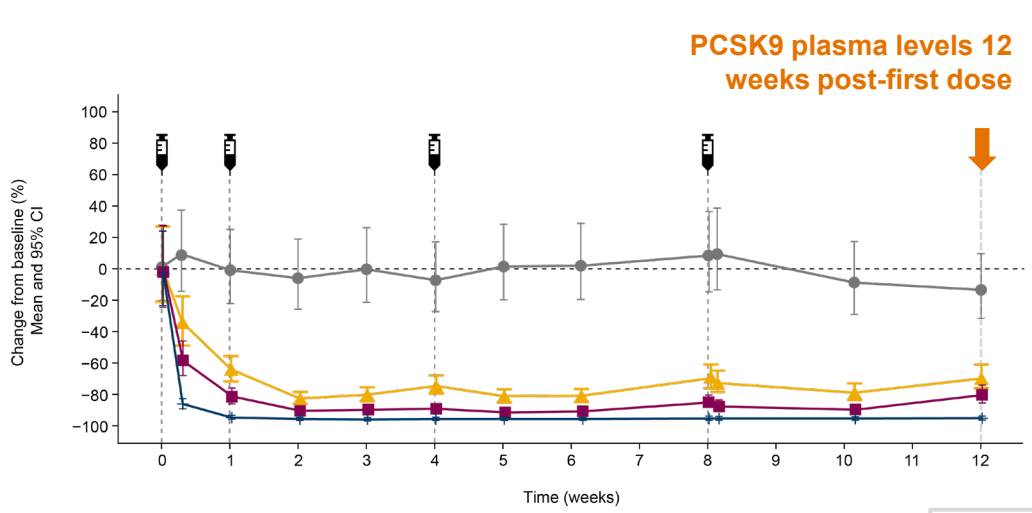
1. Schmidt K *et al*. Nucleic acids Res., 2017 45:2294-2306, Acknowledgement: Knut Andersson for illustration 2. Market data on file

ION449 Reduced PCSK9 Levels by Up to 95%

Potential for Best-in-Class PCSK9 Treatment for LDL-C Reduction

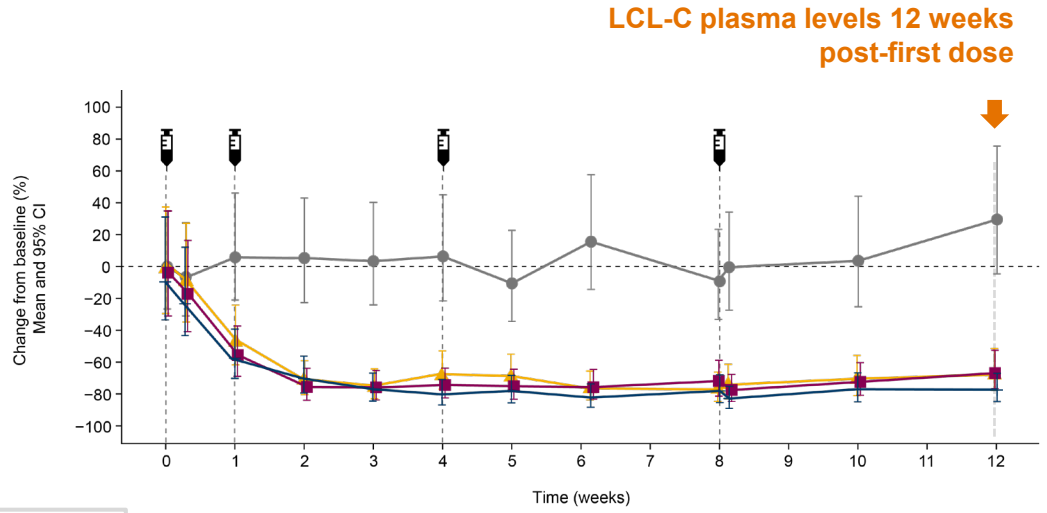
ION449 (AZD8233) Reduced Circulating PCSK9 Levels by Up to 95%

Percent change from baseline in PCSK9 levels over time



ION449 (AZD8233) Reduced Circulating LDL-C Levels by Up to 73%

Percent change from baseline in LDL-C levels over time



- Placebo (n=9)
- AZD8233 15mg (n=8)
- AZD8233 30mg (n=8)
- AZD8233 90mg (n=8)

P2b study completing, data to be presented in 2022[1]

1. Timing expectations are based on current estimates and are subject to change

Industry Leading Cardiovascular Pipeline Addressing Millions of Patients Worldwide

9
Medicines in development **today**

6
Potential **Phase 3** programs in **2022**

>10K
Patients in **Phase 3** studies by **2023**

>3
Potential **launches** by **2026**

1. Timing expectations are based on current assumptions and are subject to change

Delivering Potentially Transformational Medicines to the Market

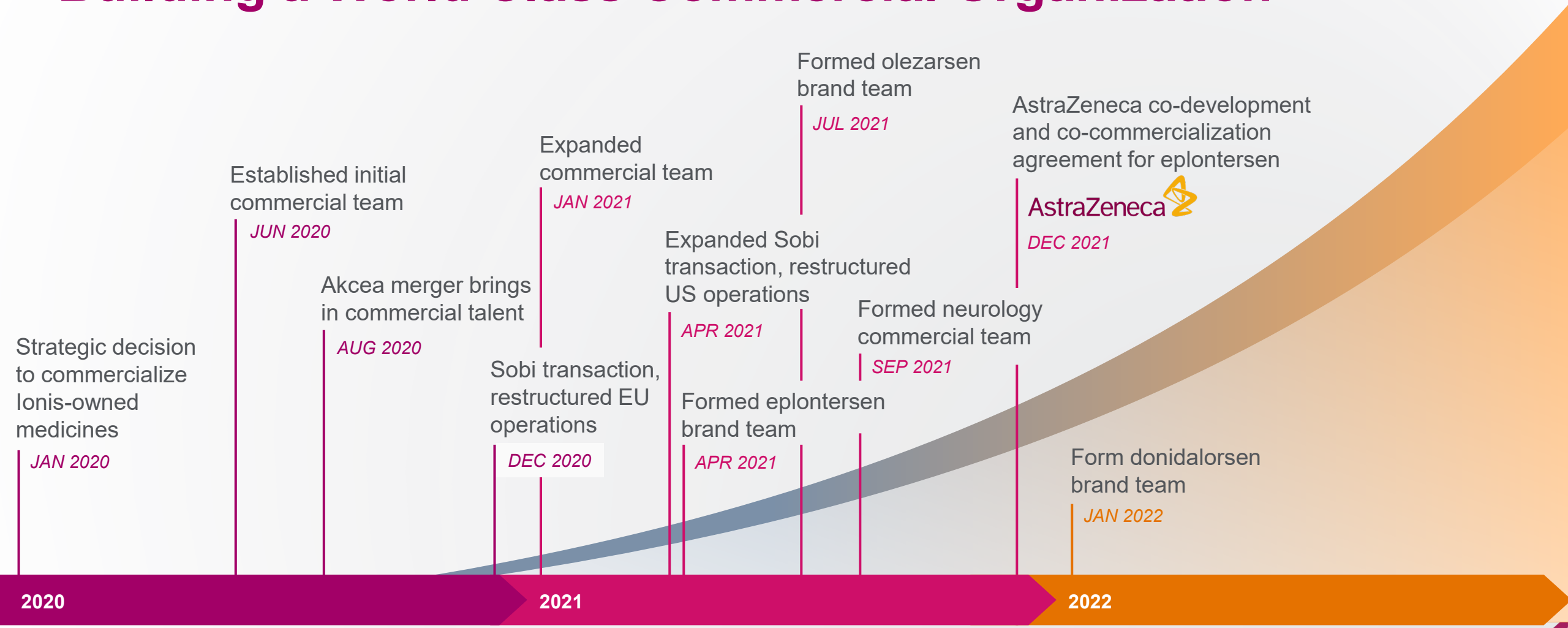
Onaiza Cadoret
Chief Corporate Development & Commercial Officer

Realizing the Promise of Our Innovative Products

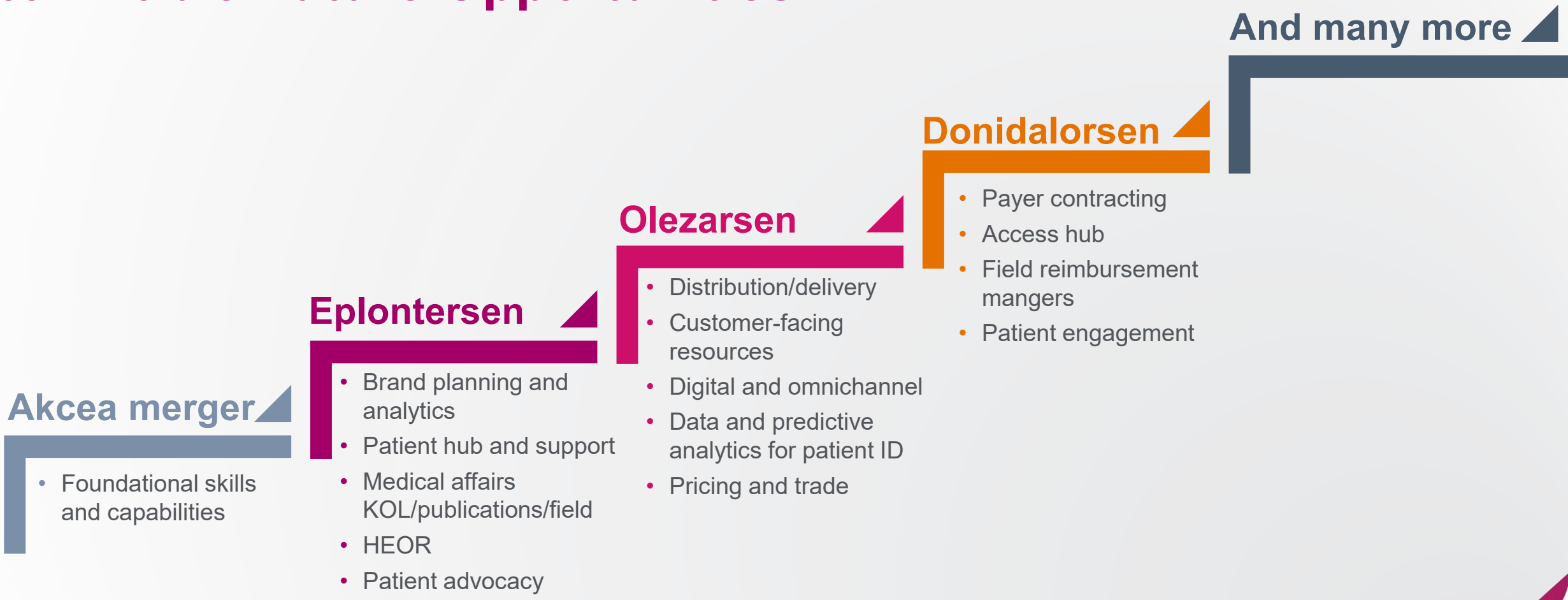
Our Commercial Vision

Maximize the value of our innovation	**Focus** **on 2 Core Franchises** cardiovascular and neurology	**Build** **Commercial Capabilities** for wholly owned medicines
Meet underserved **patient needs**, drive commercial **success** and create **value** for shareholders Focus on near-term commercial **opportunities** Portfolio planning for continued new product **innovation**	Opportunistically add products from our emerging **specialty rare franchise** that address underserved medical needs Global product strategy team with **go-to-market execution** focused on US	**Scale** and **leverage** resources as commercial portfolio grows **Well-capitalized** to invest in core capabilities and beyond

Building a World Class Commercial Organization



Building a Scalable Organization to Enable Future Opportunities



Eplontersen + Olezarsen + Donidalorsen

3 Near-term Opportunities with Aggregate Multibillion-dollar Potential[1,2]

Eplontersen

~300,000-500,000 patients
in 2 indications worldwide

First Phase 3 data readout: 2022

Potential to **change the standard-of-care** for patients with TTR amyloidosis

Estimated peak sales: 

Olezarsen

>3 million patients
in 2 indications in the US

First Phase 3 data readout: 2023

Potential **first-in-class** treatment for patients with elevated triglycerides

Estimated peak sales: 

Donidalorsen

>20,000 patients
in the US and EU

Phase 3 data readout: 2024

Potential **best-in-class** prophylactic treatment for patients with HAE

Estimated peak sales: 

Estimated peak sales:  <1 Billion  >1 Billion  Multibillion

1. Market data on file 2. Timing expectations and peak sales estimates are based on current assumptions and are subject to change

Eplontersen: Offering New Hope for Patients with ATTR Amyloidosis

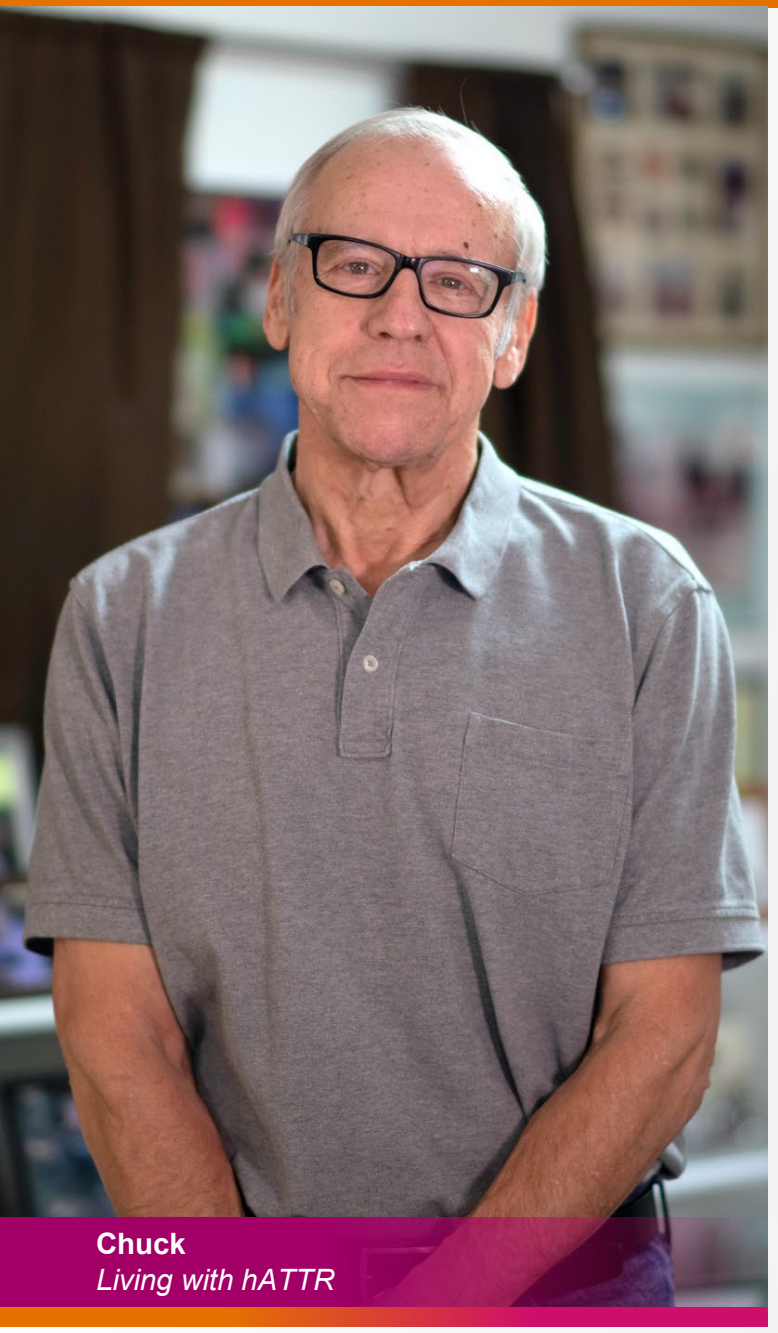
Onaiza Cadoret
Chief Corporate Development & Commercial Officer

Realizing the Potential of Eplontersen

Offering New Hope for Patients with ATTR Amyloidosis

Enhance patients' success	Rapidly penetrate and expand the ATTR market	Unlock a multibillion dollar opportunity[1]
The emerging ATTR market is **dynamic** and **growing** Patients are **underserved** and will benefit from **new** diagnostics and treatments	**Ionis industry-leading experience** in TTR amyloidosis market with **AstraZeneca's global scale and leadership** in cardiovascular disease	Eplontersen's robust clinical trial program **addresses key unmet needs** resulting in a compelling product profile and enduring differentiation

1. Market opportunity estimates are based on current assumptions and are subject to change



Chuck
Living with hATTR

ATTR Remains an Area of High Unmet Need

ATTR is a progressive disease caused by misfolded TTR protein aggregation in multiple tissues, including heart, nerve and GI tract, leading to rapid decline and low quality of life

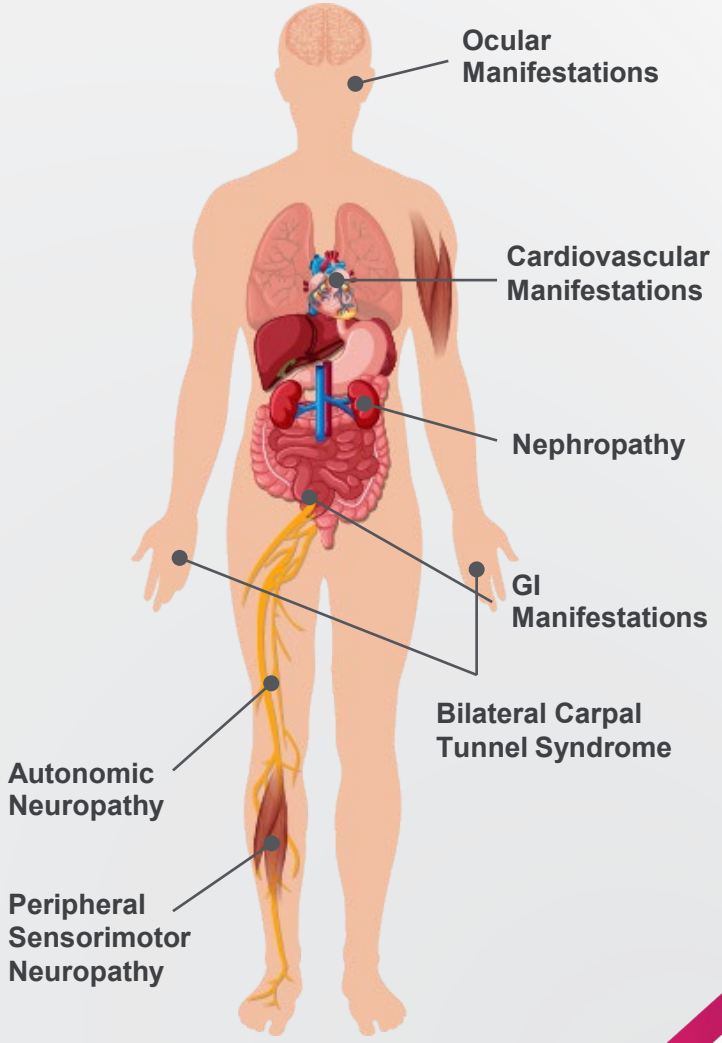
~300K-500K
patients worldwide[1,2]

