Annual Meeting of Stockholders

June 2, 2022

Nasdaq: IONS

Forward-Looking Statements

This presentation includes forward-looking statements regarding our business, financial guidance and the therapeutic and commercial potential of SPINRAZA® (nusinersen), TEGSEDI® (inotersen), WAYLIVRA® (volanesorsen), eplontersen, olezarsen, donidalorsen, ION363, pelacarsen, tofersen, 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, 2021, 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.

Ionis: A Leading Fully Integrated Biotechnology Company

Positioned for Substantial Growth

Growing Commercial Portfolio

Three marketed medicines and multiple potential new **blockbuster** products **nearing** the **market**

Rich Mid- & Late-Stage Pipeline

Growing pipeline of potentially transformational medicines **advancing towards** the **market**

Continued Technology Leadership

Our technology is advancing at a rapid pace, expanding our **reach** and **extending** our **leadership position**

Compelling Financial Profile

Ionis' strong financial position enables needed investments to support our vision and drive **substantial growth**

IONIS

Leading & Emerging Therapeutic Franchises

Cardiovascular

Addressing major cardiovascular disease risk factors

4 Ongoing Phase 3 trials

Eplontersen (CM) • Olezarsen (FCS & SHTG) • Pelacarsen (Lp(a))

9 Medicines in clinical development

- ❑ 4 in Phase 2
- ❑ 2 in Phase 1

Neurological

Addressing major neurological diseases

3 Ongoing Phase 3 trials

Eplontersen (PN) • ION363 (FUS-ALS) • Tofersen (SOD-ALS)

11 Medicines in clinical development

- ❑ 8 in Phase 2

Emerging Specialty-Rare Pipeline

Phase 3: Donidalorsen

IONIS

Rich Phase 3 Pipeline

6 Medicines for 8 Indications

		Phase 3 Data[1]	Prevalence[2]
Tofersen	SOD1-ALS	2021 2022 OLE	**~1.4K patients** in G7 countries
Eplontersen	ATTRv polyneuropathy	2022	**>40K patients** worldwide
Olezarsen	FCS	2023	**~3-5K 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
Eplontersen	ATTR cardiomyopathy	2025	**~300-500K patients** worldwide
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; ATTRv, hereditary transthyretin amyloidosis; FCS, familial chylomicronemia syndrome; SHTG, severe hypertriglyceridemia; HAE, hereditary angioedema; Lp(a), lipoprotein a; CVD, cardiovascular disease.

IONIS

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Tofersen[1]

In development for the treatment of SOD1-ALS

New OLE data presentation
ENCALS | June 3

- While tofersen missed the primary endpoint[2,3] in the **Phase 3 VALOR** study, integrated analyses from VALOR and the OLE showed **sustained biological effects** and **slowing** of **clinical decline** with **earlier treatment**
- Substantial **decrease** in plasma **NfL** seen with **tofersen** treatment
  - Plasma NfL is a key biomarker of axonal injury and neurodegeneration
- 133 patients in 31 countries **treated** through **tofersen EAP**[4]
- New, **longer-treatment OLE** data presentation at ENCALS
- Biogen remains **actively engaged** with **regulators** on potential **next steps** for tofersen

IONIS

1. Partnered with Biogen; 2. At week 28; 3. Revised ALS functional rating scale (ALSFRS-R); 4. As of 4/30/22; *NfL* = neurofilament light chain

We are Committed to Developing Treatments for All Forms of ALS

Genetic Causes

Tofersen for SOD1-ALS

- New OLE results to be presented at ENCALS June 3, 2022

ION363 for FUS-ALS

- Encouraging results published in *Nature Medicine*[1]
- Phase 3 enrollment in progress

Non-Genetic Causes

ION541 targeting ATXN2 for sporadic ALS

- Phase 1/2 underway and enrolling well

Additional programs advancing towards development

1. Korobeynikov, et al. *Nature Medicine*, 2022

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IONIS

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● Cardiovascular ● Neurology ● Specialty Rare

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Ionis Business Strategy to Maximize Value for Patients and Shareholders