~40K hATTR polyneuropathy

>300K ATTR cardiomyopathy

Indication	Peak Sales[3]
ATTR-PN	
ATTR-CM	

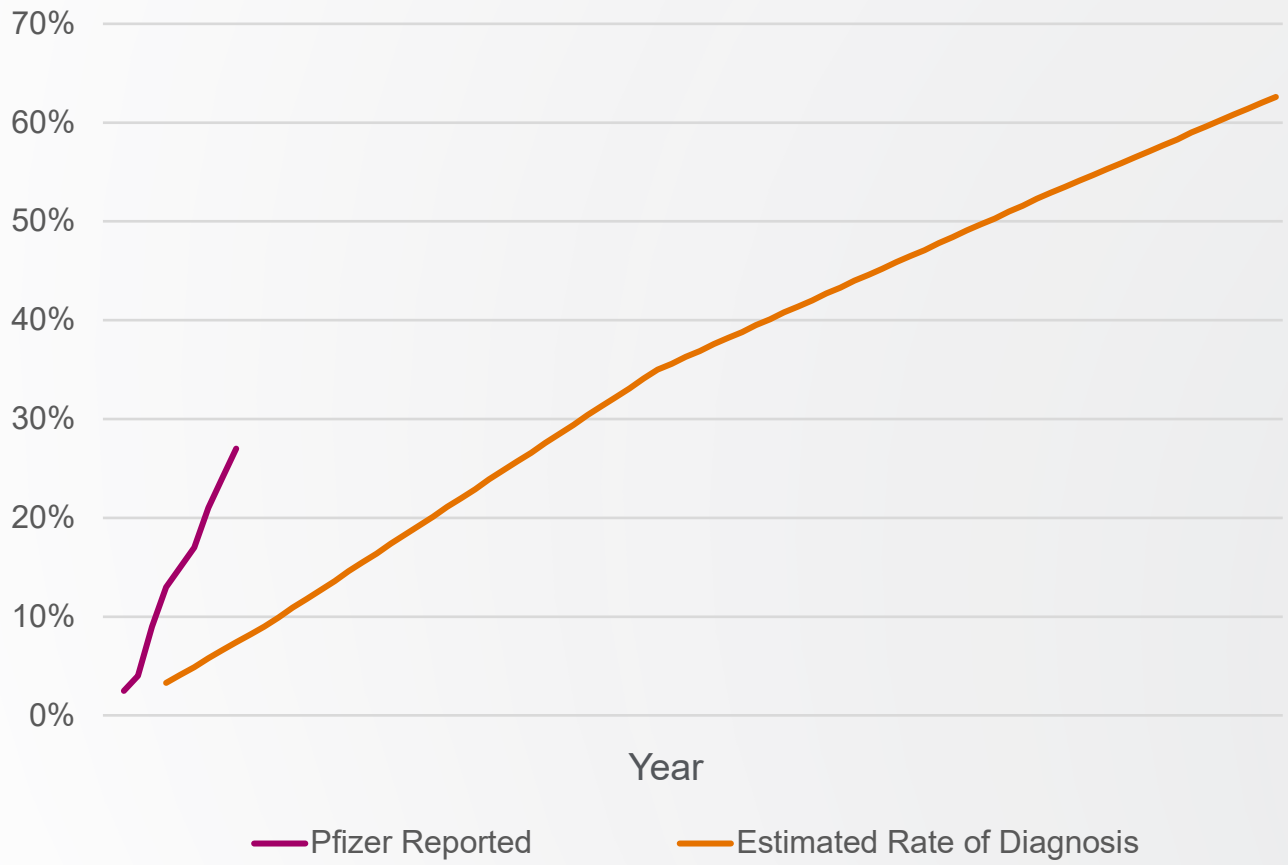
Estimated peak sales: <1 Billion >1 Billion Multibillion



Source: amyloidosis.org (https://amyloidosis.org/facts/familial/; https://amyloidosis.org/facts/wild-type/
NOTE: For illustrative purposes only. 1. Conceição I et al. *J Peripher Nerv Syst*. 2016;21:5-9. 2. Ando Y et al. *Orphanet J Rare Dis*. 2013;8:31.
3. Peak sales estimates are based on current assumptions and are subject to change

Diagnosis Rates Have Grown 3x Faster Than Predicted Accelerating Market Expansion

US ATTR-CM Diagnosis Rate[1]

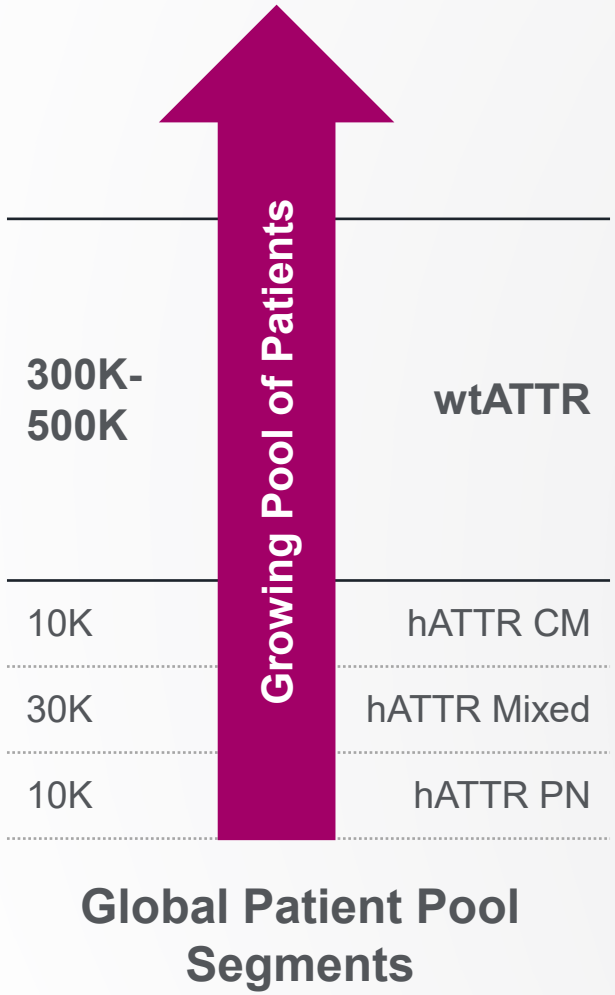


Treatment & Diagnostic Innovation Will Fuel Patient Success

- Increased utilization of PYP scintigraphy has been observed to accelerate and simplify CM diagnosis
- Launch of new treatments will increase HCP awareness and understanding of ATTR leading to improved patient outcomes

1: Reported number in Pfizer Quarterly Earnings Transcripts. 2: Quantitative HCP Research, ClearView, July 2021. PYP, pyrophosphate

Potential for Faster, Deeper Market Penetration Through AstraZeneca Collaboration



Growing Pool of Treating HCPs

<100

TTR Experts/COEs
Cardiologists & Neurologists

IONIS®

Industry-leading experience in RNA-targeted therapeutics and deep knowledge of the amyloidosis market

Specialists
Mainly Cardiologists

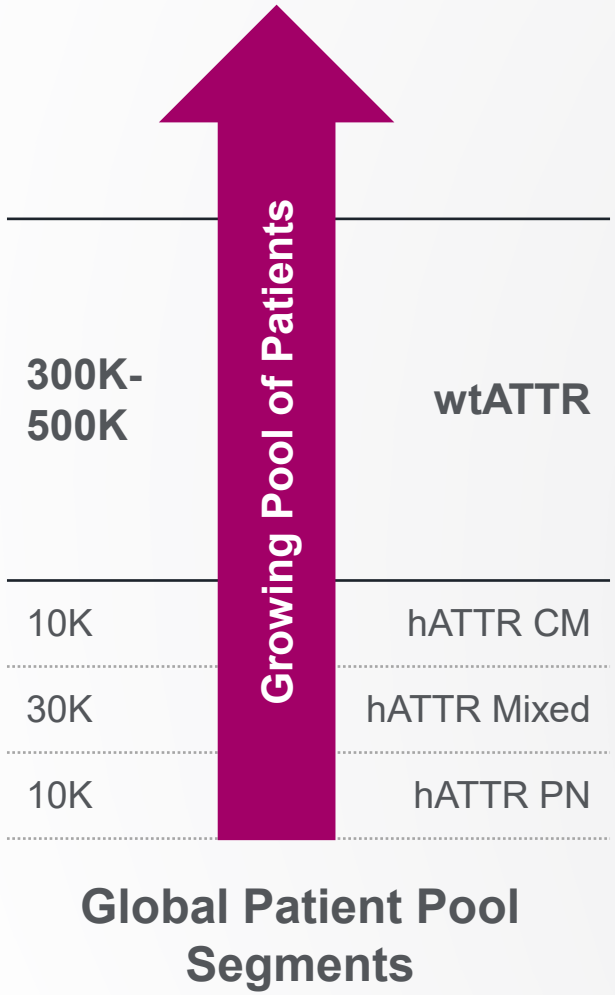
Community HCPs
Mainly Cardiologists

AstraZeneca

Global scale and leadership in cardiovascular disease drug development and commercialization

Source: Mehta. 2019. JAMA Cardiol; Prior CV Work in Cardiology; Physician Interviews; ClearView Analysis.

Potential for Faster, Deeper Market Penetration Through AstraZeneca Collaboration



IONIS®

Industry-leading experience in RNA-targeted therapeutics and deep knowledge of the amyloidosis market

+

AstraZeneca

Global scale and leadership in cardiovascular disease drug development and commercialization

Source: Mehta. 2019. JAMA Cardiol; Prior CV Work in Cardiology; Physician Interviews; ClearView Analysis.

Most Robust Clinical Program in Patients with ATTR Amyloidosis

Multiple Studies Designed to Fully Inform Patient and Physician Choice

hATTR Polyneuropathy

neuro TTRansform

A multicenter, open-label study in 168 patients with change in mNIS+7 and change in serum TTR levels at 35 weeks as co-primary endpoints

Enrollment complete
Data expected mid-2022[1]

hATTR and wtATTR Cardiomyopathy

cardio TTRansform

A global, randomized, double-blind, placebo-controlled study in up to 750 patients with cardiovascular outcomes as primary endpoint

Enrollment underway
Data expected 2024[1]

Profile-Enhancing Studies

Additional studies of eplontersen to add to the data evidence package

Progressing

1. Timing expectations and peak sales estimates are based on current assumptions and are subject to change

NEURO-TTRansform

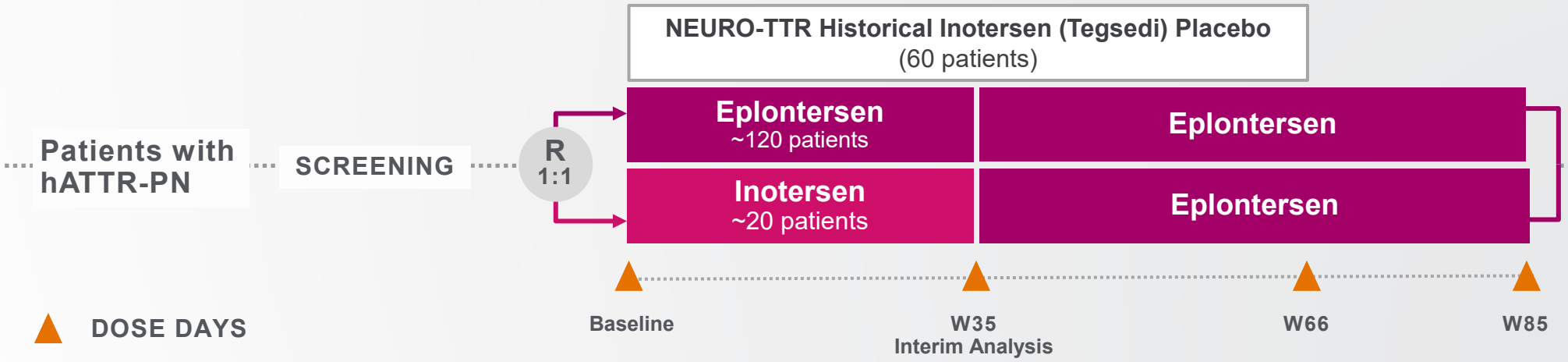
Phase 3 Study in Patients with Hereditary ATTR Polyneuropathy Underway

DESIGN

A multicenter, open-label study in 168 patients with hereditary TTR amyloid polyneuropathy (hATTR-PN)

CO-PRIMARY EFFICACY ENDPOINTS AT WEEK 66

- Change from baseline in measures of neurological impairment (mNIS+7)
- Change from baseline in the Norfolk Quality of Life Diabetic Neuropathy (QoL-DN) Questionnaire
- Percent change from baseline in serum TTR concentration
- Interim analysis at Week 35: change in baseline in mNIS+7 and percent change from baseline in serum TTR concentration



Fully Enrolled in July 2021 • Data Expected Mid-2022[1]

1. Timing expectations are based on current assumptions and are subject to change

Eplontersen Phase 3 Program Designed to Address Key Unmet Needs

1	2	3
Lack of adequate treatment	**Lack of data in combination use**	**Lack of treatment guidelines**
54% of patients experience worsening HF symptoms even while on treatment[1]	**> 40% of ATTR patients have systemic symptoms** & there is no clinical data supporting use of stabilizer + silencer[1]	**Standardized treatment guidelines** will evolve with additional evidence and marketed products

1. Physician Interviews; Patient Interviews; ClearView Analysis.

CARDIO-TTRansform

Phase 3 Study in Patients with ATTR-cardiomyopathy

cardio TTRansform

DESIGN

A global, randomized, double-blind, placebo-controlled study in up to 750 patients with hereditary or wild-type TTR amyloid cardiomyopathy

MRI sub-study to understand eplontersen impact on cardiac structure and function

PRIMARY ENDPOINT

Cardiovascular death & frequency of cardiovascular clinical events at Week 120

On track for data in 2024[1]

1. Timing expectations are based on current assumptions and are subject to change

Market Research Validates our TPP

1	2	3
Patients (n=50)	**Providers (n=130)**	**Payers (n=25)**
Patients are eager for a therapy that has the potential to **improve the systemic symptoms** that impact their QoL	**HCP** anticipate usage of **combination treatment** to be **preferred** with rapidly progressing fatal CM[1]	**Payers** anticipate **combination therapy** that is proven to be **clinically justified** will be covered by prior authorization

> *"I am willing to do anything I can to, alleviate the pain and add years to my life, even if it means I have to take another therapy." – patient*

> *I would prefer to treat patients that are declining with everything possible, but of course, I will want to see the data first." – TTR Expert*

1. Physician interviews; patient interviews; Payer interviews, ClearView Analysis.
TPP, target product profile

Eplontersen Promises to Deliver a Winning Profile That Can Unlock a Multibillion-dollar Opportunity

Target Product Profile

EFFICACY	TTR reductions that improve both PN & CM symptoms Improved morbidity and mortality over SOC +/- tafamidis therapy regimens
SAFETY	Safe, well tolerated, increased potency with well-characterized LICA platform
ADMINISTRATION	Patient-friendly autoinjector with at-home, self-administration highly preferred by HCPs HCPs agnostic on monthly vs. quarterly dosing

> *Patients with other cardiac conditions can self-administer sub-Q therapies, so my patients would not have a problem self-administering" – TTR Expert*

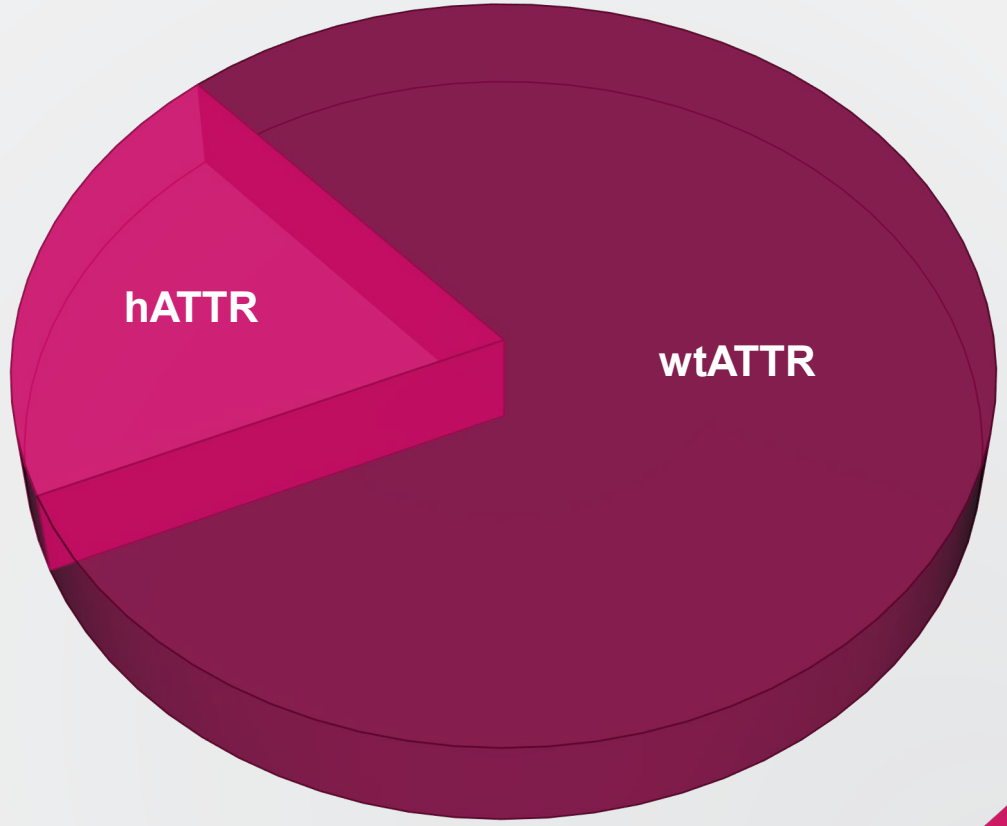
> *Since COVID, my follow-ups have been online for some patients, and I don't have the time to worry about an injection during their appointment." – TTR Expert*

Market Peak in ATTR ~$10B[1,2] Globally

Eplontersen is Positioned to be a Multibillion $ Product

- New treatments increase awareness & education
- Improved diagnosis
- New approaches to patient finding
- Treatment guidelines

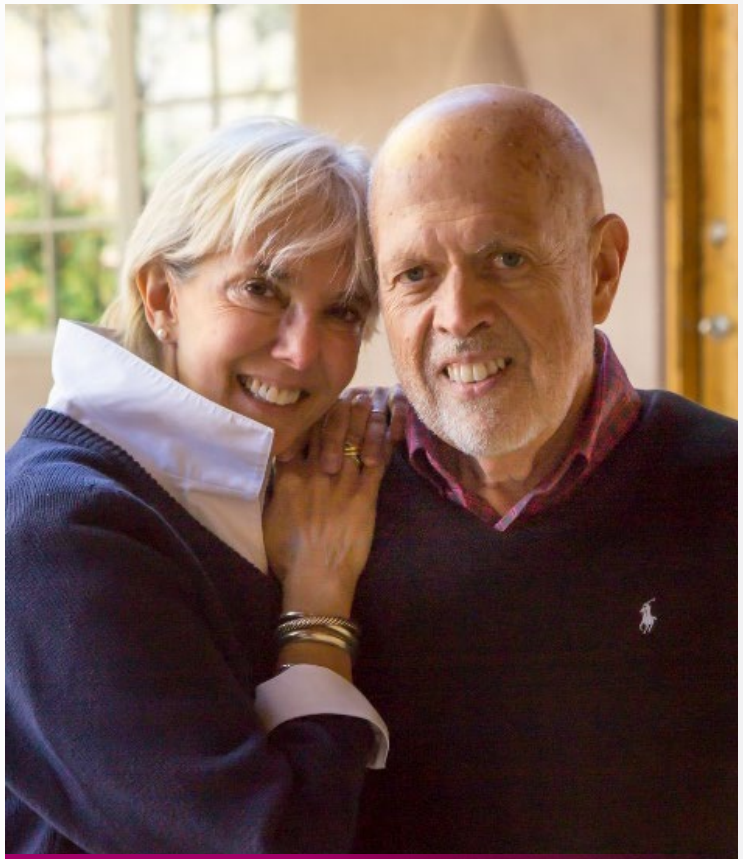
Market Estimated to Reach ~$10B[1,2]