Commercial Go-to-Market Strategy	Disciplined Expansion Over Time	Partner Strategically
Focus on 2 core franchises – cardiovascular & neurology	Expand commercial pipeline beyond near-term assets	Co-commercialize where appropriate to enable greater patient access and availability
Commercialize non-core assets with high PoS and attractive markets	Expand commercial infrastructure outside the U.S.	Out-license assets outside our core areas of focus and capabilities
Commercialize medicines in U.S. for both rare and broad indications	Build an agile commercial operating model	
Build global commercial excellence		
Establish ex-U.S. distribution/ commercial partners near-term		

Eplontersen + Olezarsen + Donidalorsen

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

LATE-STAGE PROGRAMS ALL UTILIZING IONIS' ADVANCED LICA PLATFORM

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

IONIS

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

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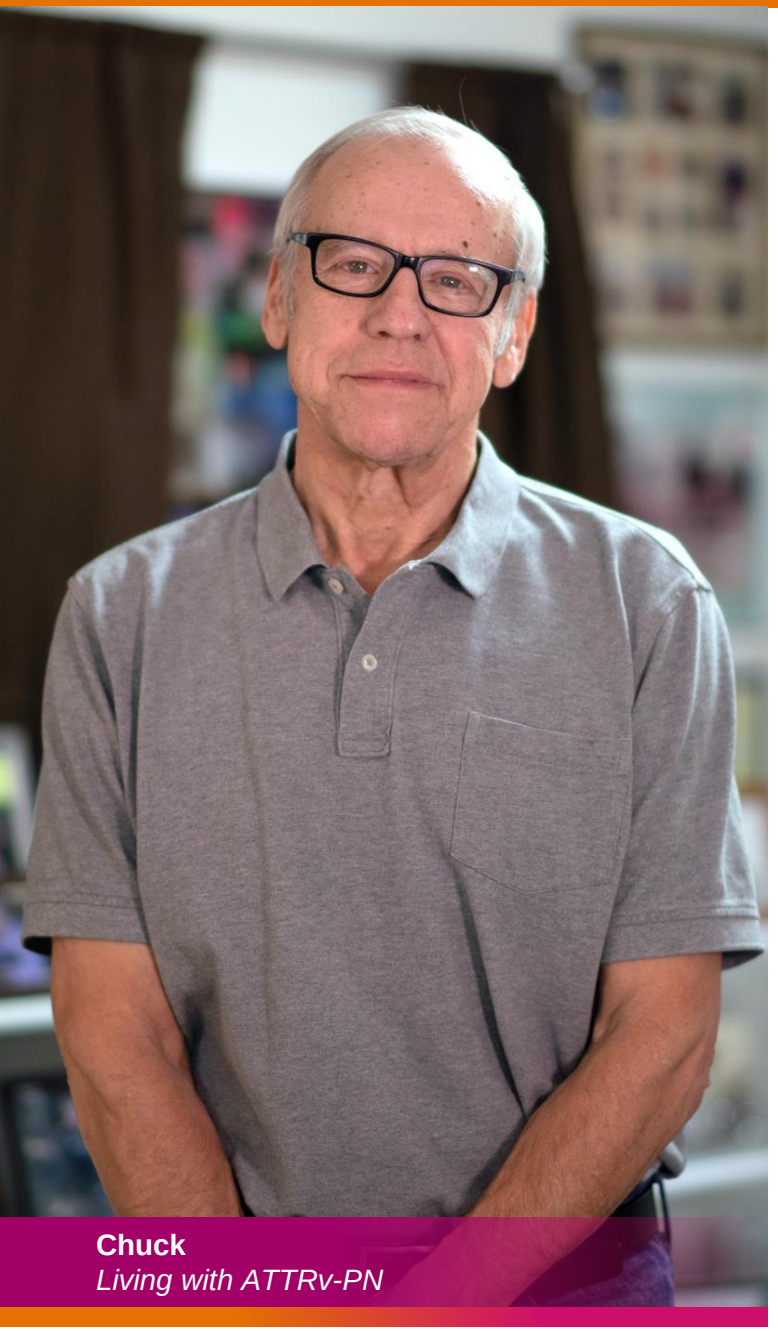
Eplontersen