1. Estimates derived by publicly disclosed estimates (Pfizer, Alnylam, Eidos) 2. Internal Ionis Sales Data

Realizing the Potential of Eplontersen

Offering New Hope for Patients with ATTR Amyloidosis

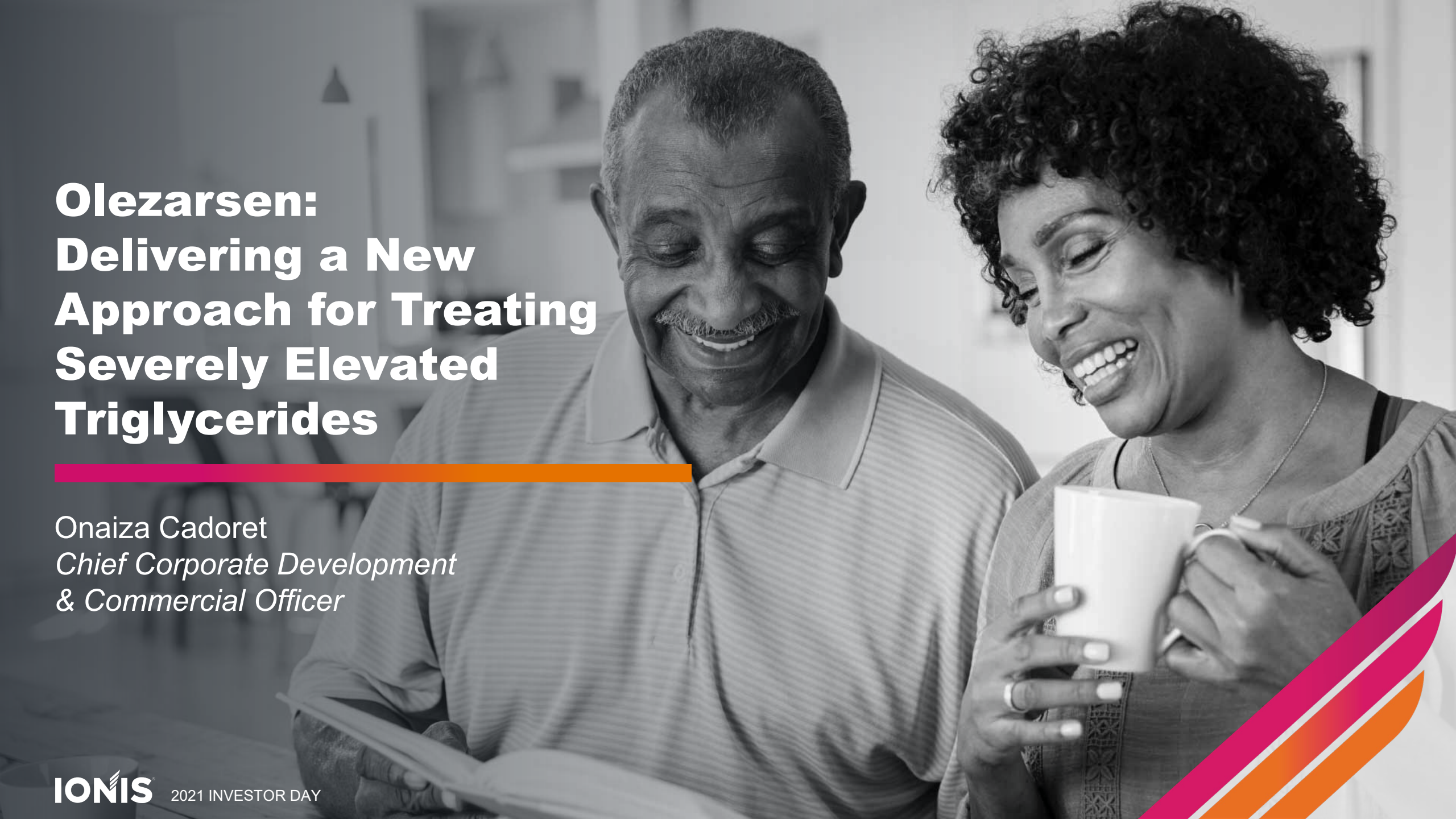


Clay
Living with ATTR

Potential to drive improved patient outcomes

Large, underserved and growing market

Positioned to reach a broad range of patients in global markets



Olezarsen: Delivering a New Approach for Treating Severely Elevated Triglycerides

Onaiza Cadoret
Chief Corporate Development & Commercial Officer

Realizing the Potential of Olezarsen

Delivering a New Approach for Treating Severely Elevated Triglycerides

High Unmet Need	Potential Category Leader	Blockbuster Market Opportunity[1]
Standard-of-care ineffective for patients with severely elevated triglycerides	**First-mover advantage** **Powerful** triglyceride lowering product profile **Clear regulatory path** with validated biomarker endpoint	**>3 million** patients in the US 1 product, 2 indications

1. Market opportunity estimates are based on current assumptions and are subject to change

ApoCIII is an Independent Cardiovascular Disease Risk Factor Associated with Increased Mortality

FCS: rare genetically defined disease

- Significant risk for acute, potentially fatal pancreatitis

SHTG: TGs ≥500mg/dL

- Cardiovascular event risk with TGs of 500-880mg/dL
- Linear risk for acute pancreatitis as levels get higher

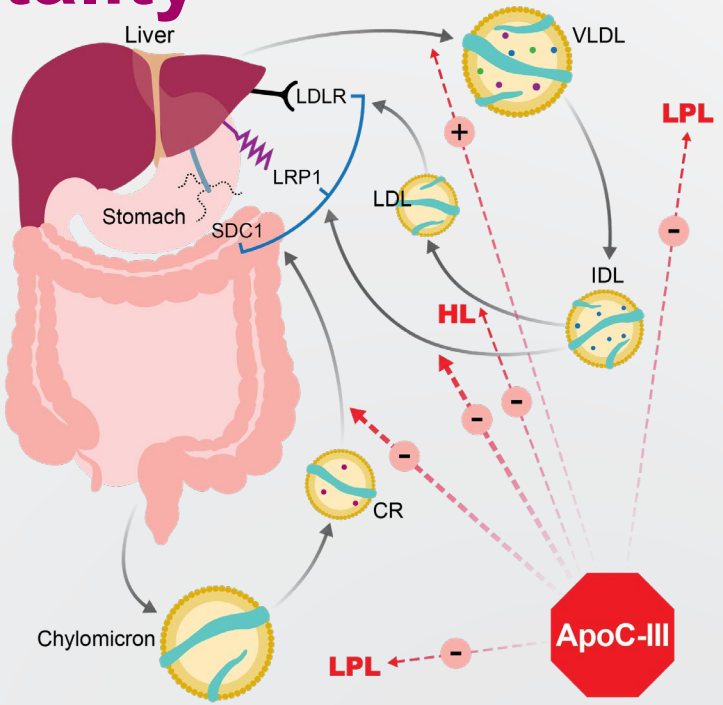


Image adapted from: Gordts PL, et al J Clin Invest. 2016;126:2855

FCS
~3,000-5,000
patients in the US[1]

SHTG (≥500mg/dL)
>3 million
patients in the US[1]

Indication	Peak Sales[2]
FCS	
SHTG	

Estimated peak sales: <1 Billion >1 Billion Multibillion

1. Market data on file 2. Peak sales estimates are based on current assumptions and are subject to change.

Fred
Living with FCS

High Unmet Medical Need for Effective TG-Lowering Treatments

Standard-of-care ineffective at lowering TG levels

Fibrates

- MDs report only 1/3 of their patients are currently taking fibrates[1]
- Generally ineffective at lowering TG levels (20-30% decrease in TGs)[1]

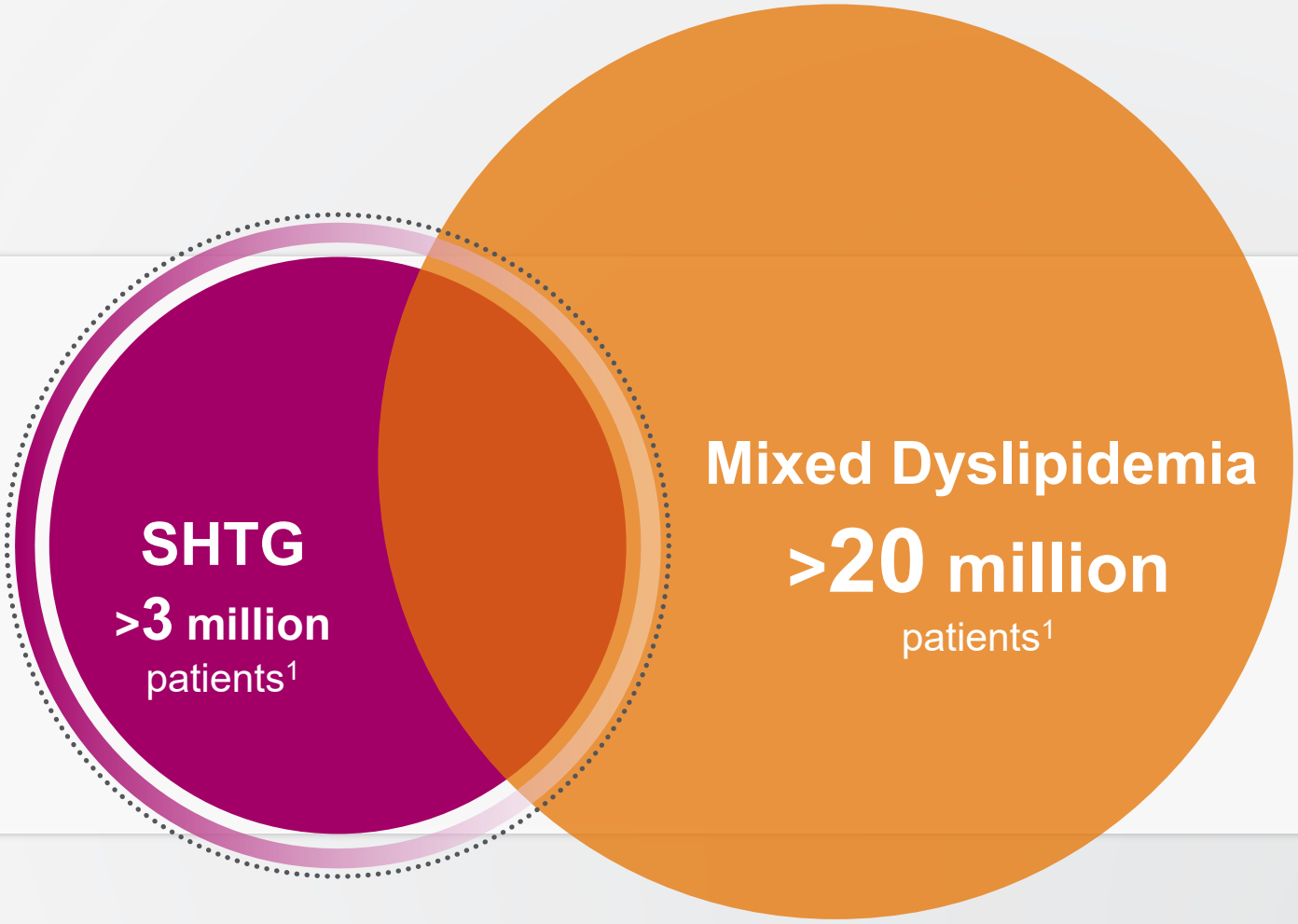
Omega 3s

- MDs report roughly 2/3 of their patients are currently taking Omega 3s[1]
- Like fibrates, relatively ineffective at lowering TGs
- ~30% decrease in TGs in clinical trials[2]

1. Aquest Patient Journey 2Q2021, 2. Icosapent ethyl PI

Olezarsen's Space for Category Leadership

Powerful TG lowering will differentiate olezarsen vs. other classes



1. Market data on file

Room for More Efficacious Agent vs. Standard-of-Care

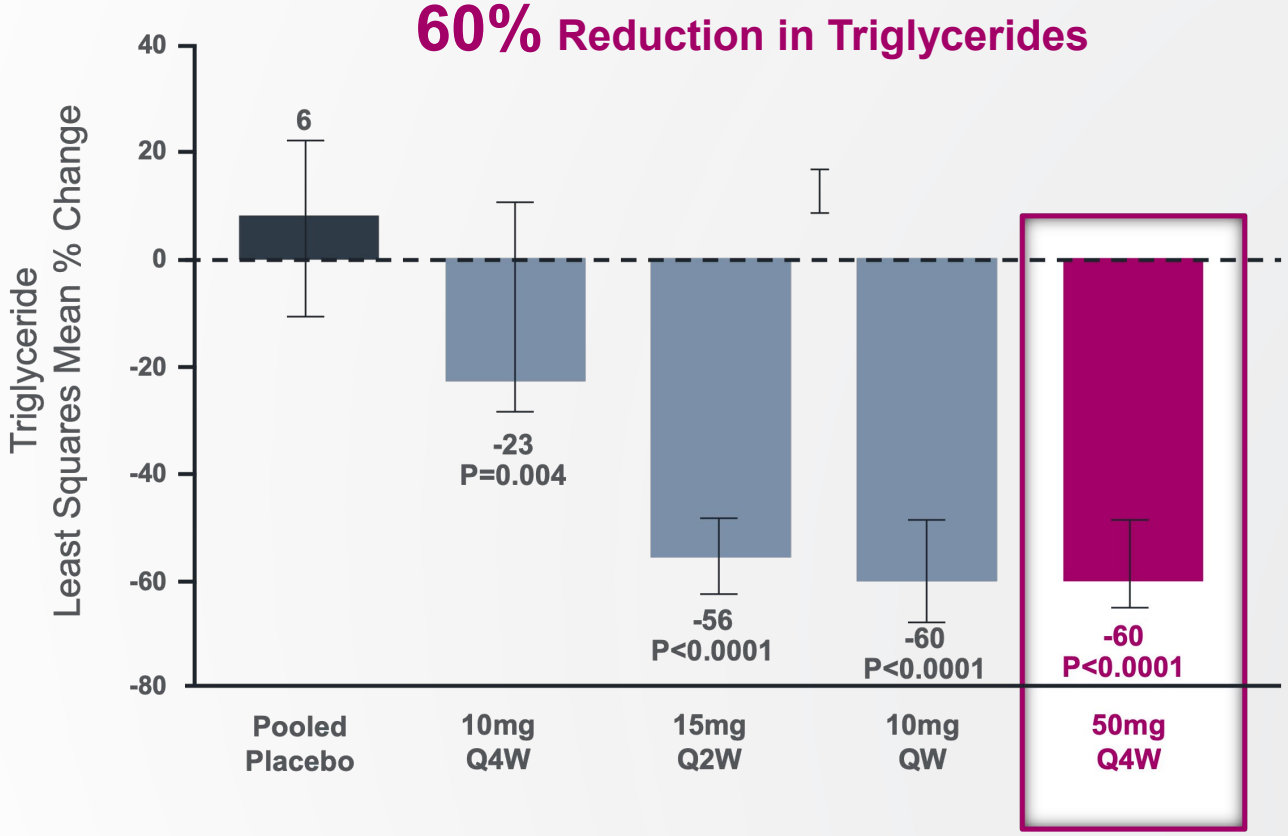
Icosapent ethyl

Parameter	Baseline	% Change
icosapent ethyl 4 g/day n=76	**680mg/dL**	**-27%**
Placebo n=76	703mg/dL	+10%
Difference **(95% confidence interval)**	**-33%*** **(-47, -22)**	

Source: icosapent ethyl PI.
Median Baseline and Percent Change from Baseline in Lipid Parameters in Patients with Severe Hypertriglyceridemia (≥500 mg/dL)
The effects of icosapent ethyl 4 grams per day were assessed in a randomized, placebo controlled, double-blind, parallel-group study of adult patients (76 on icosapent ethyl , 75 on placebo) with severe hypertriglyceridemia. Patients whose baseline TG levels were between 500 and 2,000 mg/dL were enrolled in this study for 12 weeks. The median baseline TG and LDL-C levels in these patients were 684 mg/dL and 86 mg/dL, respectively.
*p-value < 0.001 (primary efficacy endpoint)

Olezarsen Phase 2 Results

Setting a New Standard for Triglyceride Management



Phase 2 Study

- Dose-ranging, placebo-controlled study in 114 patients with CVD and TGs 200-500mg/dl
- Primary endpoint: percentage change in fasting triglycerides at 6 months

Results

- Met primary endpoint of significant triglyceride lowering
- Favorable safety and tolerability profile

Next Steps

- Phase 3 studies in FCS and SHTG with 50mg and 80mg monthly dose underway

Broad Development Program Designed to Support Approval in the Large SHTG Market

FCS

Balance
a familial chylomicronemia syndrome study

A global, randomized, double-blind, placebo-controlled study in up to 60 patients with percentage change in fasting TGs from baseline at 6 months as the primary endpoint

Enrollment underway
Data expected 2023[1]

Severe Hypertriglyceridemia

CORE
a hypertriglyceridemia study

A global, randomized, double-blind, placebo-controlled study in up to 450 patients with percentage change in fasting TGs from baseline at 6 months as the primary endpoint

Enrollment underway
Data expected 2024[1]

ESSENCE Study

Study planning underway to achieve 1,500 patient threshold

Study initiations planned
2022[1]

1. Timing expectations estimates are based on current assumptions and are subject to change

Market Research Supports Blockbuster Opportunity

40+ HCPs	600+ Patients	10 US Payers
representing 10,000+ patients[1]	FCS and SHTG[1]	representing 60 million covered lives[2]
TGs in acute pancreatitis and CV events is understood >50% have only elevated TGs (no other CV risk factors) HCPs understand a large unmet need still exists	Patients understand underlying medical need and willing to take a new medication to address TGs	Payers viewed target product profile favorably, suggesting potential for broad access

1. Aquest Research, 2021; 2. Quantitative Research, ClearView, July 2021

Olezarsen Has the Potential to Deliver a Winning Profile for the Treatment of Severely Elevated Triglycerides

Target Product Profile

EFFICACY	60% reduction in TGs in Phase 2; projected to achieve even greater TG reduction with higher Phase 3 dose
SAFETY	Safe, well tolerated, increased potency with well-characterized LICA platform
ADMINISTRATION	Once-monthly dosing with auto-injector

Targeted Market Approach for Patients with Elevated TGs

Early Adopter Population
~30%
of Patients

Expanded Patient Opportunity
~50%
of Patients

Market Development Opportunity
~20%
of Patients

>3 Million Patients in the US[1]

1. Market data on file

Realizing the Potential of Olezarsen

Delivering a New Approach for Treating Severely Elevated Triglycerides

Justin
Living with FCS

High unmet need for effective TG-lowering therapies

1 product, 2 potential indications, blockbuster market opportunity

Positioned to be a category leader

Donidalorsen: Potential Best-in-Class HAE Prophylactic Treatment: Phase 2 Results

Kenneth Newman, M.D.
VP, Clinical Development

HAE: Characterized by Unpredictable, Painful and Potentially Fatal Attacks

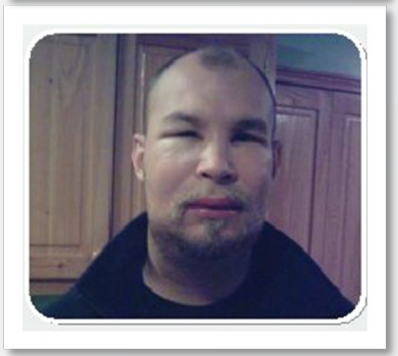
Hereditary angioedema (HAE) is a rare autosomal dominant disease caused by **insufficient or dysfunctional C1-Inhibitor** that results in dysregulation of the prekallikrein-bradykinin pathway

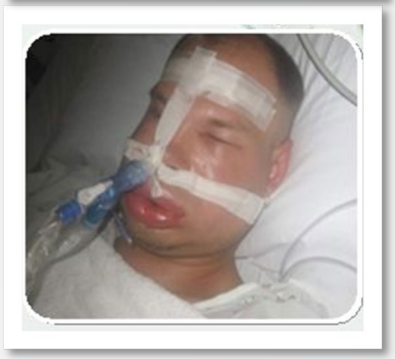
HAE symptoms

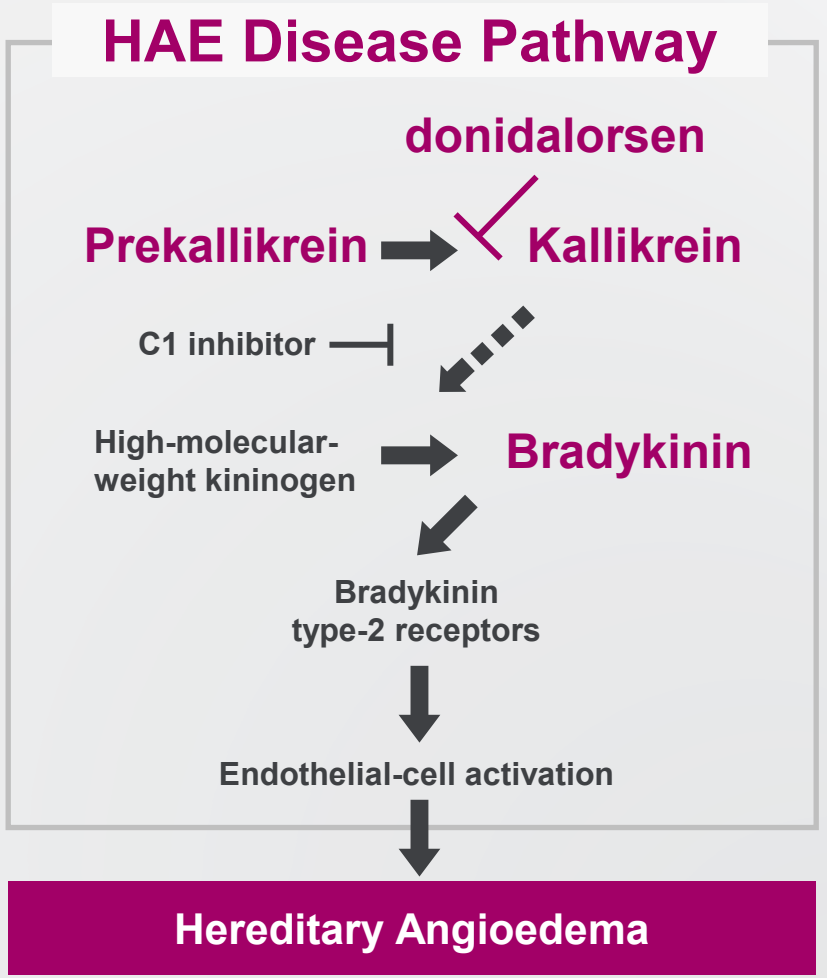
- Severe swelling of the arms, legs, face, intestinal track and throat
- Significant anxiety due to unpredictable disease pattern
- Potentially fatal swelling of the throat

> 20K

Patients in the US and EU[1]







Lumry (2103) Am. J. Manag. Care. 19:S103-S110

1. Market data on file

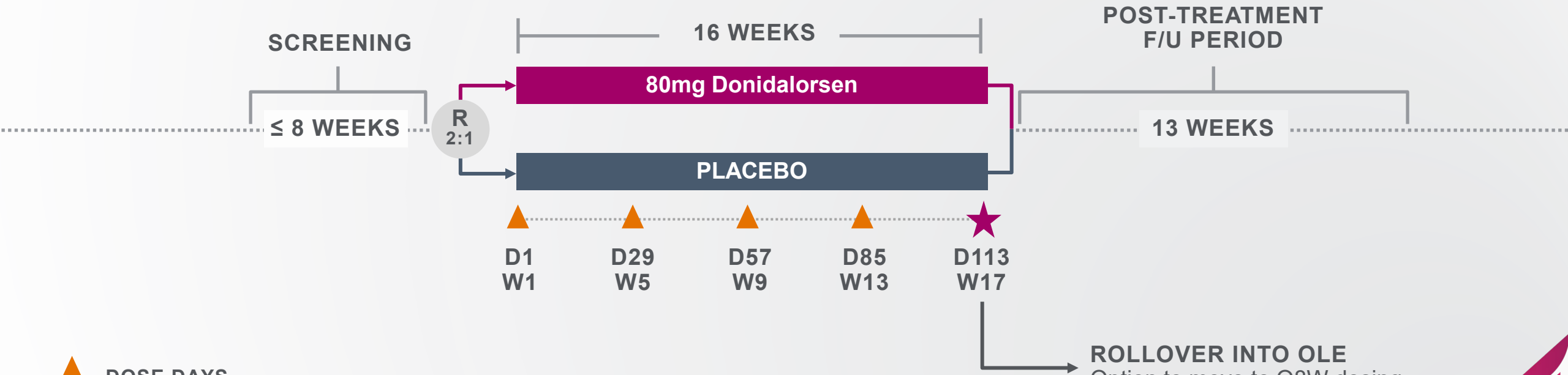
Donidalorsen Phase 2 Study in Patients with HAE

KEY INCLUSION CRITERIA

- HAE Type 1 or 2
- ≥ 18 years
- ≥ 2 attacks during screening

PRIMARY OUTCOME

Time-normalized number of HAE attacks (per month)



▲ DOSE DAYS

★ PRIMARY ENDPOINT READOUT

Donidalorsen Phase 2 Results Support Potential Best-in-Class HAE Prophylaxis Profile

- Dramatic, **rapid** and **sustained** reductions in HAE attacks
- Rapid onset of action with **robust duration**
- **Favorable** safety and tolerability profile
- Open-label extension study is progressing well with optional **bi-monthly dosing regimen**

90%
Mean reduction in monthly HAE attacks vs. placebo
(weeks 1-17)

97%
Mean reduction in monthly HAE attacks vs. placebo
(weeks 5-17)

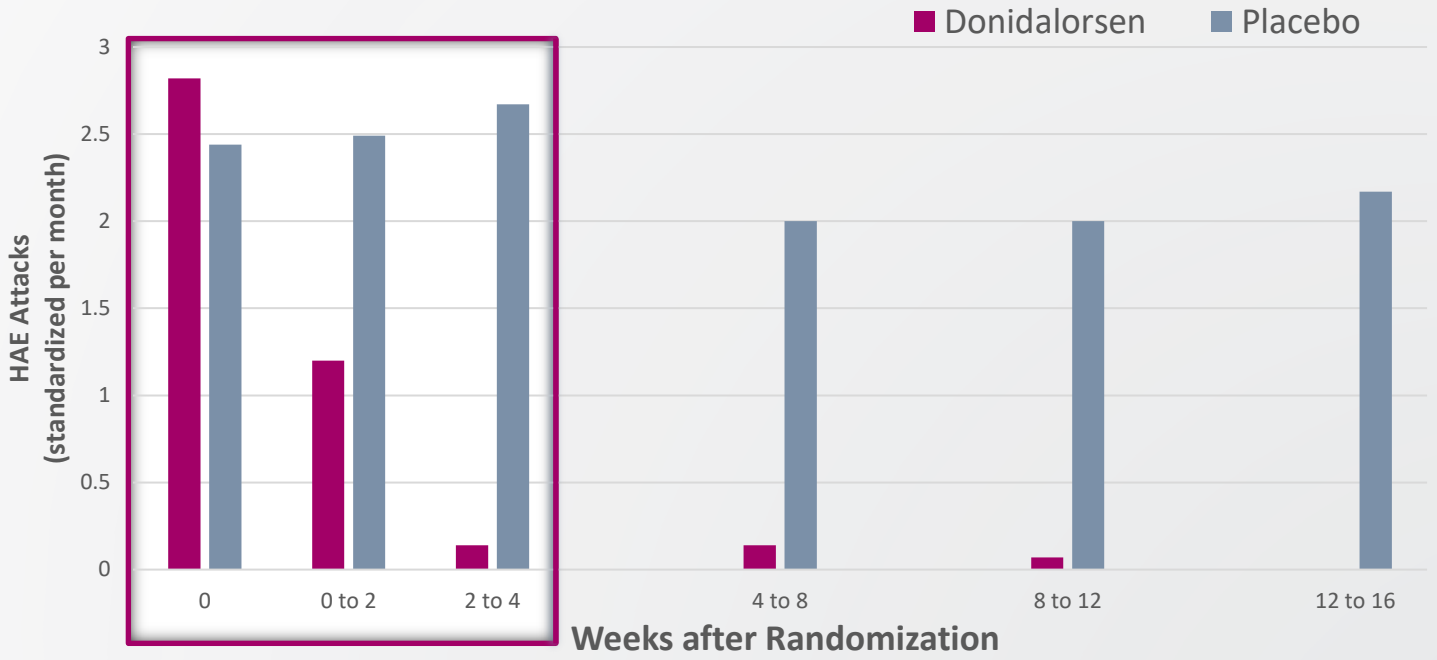
92%
Treated patients were attack-free vs. **0%** patients on placebo
(weeks 5-17)

Patient Baseline Characteristics

Characteristic	Donidalorsen (n=14)	Placebo (n=6)
Age – yrs	37.8 (14.4)	40.0 (13.8)
Female Sex – n (%)	9 (64.3)	4 (66.7)
BMI (kg/m^2)	29.6 (7.5)	26.2 (3.4)
C1-INH-HAE Type I – n (%)	13 (92.9)	5 (83.3)
Age at Onset of Angioedema Symptoms	10.6 (5.6)	16.5 (2.88)
Number of HAE Attacks in Prior 12 Months	**23.1 (16.2)**	**25.3 (22.9)**

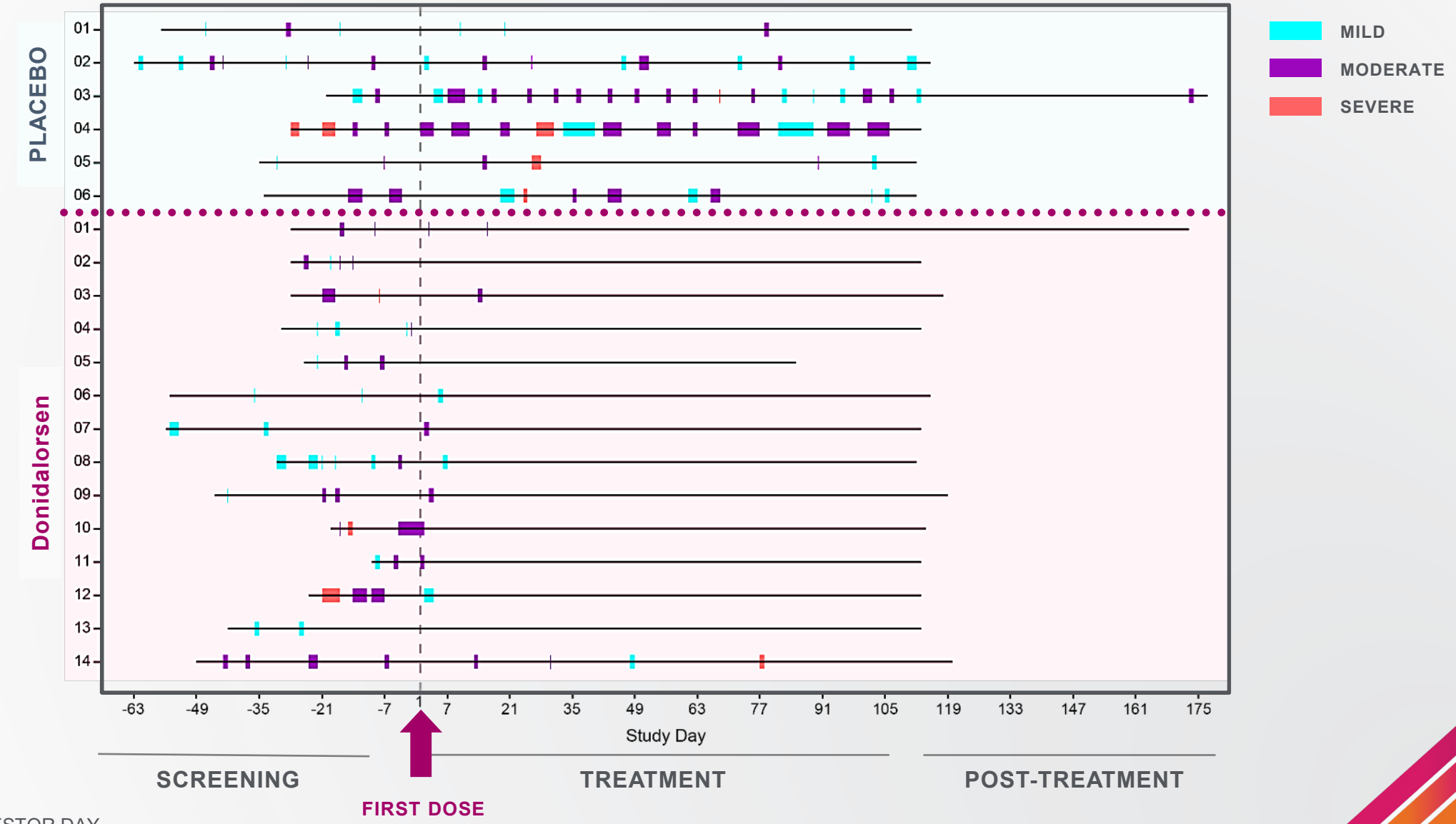
Rapid and Sustained Reduction in HAE Attacks

Primary Endpoint



Endpoint	Donidalorsen (n=14)	Placebo (n=6)	P-Value
No. of Attacks Per Month			
Mean (95% CI)	0.23 (0.08, 0.39)	2.21 (0.58, 3.85)	
Difference (95% CI)	**-90% (-96%, -76%)**		**<0.001**

Sustained Reduction in HAE Attacks



Favorable Safety and Tolerability Profile

Supports Advancing into Phase 3 Development

Incidence	Donidalorsen	Placebo
n	14	6
Any Adverse Event (%)	10 (71.4)	5 (83.3)
Any Drug-Related AE (%)	4 (28.6)	4 (66.7)

AE	Donidalorsen	Placebo
n	14	6
Headache (%)	2 (14.3)	2 (33.3)
Nausea (%)	1 (7.1)	1 (16.7)

Donidalorsen OASIS-HAE Phase 3 Study

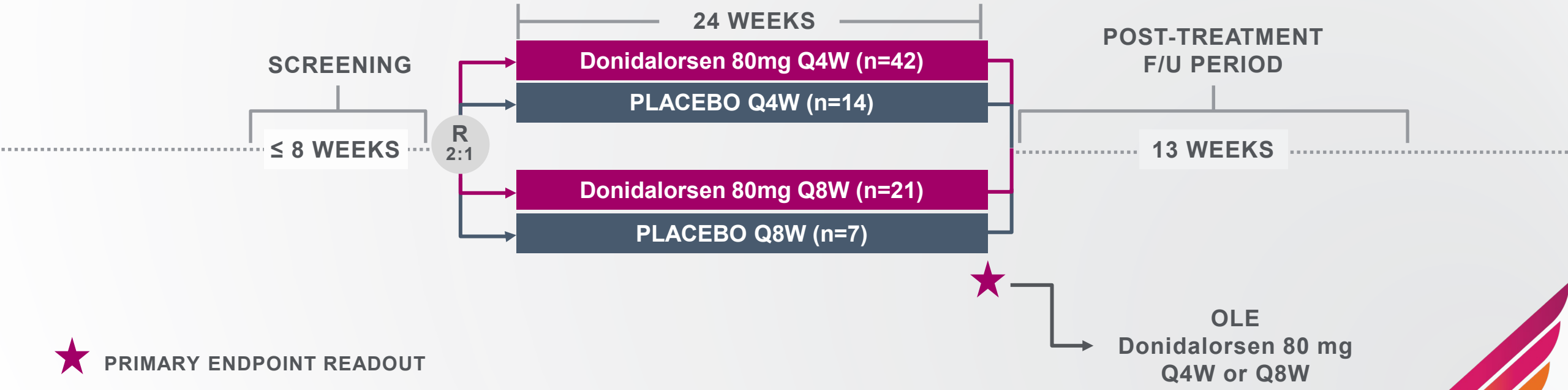
Pivotal Study in Patients with HAE

DESIGN

A randomized, double-blind, placebo-controlled study of monthly and bi-monthly subcutaneous injections of donidalorsen or placebo in up to 84 patients, age 12 and above, with HAE Type 1 and Type 2

PRIMARY OUTCOME

Time-normalized number of HAE attacks (weeks 1 - 25)



★ PRIMARY ENDPOINT READOUT

Patient photo courtesy of the US Hereditary Angioedema Association

Donidalorsen: Potential Best-in-Class Prophylactic Treatment for Patients with HAE

- In Phase 2, 92% of patients were **attack free**
- **Favorable** safety and tolerability in the study
- Potential for **bi-monthly dosing**
- Low volume **subcutaneous** injection with **ultra-fine needle**
- Plan for **auto-injector** administration

Donidalorsen: Reimagining the Treatment of Hereditary Angioedema

Onaiza Cadoret
Chief Corporate Development & Commercial Officer

HAE is an Attractive Market for Ionis

Established Market	Growing Market	Rare Disease
Well defined patient population and prescriber base in the US	Global prophylaxis market is **>$1.5B** and **growing**[1] Rapidly **increasing** rate of prophylaxis treatment	**5,000+ diagnosed** patients in the US[2]

1. Market data on file. 2. Lumry WR, Settipane RA. Hereditary angioedema: Epidemiology and burden of disease. Allergy Asthma Proc. Nov 2020

Significant Unmet Medical Need Despite Multiple Approved Therapies

- Patients **still experience breakthrough attacks** with currently marketed products
- **Approved prophylactic therapies require frequent administration** (daily, weekly or bi-weekly) that can negatively impact patient compliance
- Patients seek to **regain their freedom** from the disease and **improve their quality of life**
- Continued **need** for a **prophylactic treatment** offering HAE patients **greater efficacy**, **safety** and **tolerability** and **easy to use**

Prevalence

> 20K

Patients in the United States and Europe suffering from HAE[1]

Indication	Peak Sales[2]
HAE	

1. Market data on file 2. Peak sales estimates are based on current assumptions and are subject to change

Donidalorsen Represents a Compelling Opportunity

Addresses Unmet Needs	Potential Best-in-Class Profile	Good Fit for Ionis
Breakthrough attacks	Differentiated efficacy, dosing & favorable safety	Valuable rare disease market

Donidalorsen Phase 2 Results Support Potential Best-in-Class HAE Prophylaxis Profile

- Dramatic, **rapid** and **sustained** reductions in HAE attacks
- Rapid onset of action with **robust duration**
- **Favorable** safety and tolerability profile
- Open-label extension study is progressing well with optional **bi-monthly dosing regimen**

90%
Mean reduction in monthly HAE attacks vs. placebo
(weeks 1-17)

97%
Mean reduction in monthly HAE attacks vs. placebo
(weeks 5-17)

92%
Treated patients were attack-free vs. **0%** patients on placebo
(weeks 5-17)

HCPs See Use of Donidalorsen as a Meaningful Advance in Treating HAE

All physicians in our market research had a positive response to donidalorsen and saw it as a meaningful advance in treating HAE as it potentially addresses key unmet needs

Interest

Initial Reaction	% of HCPs
Positive	100%
Neutral	0
Negative	0

Differentiation

Element	% of HCPs Finding Element Compelling
Dosing	100%
Onset of Action	53%
Zero Attacks	53%

Source: Ionis primary qualitative market research 1Q2021, Allergist / Immunologist respondents

Patients Have Strong Interest in Donidalorsen

When presented a blinded profile of donidalorsen during market research, almost all patients indicated they would be interested in trying donidalorsen

Interest in Trying Donidalorsen	
Definitely	71%
Possibly	21%
Probably Not	7%

> *I'd be very interested. It does everything I want. Reduces severity and duration. If I do well, it might be once every eight weeks instead of twice a month.*

> *I would definitely be interested in it because it seems as effective, if not more, than where I'm at now, on top of being convenient.*

> *I would be extremely interested. If it was available tomorrow, I'd go ask my doctor about it. (To switch) It wouldn't take much… Taking it once a month, and potentially only once every two months is very attractive.*

Source: Ionis primary qualitative market research 1Q2021


Strong Product Profile
Patient Engagement & Advocacy
Access & Patient Support Hub
Generate Real World Data
Driving Switch
Driving Donidalorsen Success

Efficient and Targeted Market Approach

Concentrated Prescriber Base	Targeted Sales Force	Direct-to-Patient Engagement
Majority of HAE patients in the US are treated by allergists ~500 allergist/immunologists manage >50% of HAE patients	~50-80 customer-facing FTEs targeting top allergist & immunologist prescribers	Patient motivation for switch High touch patient services Digital tools for continued engagement and adherence