Next-Generation (LICA) Silencer to Treat All Forms of Systemic TTR Amyloidosis

IONIS



Chuck
Living with ATTRv-PN

TTR Amyloidosis (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

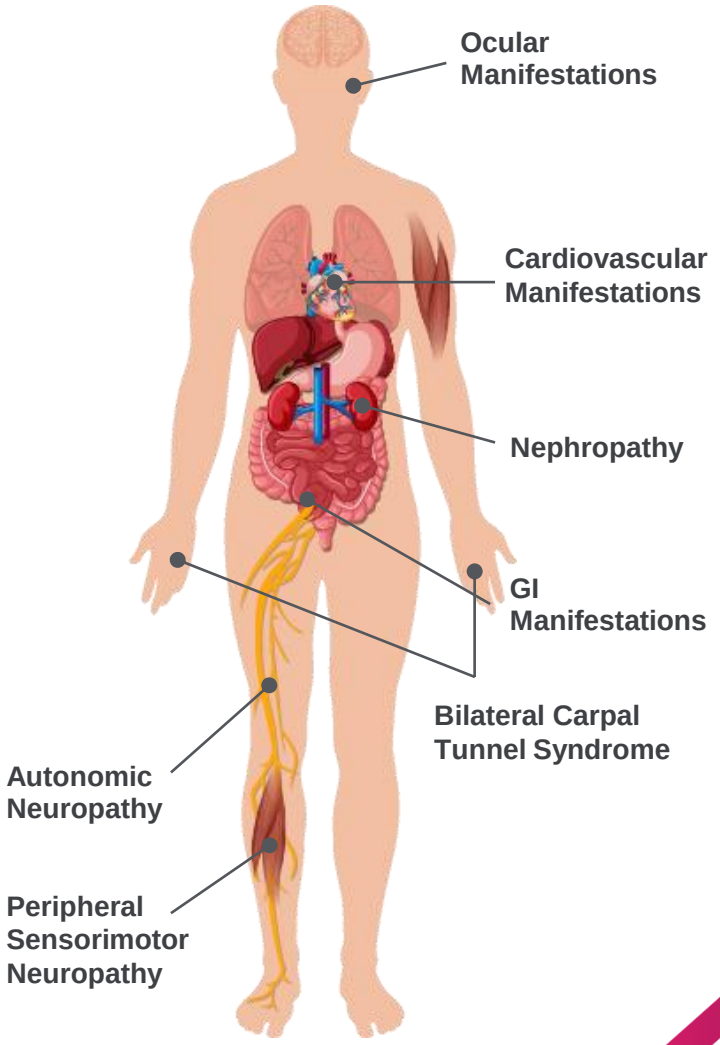
~300K-500K
patients worldwide[1,2]

~40K ATTRv polyneuropathy

>300K ATTRv & wt 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

Eplontersen Phase 3 Program Designed to Fully Inform ATTR Amyloidosis Patient and Physician Choice

ATTRv 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]

ATTR Cardiomyopathy

cardio TTRansform

A global, randomized, double-blind, placebo-controlled, 140-week study in up to 1,000 patients with cardiovascular outcomes as primary endpoint

Enrollment underway

Data expected H1:2025[1]

ATTR Amyloidosis

TTRansform beyond

Additional profile-enhancing studies in patients with ATTRv-PN and ATTRv/ ATTRwt-CM to bolster the eplontersen data evidence package

Underway

IONIS

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

Eplontersen: Potential for Faster, Deeper Market Penetration Through AstraZeneca Collaboration

IONIS + AstraZeneca

Industry-leading experience and deep knowledge of the amyloidosis market

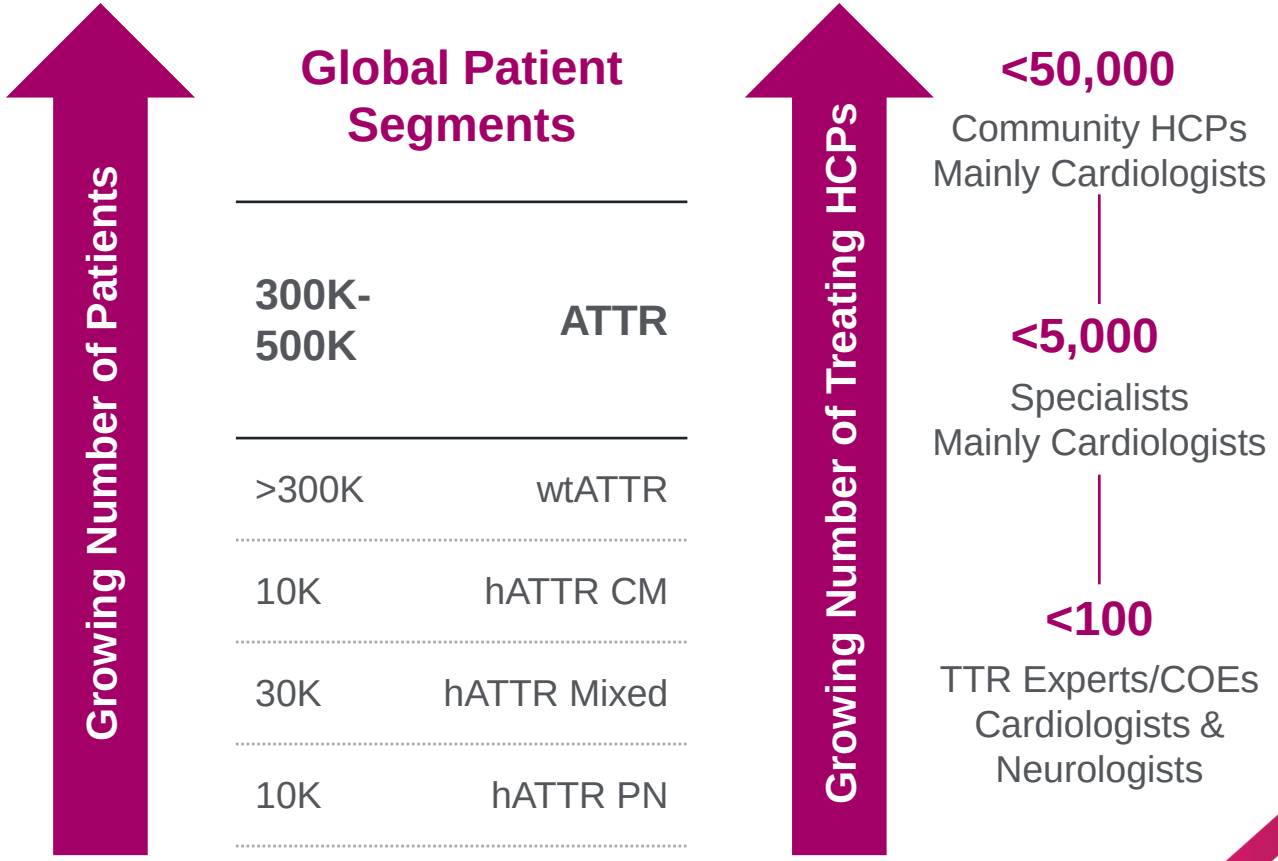
Role

- Leading Phase 3 trials
- Deploy and execute Medical Affairs and back-office functions

Global leadership and scale in cardiovascular disease

Role

- Deploy global salesforce
- Execute global launch activities



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

Eplontersen Phase 3 Program: Current Status and Next Steps[1]

neuro TTRansform

- Exceeded enrollment goal
- On track for Phase 3 data in patients with ATTRv-PN mid-2022 (35-week interim analysis)
- Potential to file for U.S. marketing authorization before year-end 2022
- Projected to launch in the U.S. in 2023

cardio TTRansform

- Largest ATTR-CM study to date, designed to demonstrate benefit in a broad, diverse patient population most representative of the current treatment landscape, positioning eplontersen to compete effectively
- On track to complete enrollment in 2022
- On track for Phase 3 data in 1H 2025

IONIS

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

Olezarsen

Next-Generation (LICA) Silencer
to Treat Diseases Caused by
Severely Elevated Triglycerides