Red

Patient photo courtesy of the US Hereditary Angioedema Association

Realizing the Potential of Donidalorsen

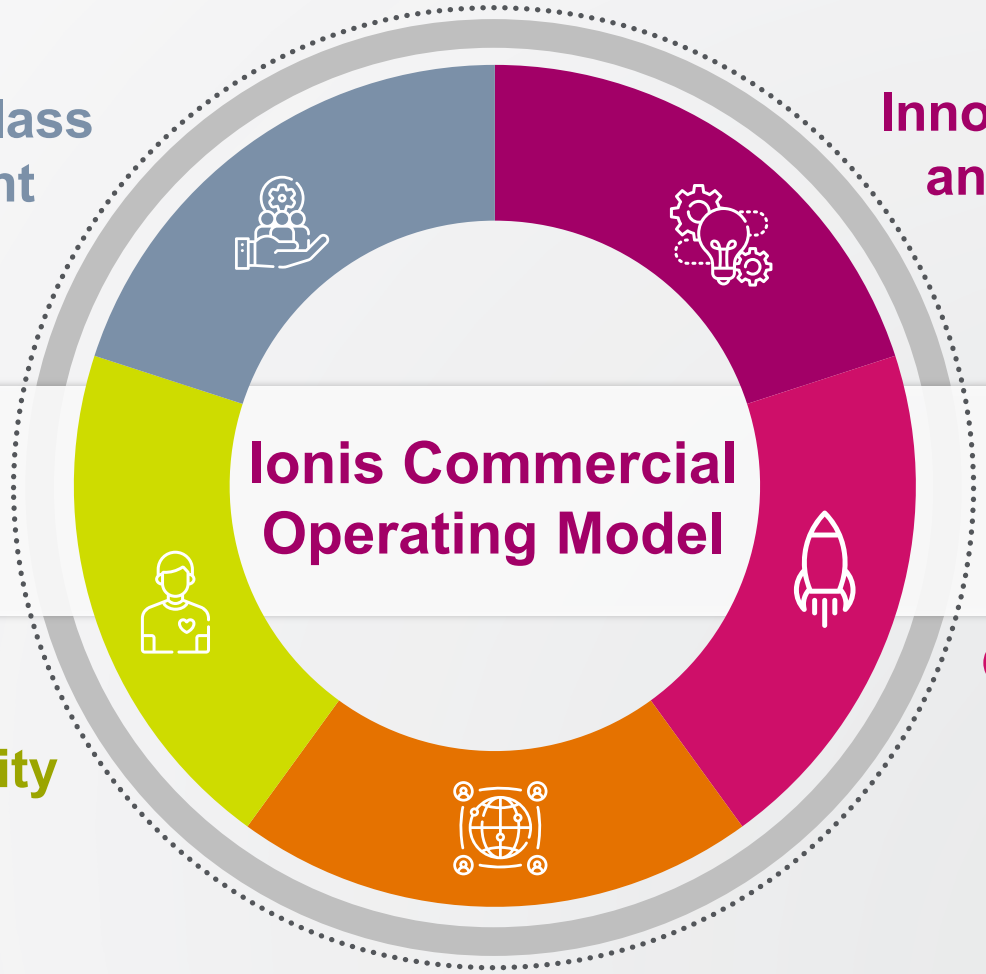
Reimagining the Treatment of Hereditary Angioedema

- Rare disease with developed market and identified patients
- Strong Phase 2 data supports potential to address high unmet needs
- Attractive product profile with potential for best-in-class efficacy, safety, and monthly dosing with potential for bi-monthly dosing
- High-value, high-margin opportunity

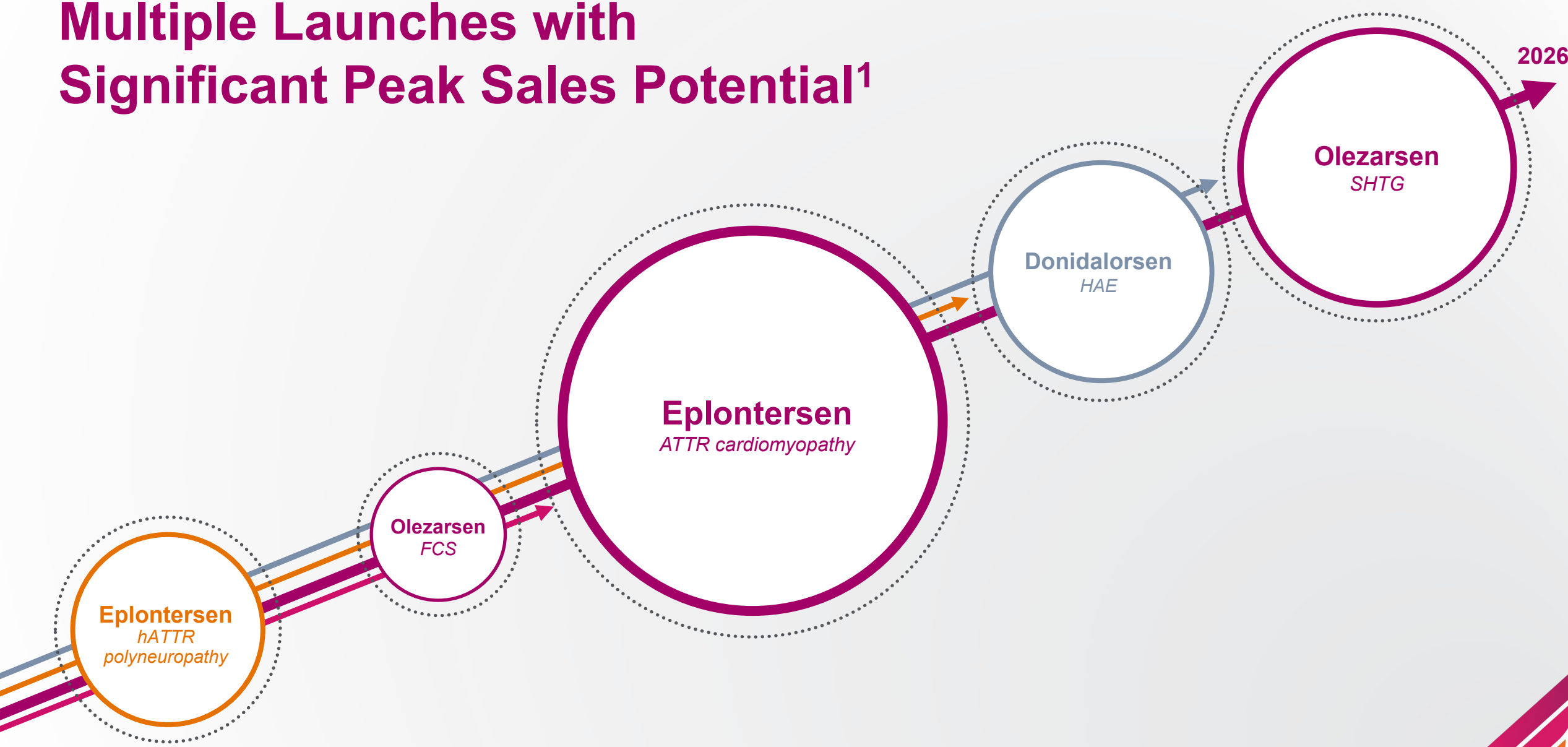
Realizing the Promise of Our Innovative Products

Our Commercial Vision

Maximize the value of our innovation	**Focus** **on 2 Core Franchises** cardiovascular and neurology	**Build** **Commercial Capabilities** for wholly owned medicines
Meet underserved **patient needs**, drive commercial **success** and create **value** for shareholders Focus on near-term commercial **opportunities** Portfolio planning for continued new product **innovation**	Opportunistically add products from our emerging **specialty rare franchise** that address underserved medical needs Global product strategy team with **go-to-market execution** focused on US	**Scale** and **leverage** resources as commercial portfolio grows **Well-capitalized** to invest in core capabilities and beyond


World-class Talent
Innovative and Agile
Ionis Commercial Operating Model
Patient Centricity
Global Strategy, US Execution
Inter-connectivity Amongst R, D & C

Multiple Launches with Significant Peak Sales Potential[1]



1. Timing expectations and peak sales estimates are based on current assumptions and are subject to change

Advances in Antisense Technology

Eric Swayze, Ph.D.
EVP, Research

Advances in Antisense Technology

Ionis Technology Today

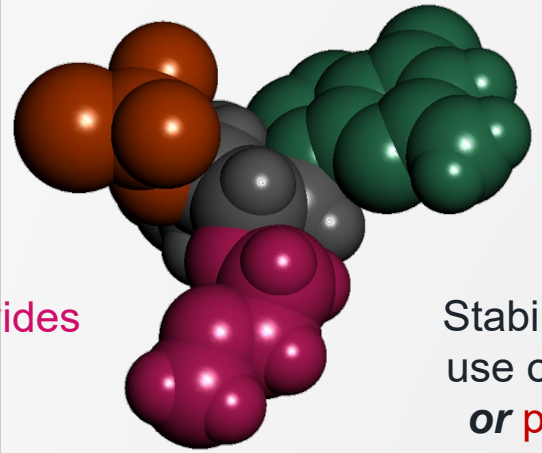
- Ionis technology has delivered our pipeline of medicines
- Key chemical technology is unique to Ionis and is performing today and will continue to add value in tomorrow's antisense medicines

Key Advancements in Technology

- New Bicycle peptide LICA
- New mesyl phosphoramidate (MsPA) backbone

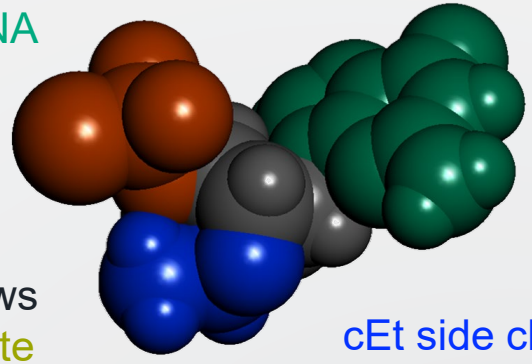
Benefits of MOE and cEt Chemistry

MOE side chain provides great binding affinity, potency and safety



Heterocyclic Base Recognizes target RNA

Stability of MOE and cEt allows use of ***either*** phosphorothioate ***or*** phosphodiester backbone



cEt side chain improves binding affinity and potency

- Great potency due to high binding affinity and stability
- High stability in biological systems gives long duration
- Attractive safety and tolerability profile

- Further increases potency by greatly increasing affinity to target RNA
- Maintains the extended dosing interval and safety profile
- Improves therapeutic index and facilitates activity in new tissues

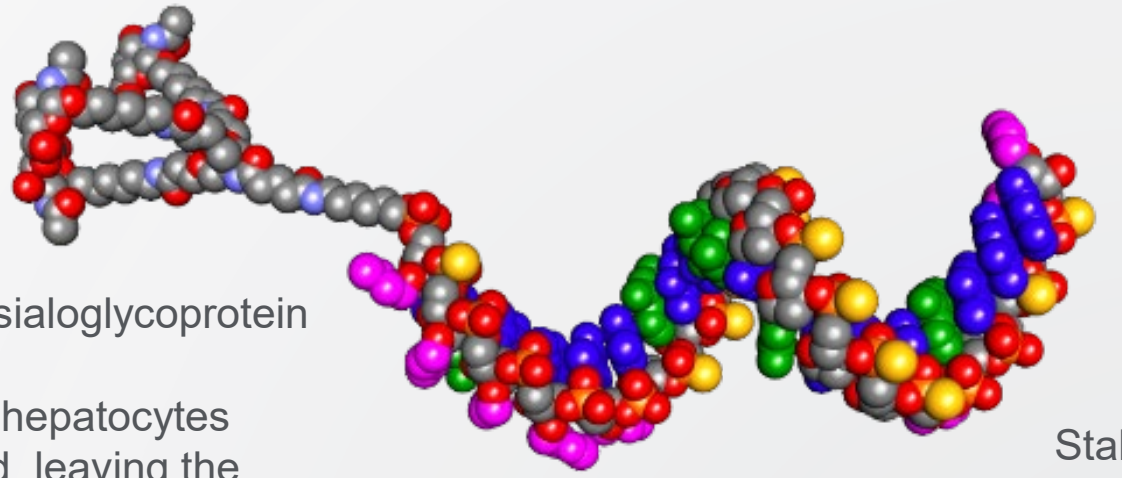
Teplova, et al. *Nat. Struct. Biol.* 1999, *6*, 535-539

Pallan, et al. *Chem Commun (Camb)* **2012**, *48*, 8195-8197

Liver LICA Technology Has Been Transformational

Trivalent "GalNAc" carbohydrate clusters

- Deliver cargo via the Asialoglycoprotein Receptor (ASGR)
- Specifically target liver hepatocytes
- Are rapidly metabolized, leaving the ASO in the cell (functions as a prodrug)



Stability of MOE and cEt allows use of ***either*** phosphorothioate ***or*** phosphodiester backbone

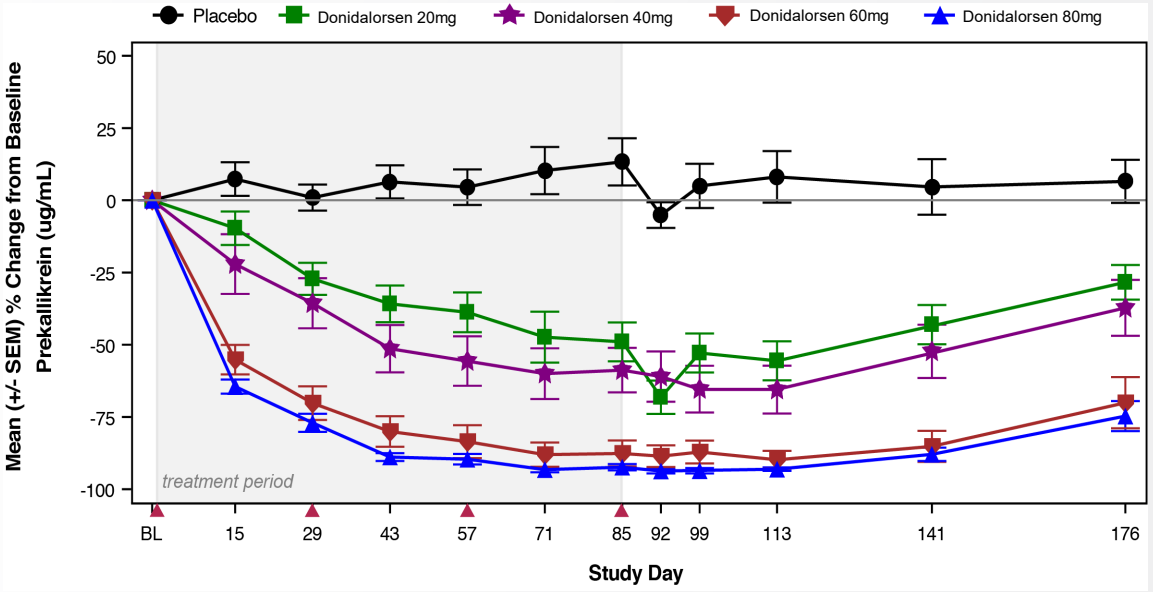
- Increases potency ~20-30x by increasing the fraction of drug delivered to the hepatocyte
- Allows an extended dosing interval to match drug half life
  - <100mg/month
  - Amenable to low volume monthly at home administration via easy-to-use autoinjector
- Reduced dose and frequency dramatically improves therapeutic index and safety profile

Prakash, *et al.* (2016) *J. Med. Chem.*, **59**, 2718-2733
Shemesh, *et al.* (2016) *Mol Ther Nucleic Acids*, **5**, e319
Yu, *et al.* (2016) *Nucleic Acid Ther.*, **26**, 372-380;

Optimized Liver LICA Designs Support Extended Dosing Frequency in Humans With High Target Suppression

Donidalorsen (MOE LICA) Maintains PKK Reduction 8 Weeks Post Last Dose

Percent change from baseline in PKK levels over time

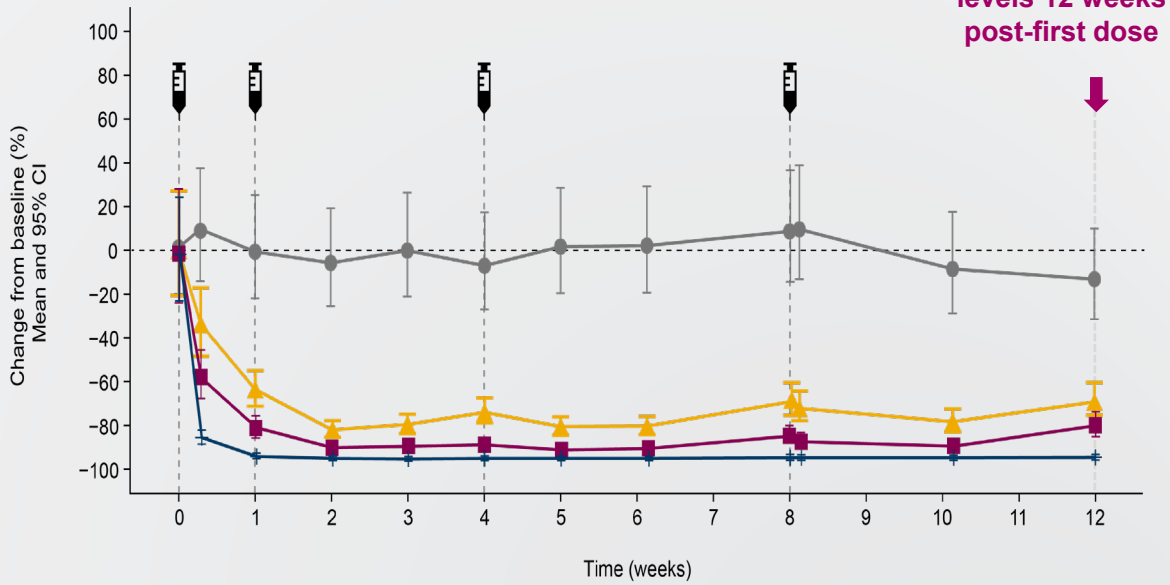


Change from baseline [%] (SD)	Day 85 (week 12)	Day 141 (week 20)
Donidalorsen 80mg	–92 (±2.7)	–88 (±5.8)

ION449 (AZD8233) (cEt LICA) Reduced Circulating PCSK9 Levels by Up to 95%

Percent change from baseline in PCSK9 levels over time

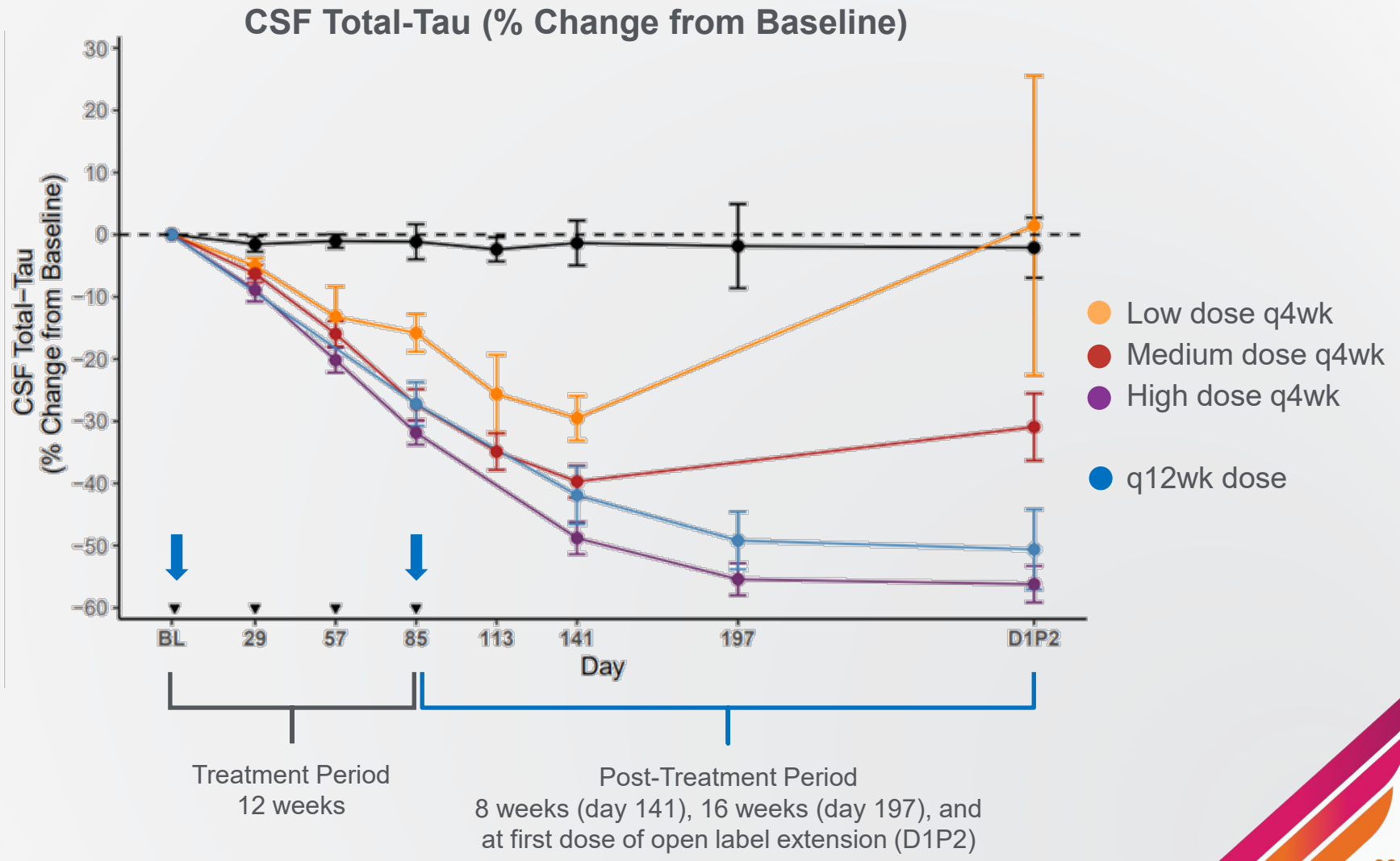
PCSK9 plasma levels 12 weeks post-first dose