IONIS

Fred
Living with FCS

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

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

Elevated triglycerides associated with major medical issues

- Acute pancreatitis, with attendant significant morbidity and mortality
- Higher risk of cardiovascular disease
- Effective treatment options lacking

ApoCIII

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

IONIS

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

Broad Olezarsen 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 ~60 patients with FCS; primary endpoint is percentage change in fasting TGs from baseline at 6 months

Enrollment underway
Data expected 2023[1]

Severe Hypertriglyceridemia

CORE
a hypertriglyceridemia study

A global pivotal study in up to 540 patients with SHTG (TG>500mg/dL); primary endpoint is percentage change in fasting TGs from baseline at 6 months

Enrollment underway
Data expected 2024[1]

CORE2
a hypertriglyceridemia study

A second, global pivotal study in up to 390 patients with SHTG (TG>500mg/dL); primary endpoint is percentage change in fasting TGs from baseline at 6 months

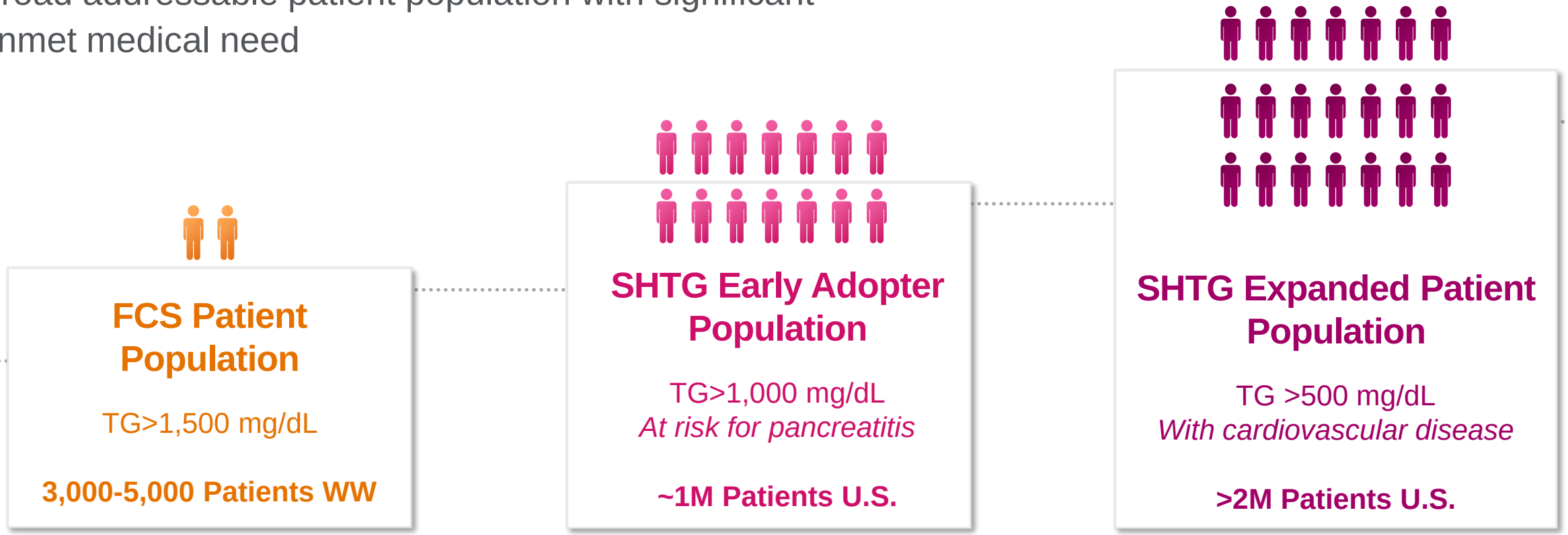
Initiation expected 2022
Data expected 2024[1]

IONIS

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

Olezarsen: Potential to Change the Standard of Care for Patients with Severely Elevated Triglycerides[1]

Broad addressable patient population with significant unmet medical need



>3 Million patients in the U.S

1. Market data on file

Olezarsen Phase 3 Program: Current Status and Next Steps[1]

Compelling potential first-in-class efficacy for triglyceride-related diseases demonstrated in Phase 2 – data published in the *European Heart Journal*[2]

Balance a familial chylomicronemia syndrome study

Phase 3 study in FCS: full enrollment expected 2022 with data expected in 2023; preparing to file for marketing authorization assuming positive data

CORE a hypertriglyceridemia study

- Phase 3 CORE study in SHTG actively enrolling with data expected in 2024

CORE2 a hypertriglyceridemia study

- Phase 3 CORE-2 study to support SHTG filing to begin enrolling in 2022 with data expected in 2024

IONIS

1. Timing expectations and peak sales estimates are based on current assumptions and are subject to change; 2. *European Heart Journal*, Tardif et al. 2022

Donidalorsen

Next-Generation (LICA) Silencer as a Potential Best-in-Class Prophylactic Treatment for Hereditary Angioedema

IONIS

HAE Characterized by Unpredictable, Painful and Potentially Fatal Attacks

Hereditary Angioedema (HAE)

- Rare genetic disease
- Dysfunctional C-1 inhibitor
- Severe and potentially fatal swelling of the arms, legs, face and throat

Donidalorsen

- Targets the root cause of HAE, bradykinin overproduction

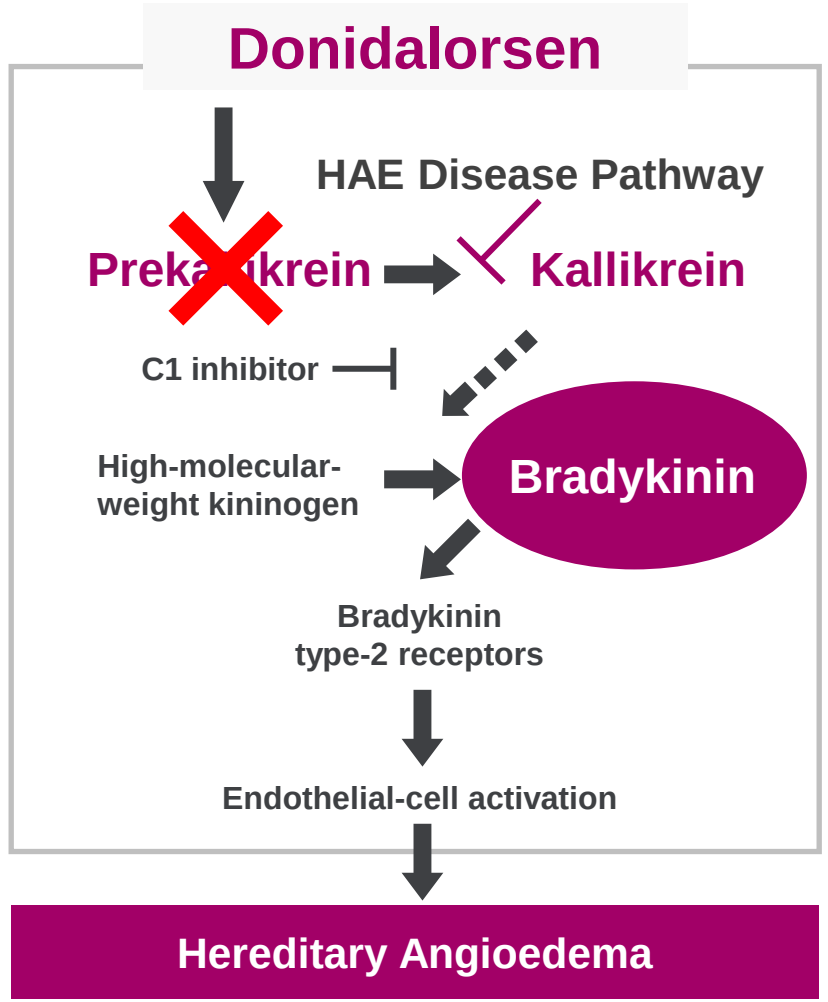
Prevalence

> 20K

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

Indication	Peak Sales[2]
HAE	↑

Estimated peak sales: ↑ <1 Billion ↑↑ >1 Billion ↑↑↑ Multibillion



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

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

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

- **Rapid** and **sustained** reductions in HAE attacks
- Highly significant and meaningful **improvements in quality of life**
- **Favorable safety** and tolerability profile

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)

IONIS

*Fijen, et al. Inhibition of Prekallikrein for Hereditary Angioedema. *N Engl J Med* **2022**, *386*, 1026–1033.