	Change from baseline 12 weeks post-first dose [%] (95% CI)
ION449 (AZD8233 15mg)	–69.7 (–76.6, –60.7)
ION449 (AZD8233 30mg)	–79.9 (–84.8, –73.4)
ION449 (AZD8233 90mg)	–95.3 (–96.3, –94.0)

Optimized CNS Designs Demonstrate Effective and Durable Target Suppression in Humans

- 2 quarterly doses (⬇) of IONIS-MAPT$_{Rx}$ reduced and maintained Tau suppression up to the initiation of the open label extension
- Supports an extended dosing frequency for CNS ASO medicines



Advances in Antisense Technology

Ionis Technology Today

- Ionis technology has delivered our pipeline of medicines
- Key chemical technology is unique to Ionis and is performing today and will continue to add value in tomorrow's antisense medicines

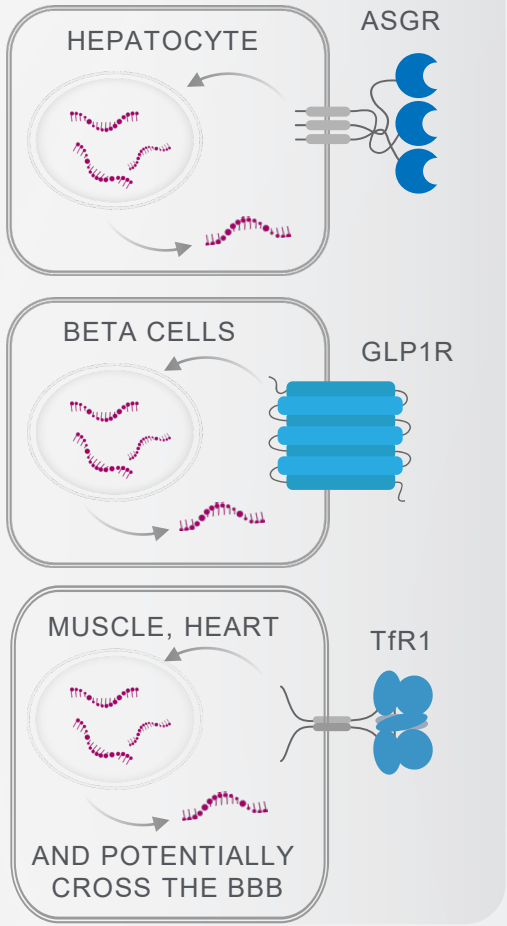
Key Advancements in Technology

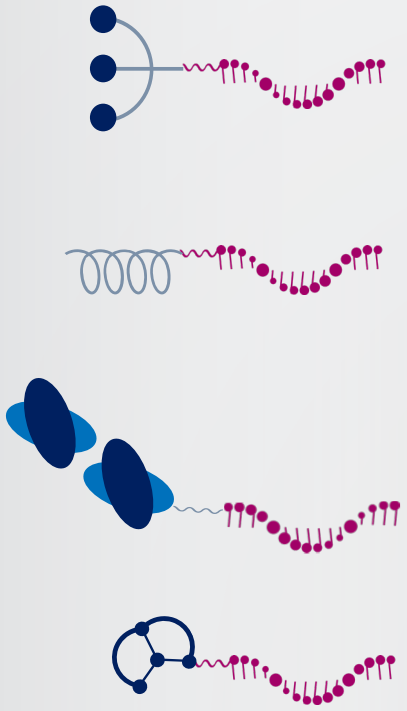
- New Bicycle peptide LICA
- New mesyl phosphoramidate (MsPA) backbone

Ionis LICA Platform Continues to Expand

Multiple Tissues

- Liver
- Pancreas
- Muscle
- Many others in research stage

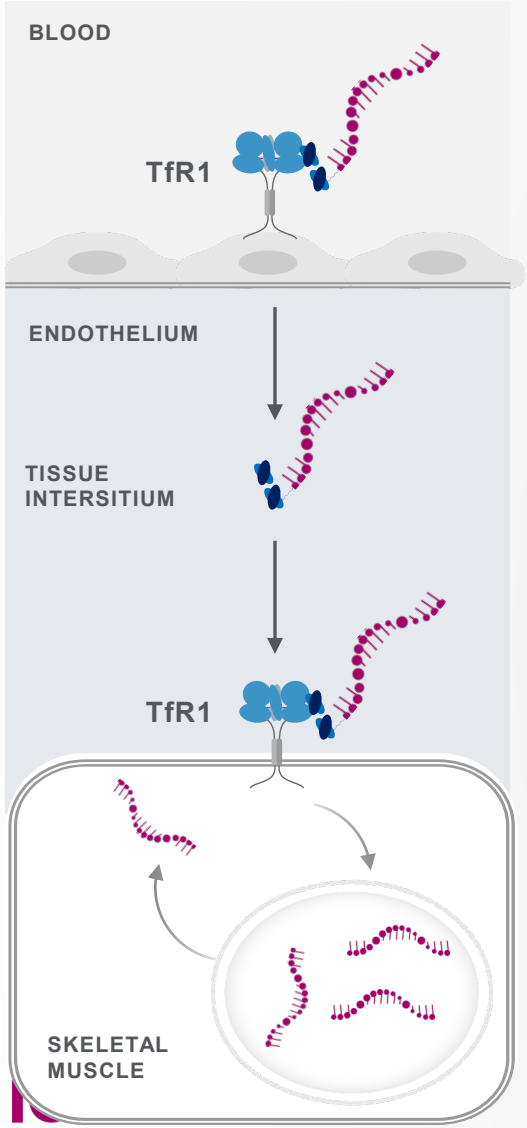




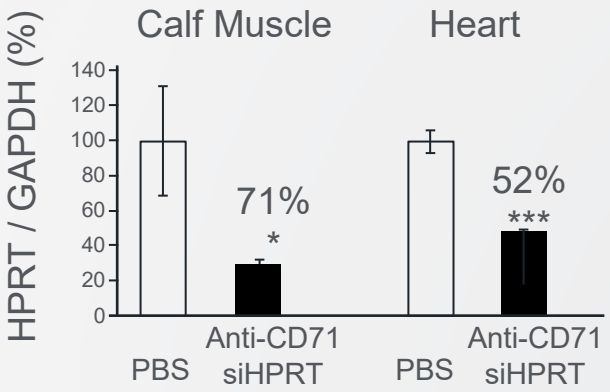
Multiple Ligands

- Carbohydrates
- Peptides
- Antibodies and FAB fragments
- Bicycle peptides

Employing the Transferrin Receptor 1 (TfR1) Enhances ASO Potency in Muscle Tissues



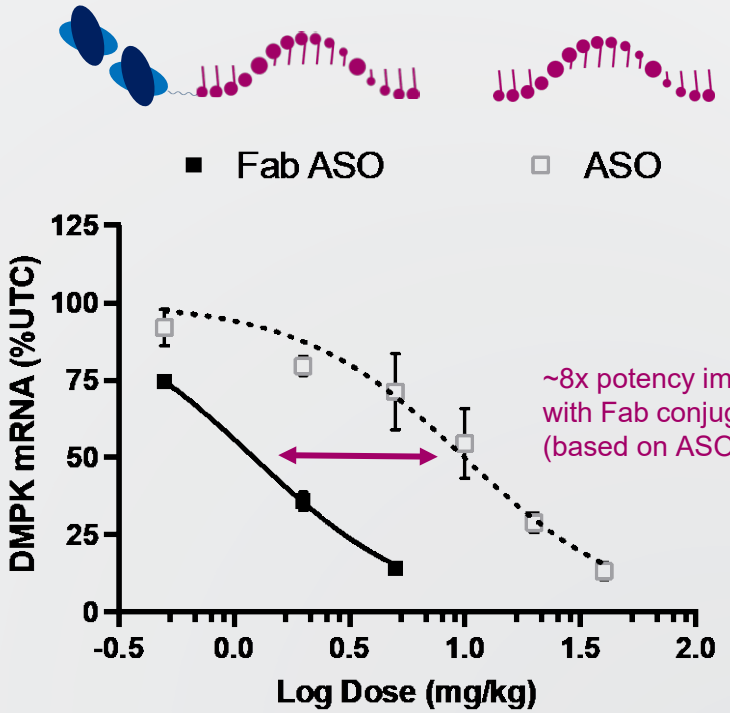
Initial Literature Report



10 mg/kg HPRT siRNA conjugated transferrin receptor antigen binding fragment (Fab) 72 h post dosing in C57BL/6 mice

Sugo et al., *J. Control. Rel.* **2016**, *237*, 1-13

Ionis Validation with Fab-ASO

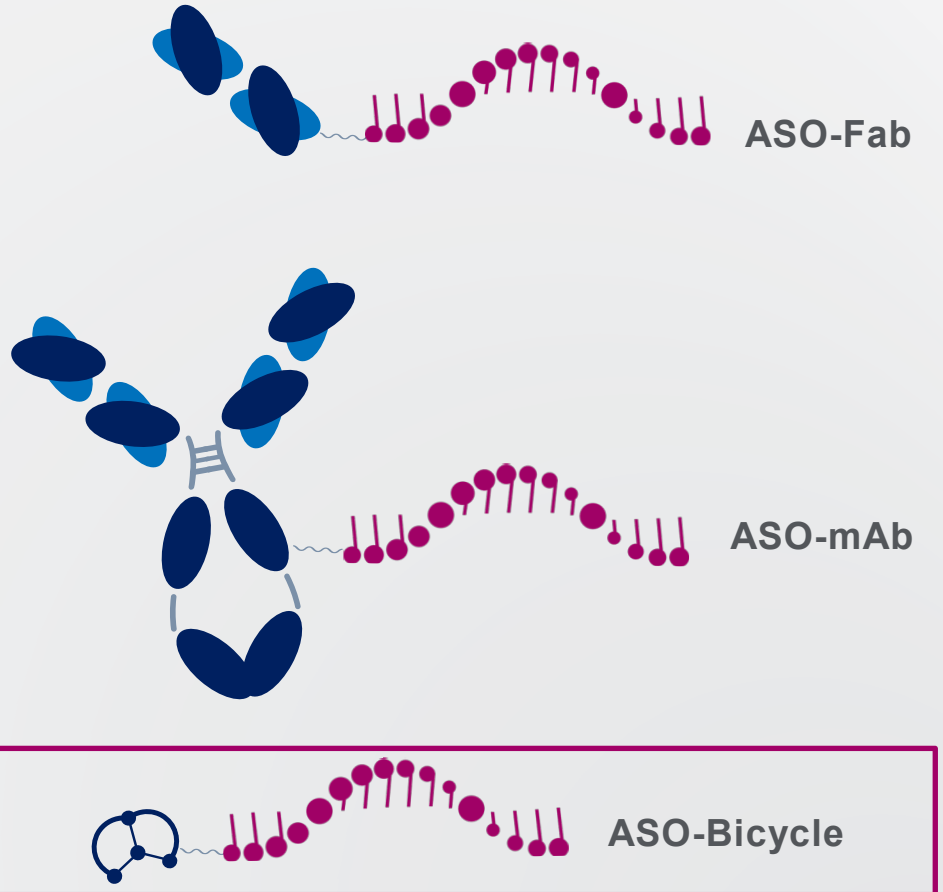


Fab-ASO or unconjugated DMPK cEt ASO dosed weekly for 3 weeks in C57BL/6 mice
Target mRNA in quadricep muscle shown, other muscles have similar reduction

The Problem with Antibody Ligands: They Are Big, and Increase Total Dose of Drug Administered

Amount of LICA Conjugate Required to Deliver 3mg/kg ASO or siRNA

Compound	Mol wt	Conjugate Dose (mg/kg)	Theoretical Clinical Dose (mg)
ASO	~5400	--	210
ASO-Fab siRNA-Fab	~55000 ~65000	~33	2140 910
ASO-mAb siRNA-mAb	~155000 ~165000	~93	6030 2310
ASO-centyrin	~15000	~9	580
ASO-Bicycle siRNA-Bicycle	~7400 ~17000	~4	**290** **240**

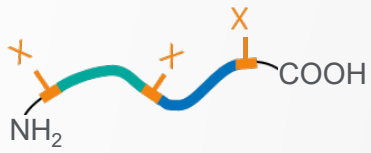


Bicycle Technology

Constrained Peptides on Phage Display Further Optimized Using Medicinal Chemistry and Structural Biology

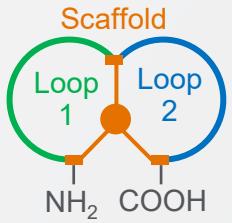
bicycle therapeutics

Linear Peptide

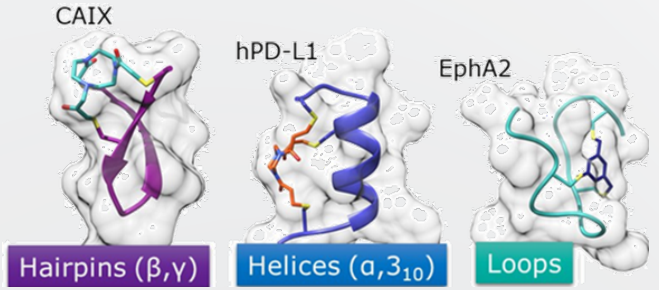


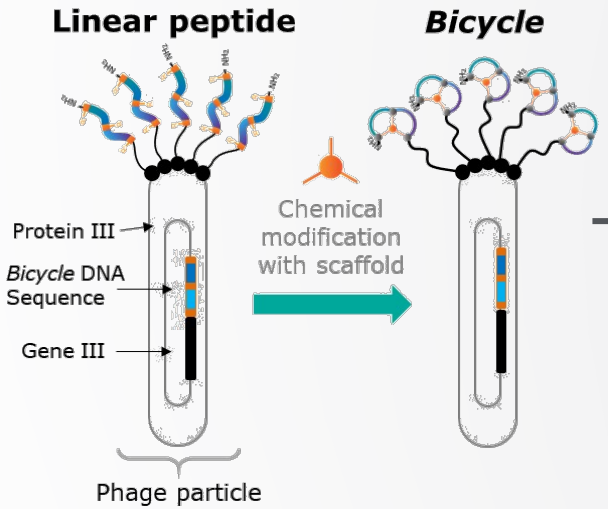
Chemical modification with scaffold

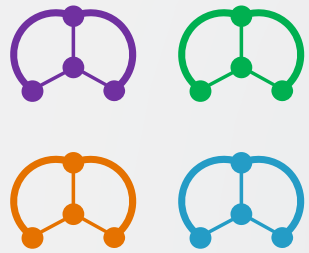
Bicycle



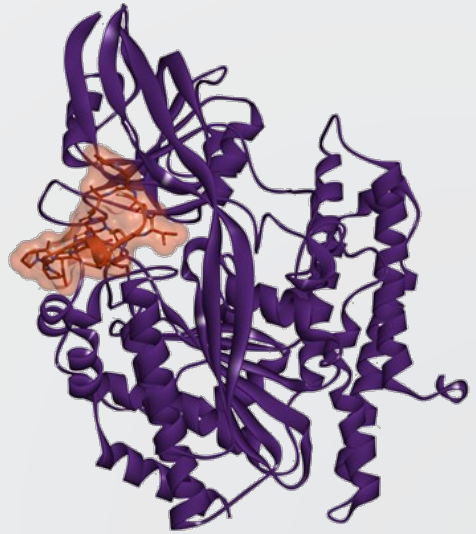
Form biologically relevant 3D structures







Target binding *Bicycles*



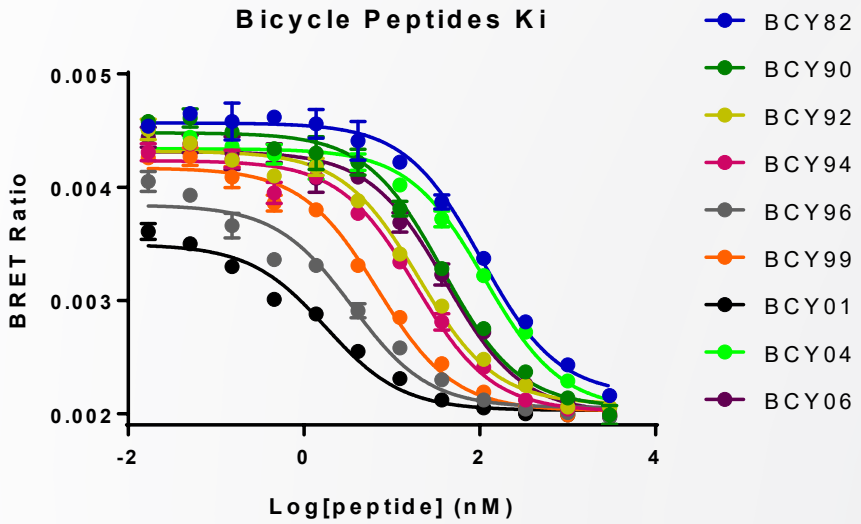
Crystal structure of human TfR1 (purple) bound to a Bicycle lead (red)

Diverse *Bicycle* phage libraries (>10^{17})

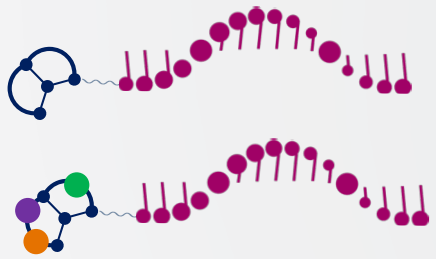
Optimize leads using medicinal chemistry

Refine leads using structural biology

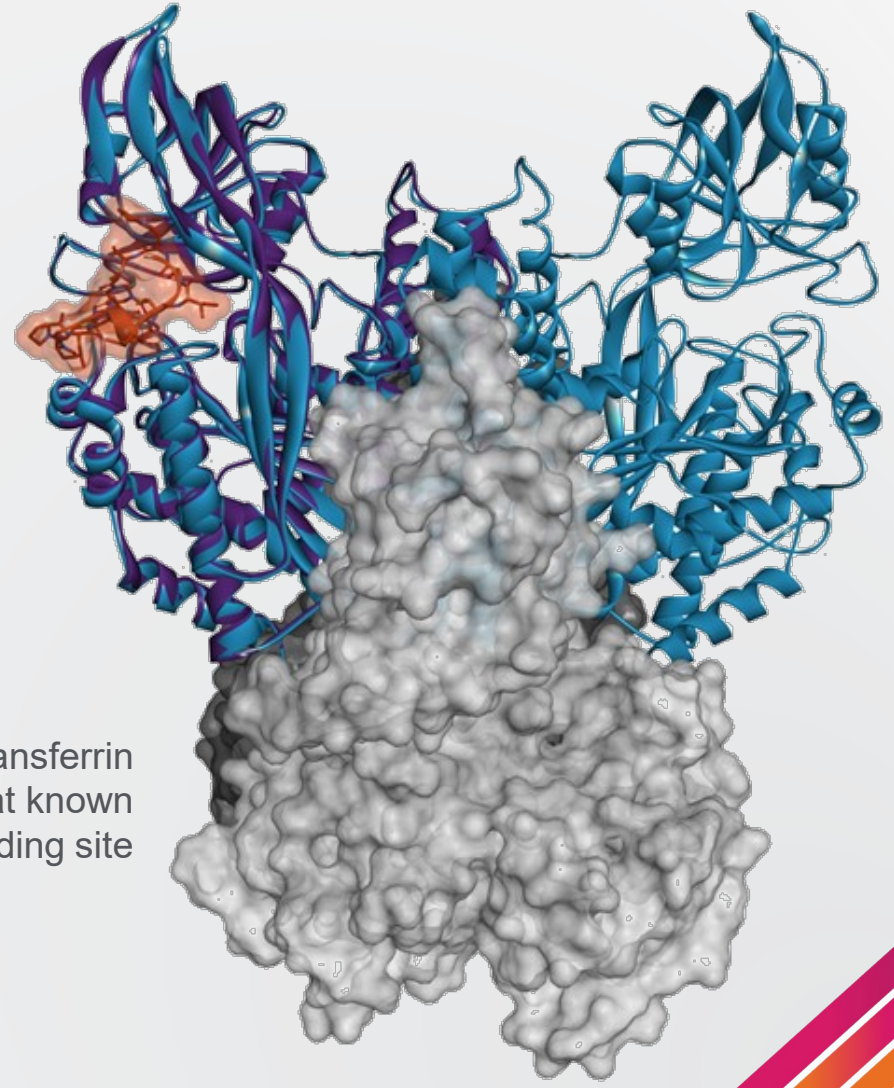
Bicyclic Peptides Show High Affinity Binding for hTfR1 and Have a Binding Site Distinct from Transferrin



CONJUGATE	Ki (nM)
BCY82-ASO	55
BCY90-ASO	20
BCY92-ASO	11
BCY94-ASO	10
BCY96-ASO	2
BCY99-ASO	4
BCY01-ASO	1
BCY04-ASO	60
BCY06-ASO	22



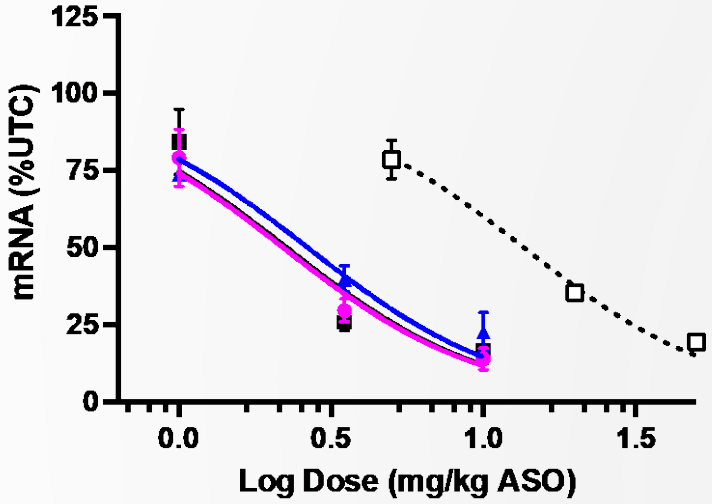
Crystal structure of **human TfR1 (blue)** bound to a **Bicycle lead (red)**



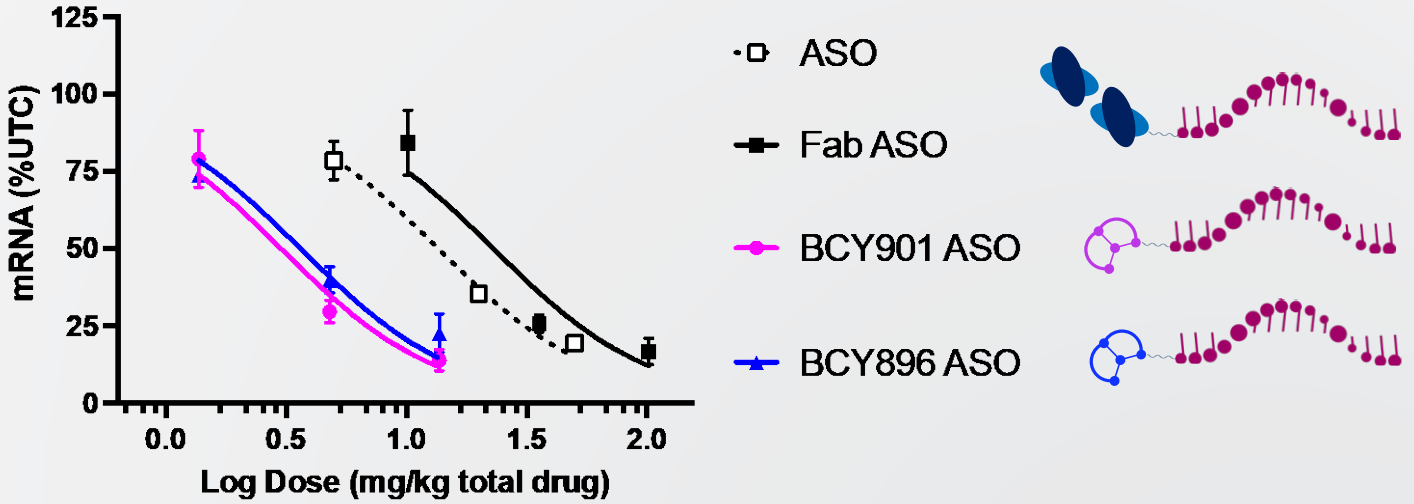
Human transferrin docked at known binding site

hTFR1 Targeting *Bicycle*-ASO Conjugates Improve Potency Relative to ASO and Fab-ASO Conjugates

Potency Based on Mass of ASO Administered



Potency Based on Mass of Total Drug Administered



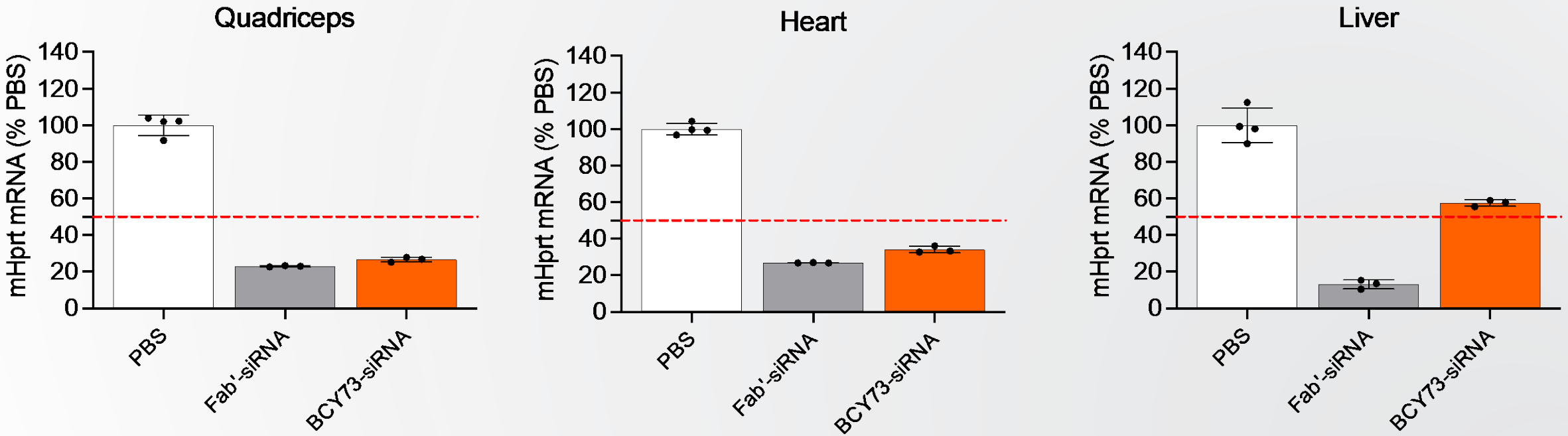
Bicycle-ASO, Fab-ASO or unconjugated DMPK cEt ASO dosed three times over 2 weeks in hTfR1$^{KI/+}$ mice
Target mRNA in quadricep muscle shown, other muscles have similar reduction

- Potency of Bicycle-ASO and Fab-ASO is the same on a molecular basis
- But Fab is large – so based on total drug mass, Bicycle ASO is more potent

Bicycle-siRNA Conjugate is Equally Active in Muscle as Fab-siRNA Conjugate (Based on siRNA mass)

FAB'-siRNA (~15mg/kg total mass)

BCY73-siRNA (~4mg/kg total mass)



Bicycle-siRNA or Fab-siRNA targeting mouse Hprt mRNA dosed weekly for 3 weeks in hTfR1$^{KI/+}$ mice at a dose of at 3.5mg/kg siRNA (4mg/kg siRNA-bicycle, 15mg/kg siRNA-Fab). Target mRNA in quadricep muscle shown, other skeletal muscles have similar reduction.

Bicycle TfR1 LICA – Key Points

- Bicycles efficiently target oligonucleotide drugs to muscle and heart tissue
- Bicycles are small (low molecular weight, and in this case smaller is better)
  - Reduces total dose required compared to an antibody delivery strategy by 10-20 fold
  - Potential for increased dosing flexibility
- Easy to manufacture (expected to reduce cost of goods)
- Can be optimized via standard medicinal chemistry techniques

Bicycle TfR1 LICA – Next Steps

- Optimize final design
- Implement manufacturing process
- Identify Bicycle conjugated drug candidates
  - Apply to heart and skeletal muscle targets
  - Determine optimal modality for each target (ASO, siRNA, etc.)
  - Identify and develop the best drug
- Explore potential to use Bicycles to cross blood-brain barrier

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- Key chemical technology is unique to Ionis and is performing today and will continue to add value in tomorrow's antisense medicines

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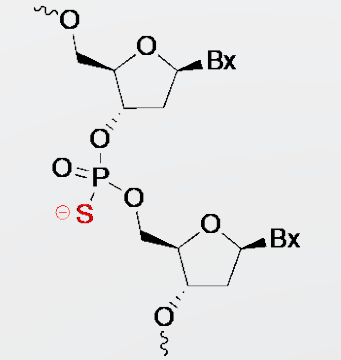
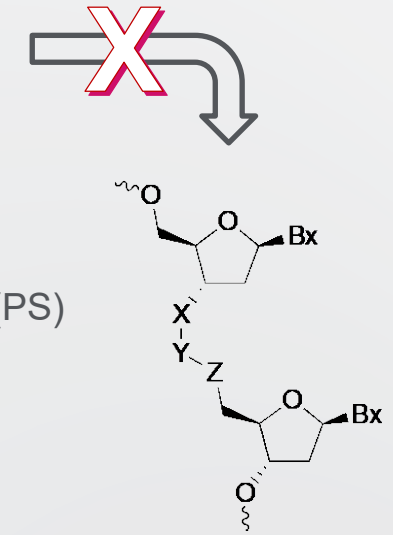
- New Bicycle peptide LICA
- New mesyl phosphoramidate (MsPA) backbone

Objectives in Designing the Next-Generation Backbone

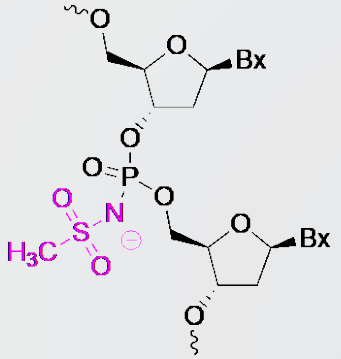
- Maintain or improve potency
- Improve duration of effect relative to existing designs
  - Comparable to benchmark siRNA designs
  - Phosphorothioate (PS) DNA is the weak point
    (Splicing ASOs with full MOE have year long duration)
- Reduce non-specific protein binding
  - Expected to reduce side effects and high dose toxicities
  - Especially pro-inflammatory effects
- Retaining other important attributes
  - Binding affinity for RNA target
  - Support enzymatic mechanisms (RNaseH1 and Ago2 activity)
  - Chemical stability
  - Ease and cost of manufacture



Phosphorothioate (PS)



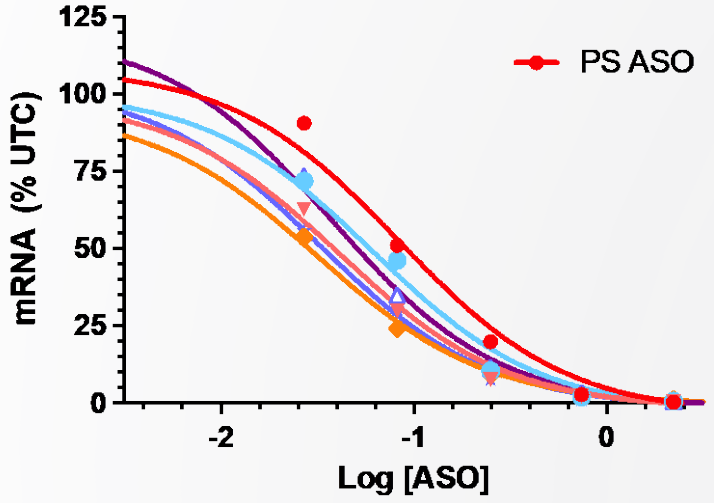
- Hundreds of backbones explored
- None had the desired features



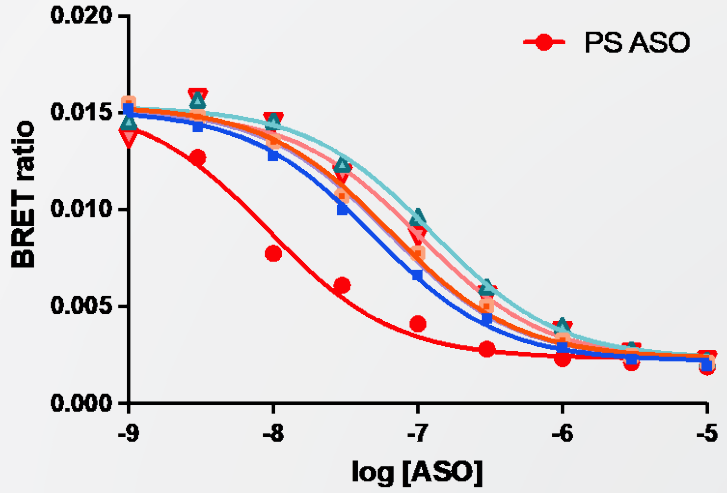
Mesyl Phosphoramidate (MsPA)
meets these key objectives

MsPA Backbone Represents a Breakthrough For ASO Design

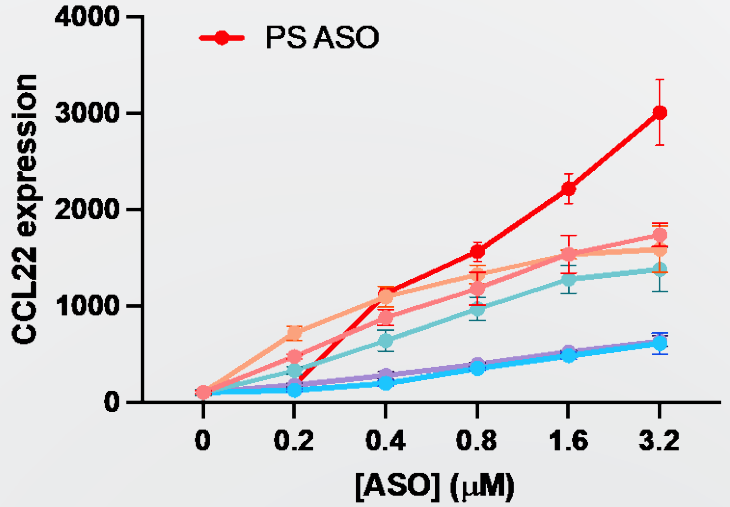
MsPA Maintains Potency



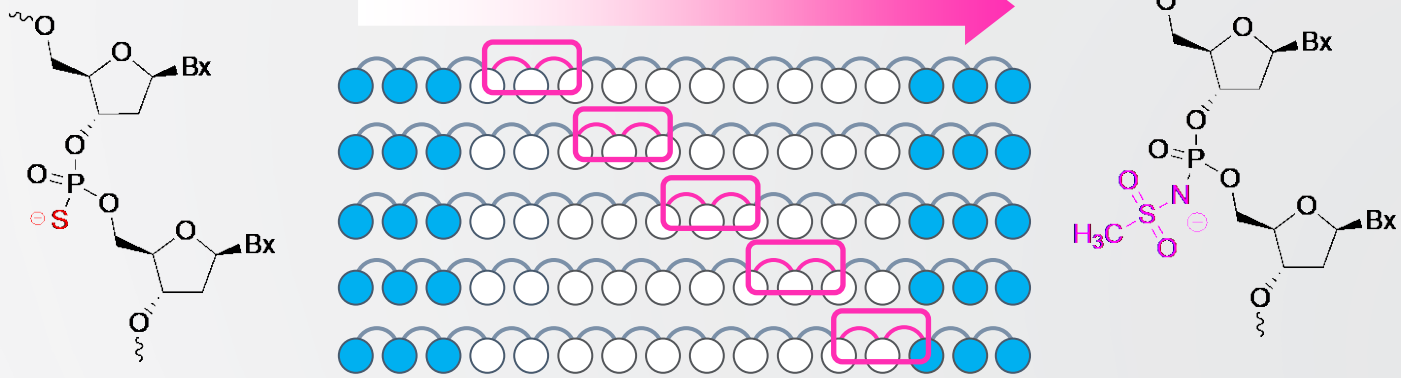
MsPA Reduces Protein Binding



MsPA reduces immune stimulation



Replace PS with MsPA



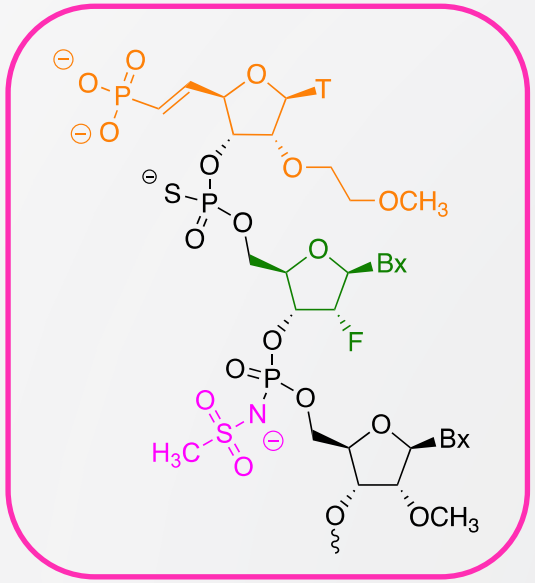
Anderson, et al. *Nucleic Acids Research* **2021**, *49* (16), 9026–9041

Can MsPA Improve siRNA Designs?

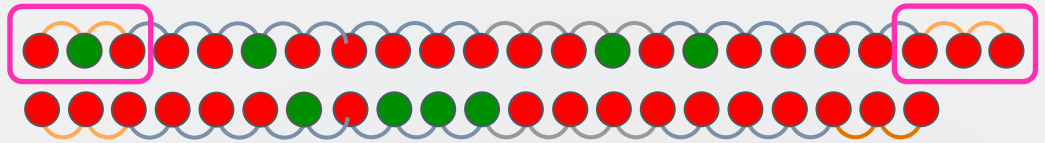
Vinyl Phosphonate (VP) is a privileged modification that improves potency
Lima, et al. *Cell* **2012**, *150* (5), 883–894

2’-F is critical at position 2 for activity

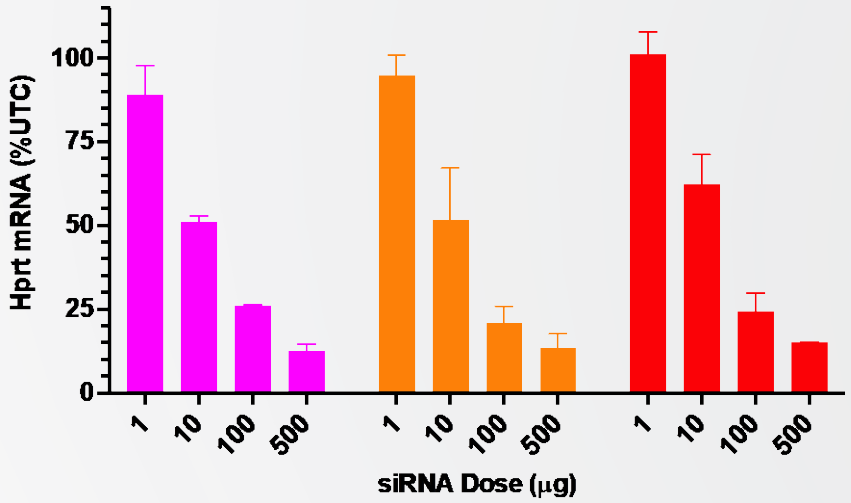
MsPA adjacent to 2’-F increases stability of labile 2’-F linkage



’Standard’ siRNA Design



MsPA, OMe, F, PO, PS



- Standard Design + 5’VP
- 3’ MsPA + 5’VP
- 3’ and 5’ MsPA + 5’VP

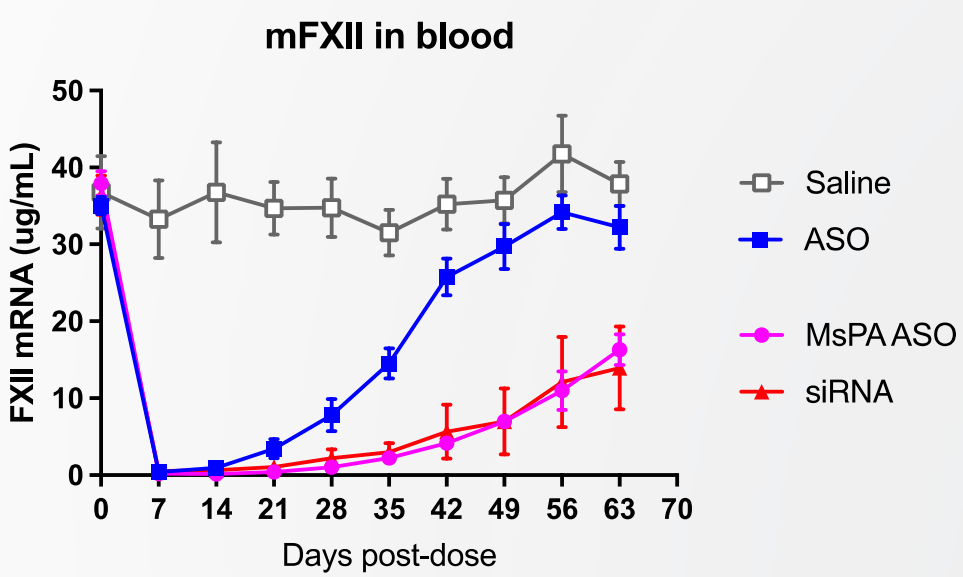
siRNA with antisense strand modified as above and C16 conjugated sense strand dosed ICV in C57/BL6 mice. Target mRNA in thoracic cord shown

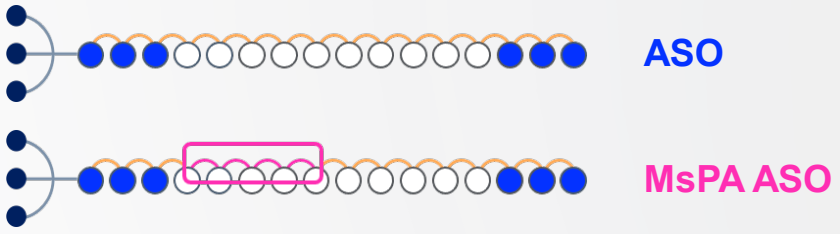
MsPA Increases Stability – Can This Improve Duration?

- Current platform delivers great drug profiles with infrequent dosing and consistent target suppression
  - $MAPT_{Rx}$ data suggest CNS durability to support > every 6-month dosing
  - Liver LICA supports monthly to bimonthly dosing regimens
  - Splicing ASOs with no DNA have >1 year duration of effect in mouse
- Hypothesis: Substitution of MsPA at weak points in an ASO (the PS DNA) should improve durability due to increased stability
- Note: Mouse duration underpredicts human duration by 3-5x, but can guide optimization
  - Mouse metabolism is faster than human, but the observed metabolite profile is similar
  - Example is olezarsen
    - Single dose in human transgenic mouse gave 85% APOC3 reduction which returned to 50% at 3 weeks
    - In human SAD, top dose gave 90% APOC3 reduction, which returned to 50% at 13 weeks
  - Suggests improvements in mouse duration beyond ~5-week timeframe are meaningful

MsPA Modification Can Enhance Duration of ASOs and siRNA in Mouse Liver

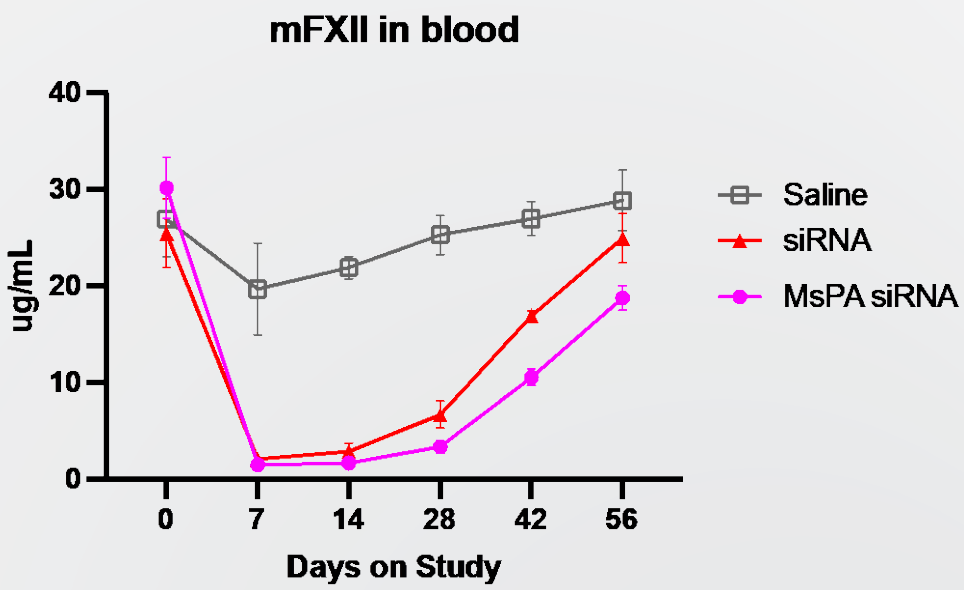
MsPA ASO

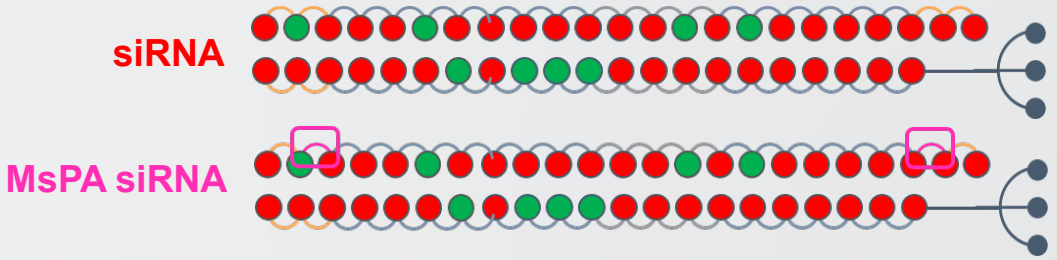




ASO dose 8mg/kg, siRNA dose 5mg/kg by subcutaneous injection
Anderson, et al. *Nucleic Acids Research* **2021**, *49* (16), 9026–9041

MsPA siRNA





siRNA dose 1mg/kg by subcutaneous injection

cEt, DNA, MsPA, OMe, F, PO, PS

MsPA Backbone – Key Points

- Increases stability over both PO and PS backbone
  - This increases duration of effect
- Maintains potency in multiple oligonucleotide mechanisms
  - ASO mechanism with MsPA substitutions in DNA portion of ASO
  - siRNA mechanism
- Reduces non-specific protein binding relative to PS linkage
  - This increases therapeutic index
    (e.g. by reducing proinflammatory effects)

MsPA Backbone – Next Steps

- Optimize designs and strategies to use in multiple mechanisms and tissues
  - ASO, splice modulation, siRNA, etc.
  - Muscle LICA, liver LICA, kidney, CNS, etc.
- Implement manufacturing process
- Identify MsPA drug candidates with optimal performance

Ionis Technology Advancements – Key Points

- Ionis technology has delivered our pipeline of medicines – which are performing well in the clinic today
- New technology advancements continuously improve our platform
  - Bicycle LICA has the potential to be best-in-class for muscle targeting
  - Broad LICA strategies for multiple tissues continue to progress
  - MsPA backbone represents a breakthrough as a new alternative to existing backbones
- This chemical technology is unique to Ionis and will continue to add value in tomorrow's antisense medicines
  - All oligonucleotide drug mechanisms
  - Across all franchise areas
  - New targets with unmet need
  - Lifecycle management for existing programs

Financial Growth Today and Tomorrow

Beth Hougen
Chief Financial Officer

GROWTH

IONIS

Build-Out Ionis Pipeline

Commercialize Our Products

Expand & Diversify Technology

Deliver Abundance of New Medicines To Market

Validated Platform Technology

Rich Mid- & Late-Stage Pipeline

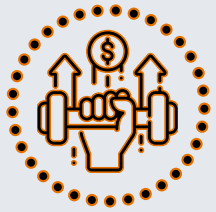
Financial Strength

Commitment to Innovation Leadership

Highly Dedicated Employees

Attractive Financial Profile

Building our Business on Solid Financials



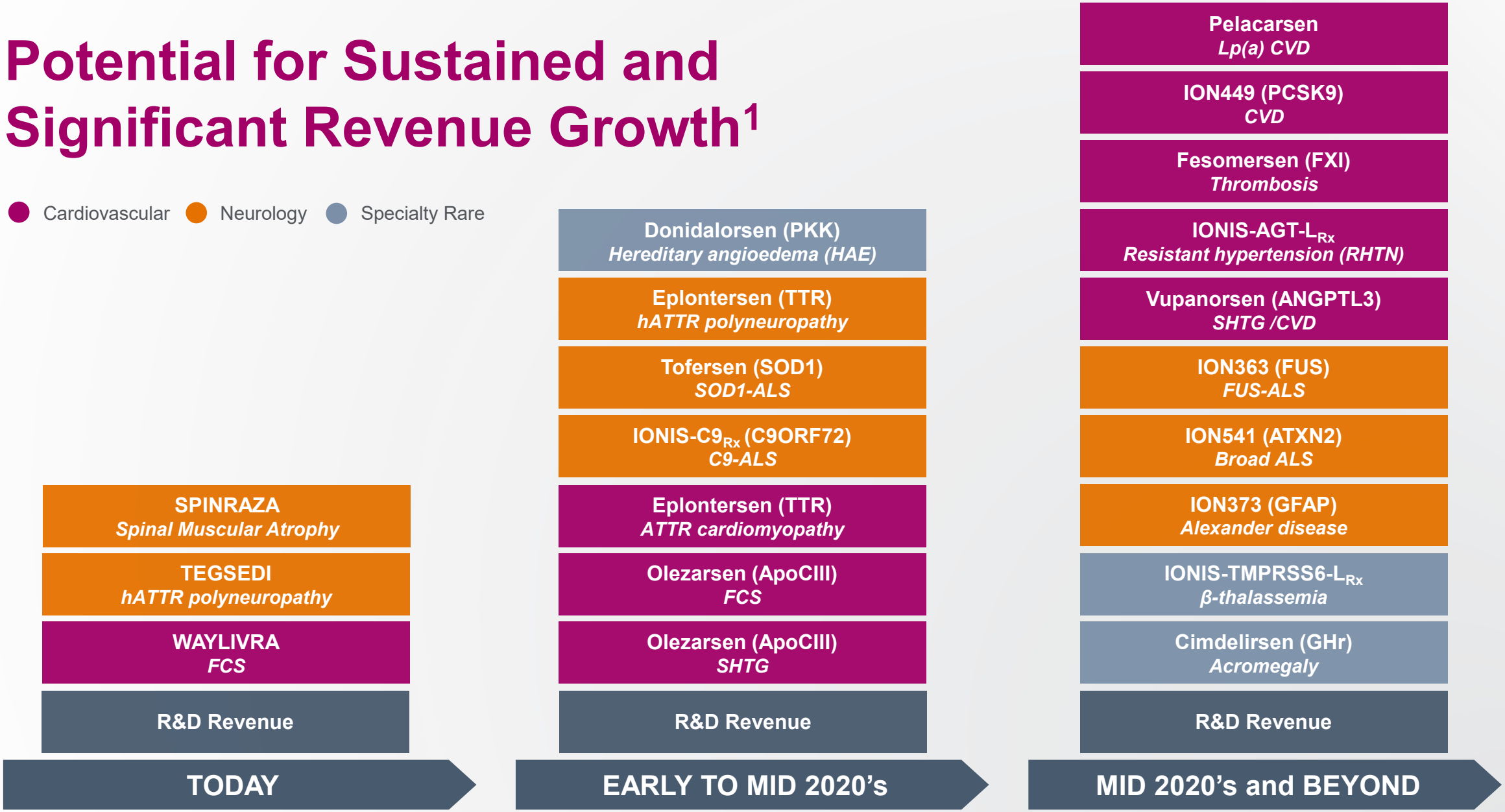
Financial Strength

- Well capitalized with ~$2 billion in cash
- Multiple sources of revenue with diverse margin profiles
- Numerous opportunities for revenue growth as we
  - Bring new products to market
  - Advance partnered programs
  - Enter new collaborations

Financial Flexibility to Support Ongoing Investments

✓ **Strengthening commercial foundation**	Commercial buildout to support 3 near-term product launches with multibillion-dollar sales potential
✓ **Advancing pipeline**	Rich pipeline focused on addressing substantial unmet needs
✓ **Broadening reach of technology**	Continuing to innovate our technology to remain best-in-class

Potential for Sustained and Significant Revenue Growth[1]



1. Market opportunity and timing expectations are based on current assumptions and are subject to change.

Eplontersen + Olezarsen + Donidalorsen

3 Near-term Opportunities with Aggregate Multibillion-dollar Potential[1]

Eplontersen

Multibillion-Dollar Opportunity

Olezarsen

Blockbuster Opportunity

Donidalorsen

High-Value, High-Margin Opportunity

1. Market opportunity and peak sales estimates are based on current assumptions and are subject to change

Eplontersen + Olezarsen + Donidalorsen

3 Near-term Opportunities with Aggregate Multibillion-dollar Potential[1]

Eplontersen

Multibillion-Dollar Opportunity

- Joint development & commercialization agreement with AstraZeneca
- Significant upfront + approval milestones
- Substantial royalties on net sales
- Sales milestones up to nearly $3 billion
- Strengthens balance sheet and lowers costs
- Accelerate commercial infrastructure build

Olezarsen

Blockbuster Opportunity

Donidalorsen

High-Value, High-Margin Opportunity

Estimated peak sales: <1 Billion >1 Billion Multibillion

1. Market opportunity and peak sales estimates are based on current assumptions and are subject to change

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Olezarsen

Blockbuster Opportunity

- Conducting broad Phase 3 program
- Building on eplontersen infrastructure
- Potential for highly significant revenue growth
- Margin profile consistent with cardiovascular disease drugs
- Blockbuster opportunity

Donidalorsen

High-Value, High-Margin Opportunity

Estimated peak sales: <1 Billion >1 Billion Multibillion

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Donidalorsen

High-Value, High-Margin Opportunity

- Modest investment required
- Pivotal study designed to support strong switch market penetration
- Targeted commercial organization
- Best-in-class profile with high-value, high-margin potential

Estimated peak sales: <1 Billion >1 Billion Multibillion

1. Market opportunity and peak sales estimates are based on current assumptions and are subject to change

Building on Today's Momentum

Sustaining Future Growth

14 Phase 2 Medicines

6 Phase 1 Medicines

Prolific R&D Engine

Partnerships Generate Substantial Revenue and Cash

Building Upon a Substantial and Sustainable Base

P&L benefit as partners fund development and commercialization costs

Thoughtful Corporate Responsibility in Everything We Do

Our inaugural Corporate Responsibility Report will be published in December 2021

Positioned to Deliver Enhanced Shareholder Value

1

Well Capitalized

to drive significant **near-term revenue growth** and support a promising future

2

Significant Market Opportunities

beginning with **eplontersen, olezarsen and donidalorsen**

3

Building on Momentum

through our prolific research engine and **world class research, development and commercial organizations**

Concluding Remarks

Brett Monia, Ph.D.
Chief Executive Officer

4 Key Questions We Answered Today

1

Which near-term products will we prioritize for commercialization?

2

What is our go-to-market plan for our prioritized assets?

How will we succeed?

3

How will we extend our technology leadership?

How will this drive continued success versus competition?

4

Do we have the resources to achieve our vision?

What are our growth expectations?

4 Questions We Answered Today

1

Which near-term products will we prioritize for commercialization?

Eplontersen

- hATTR-Polyneuropathy
- ATTR-Cardiomyopathy

Olezarsen

- Familial Chylomicronemia Syndrome (FCS)
- Severe Hypertriglyceridemia (SHTG)

Donidalorsen

- HAE prophylaxis

4 Questions We Answered Today

2

What is our go-to-market plan for our prioritized assets?

How will we succeed?

Eplontersen is well positioned to rapidly penetrate and expand the ATTR market

- Expect a very attractive drug profile for patients
- Broad Phase 3 program designed to address usage with and without stabilizers with strong evidence to inform clinicians
- Drive patient awareness and grow the market with improved diagnostic tools and physician/patient education
- Utilize combined and complementary strengths of Ionis and AstraZeneca to reach more patients globally

4 Questions We Answered Today

2 (continued)

What is our go-to-market plan for our prioritized assets?

How will we succeed?

Olezarsen

- First-mover advantage to achieve category leadership in FCS and SHTG
- Provide a more efficacious, best-in-class agent for patients with high triglyceride diseases
- Change the standard-of-care

Donidalorsen

- Deliver on the attractive best-in-class value proposition for HCPs and patients
- Implement strategies to drive treatment switch based on a robust product profile, patient engagement and access support

4 Questions We Answered Today

3

How will we extend our technology leadership?

How will this drive continued success versus competition?

We will continue investing in our technology to ensure continued leadership in RNA-targeted therapeutics

- New LICA strategies emerging to expand our targeted delivery capabilities, opening up new opportunities for drug discovery in the near- and long-term
- Medicinal chemistry advancements to further enhance drug profiles for newly emerging drugs and for lifecycle management of prioritized existing programs
- Genomics investments delivering on novel, genetically-validated targets to extend our leadership in drug discovery

4 Questions We Answered Today

4

Do we have the resources to achieve our vision?

What are our growth expectations?

- YES – We are well capitalized with ~$2B in cash to drive significant **near-term** & **long-term revenue growth** and support achieving our vision
- Substantial revenue growth opportunities from
  - Eplontersen + olezarsen + donidalorsen
  - Mid- and late-stage pipeline
  - Additional commercialization opportunities
  - New and existing partner opportunities

GROWTH

IONIS®

Build-Out Ionis Pipeline

Commercialize Our Products

Expand & Diversify Technology

Deliver Abundance of New Medicines To Market

Validated Platform Technology

Rich Mid- & Late-Stage Pipeline

Financial Strength

Commitment to Innovation Leadership

Highly Dedicated Employees

A Glimpse Towards an Exciting 2022

- Report eplontersen hATTR-PN Phase 3 data
- File for eplontersen marketing authorization
- Advance and expand Phase 3 pipeline
  - Enrollment completions
  - New Phase 3 starts
  - Phase 3 updates
- Report data from numerous mid-stage programs and initiate multiple first-in-patient studies
- Incorporate technology advancements into new medicines
- Progress launch preparations

Building a Leading Biotech Company

Well-positioned to accelerate growth & maximize success across all aspects of our business

Numerous **attractive product opportunities** rapidly approaching market

Growing & advancing **Phase 3 pipeline**

Progress towards becoming a successful **fully-integrated research, development & commercial organization** is on track

Technology advancements are extending our leadership position & expanding our therapeutic capabilities

2022 is shaping up to be an important and exciting year for Ionis and all stakeholders


IONIS®
Q&A