Donidalorsen Phase 3 Program Designed to Support Approval and Broad Market Penetration as an HAE Prophylactic Treatment

Hereditary Angioedema Prophylaxis

OASIS

- Global pivotal study, ~84 HAE patients, ages ≥12
- Dosed monthly and bi-monthly for 24 weeks
- Primary endpoint, time-normalized number of HAE attacks

Enrollment underway
Data expected 2024[1]

OASIS plus

- Global open-label extension study to demonstrate long-term durability in patients completing OASIS study
- Open to HAE patients previously treated with other prophylactic therapies

Screening underway
Data expected 2024[1]

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

Donidalorsen: Compelling Opportunity in Attractive HAE Market[1]

Established and Growing Market	Unmet Need	Potential Best-in-Class Profile
Global prophylaxis market is **>$1.5B** and **growing**	**~6,000** patients in the US	Compelling **efficacy** with **rapid onset** of action[2]
Rapidly **increasing** rate of prophylaxis treatment	Potential for **breakthrough attacks**	Favorable **safety** and **tolerability**
Well defined US patient population and prescriber base	Patients experience significant **fear** and **anxiety**	**Monthly,** at-home administration

1. Market data on file; 2. Based on Phase 2 data and market data on file

Donidalorsen Phase 3 Program: Current Status and Next Steps[1]

Compelling potential best-in-class profile for HAE prophylaxis demonstrated in Phase 2 – data published in *NEJM*[2]

OASIS

Phase 3 study actively enrolling

- Evaluating monthly and bi-monthly dosing regimens
- On track for data in 2024

OASIS plus

Open-label study expected to begin enrolling in 2H 2022

- Designed to demonstrate durable efficacy with long-term treatment in patients completing the Phase 3 OASIS study
- HAE patients previously maintained on other prophylactic therapies

IONIS

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Rich Mid- and Late-Stage Pipeline

		MID-STAGE (Phase 1/2 - Phase 2)	LATE-STAGE (Phase 3)	COMMERCIAL RIGHTS
Eplontersen	ATTRv polyneuropathy		●	Cost-sharing & royalty bearing
Olezarsen (APOCIII)	FCS		●	Global
Eplontersen	ATTR cardiomyopathy		●	Cost-sharing & royalty bearing
Olezarsen (APOCIII)	SHTG		●	Global
Pelacarsen	Lp(a) CVD		●	Milestones & up to low 20% royalties
Donidalorsen (PKK)	Hereditary angioedema		●	Global
ION363 (FUS)	FUS/ALS		●	Global
Tofersen	SOD1-ALS		●	Milestones & up to mid-teen royalties
ION449 (PCSK9)	CVD	●		Milestones & up to low teen royalties
Fesomersen (FXI)	Clotting disorders	●		Milestones & up to high 20% royalties
IONIS-AGT-L_{Rx}	Treatment-resistant hypertension	●		Global
ION373 (GFAP)	Alexander disease	●		Global
Tominersen	Huntington's disease	●		Milestones & up to mid-teen royalties
IONIS-$MAPT_{Rx}$	Alzheimer's disease	●		Milestones & up to mid-teen royalties
ION541 (ATXN2)	Broad ALS	●		Milestones & up to mid-teen royalties
ION260 (ATXN3)	SCA3	●		Milestones & up to mid-teen royalties
ION464 (SNCA)	MSA & Parkinson's disease	●		Milestones & up to mid-teen royalties
ION859 (LRRK2)	Parkinson's disease	●		Milestones & up to mid-teen royalties
ION582 (UBE3A)	Angelman syndrome	●		Milestones & up to mid-teen royalties
Sapablursen (TMPRSS6)	b-thalassemia/polycythemia vera	●		Global
Cimdelirsen (GHR)	Acromegaly	●		Global

IONIS

● Cardiovascular ● Neurology ● Specialty Rare

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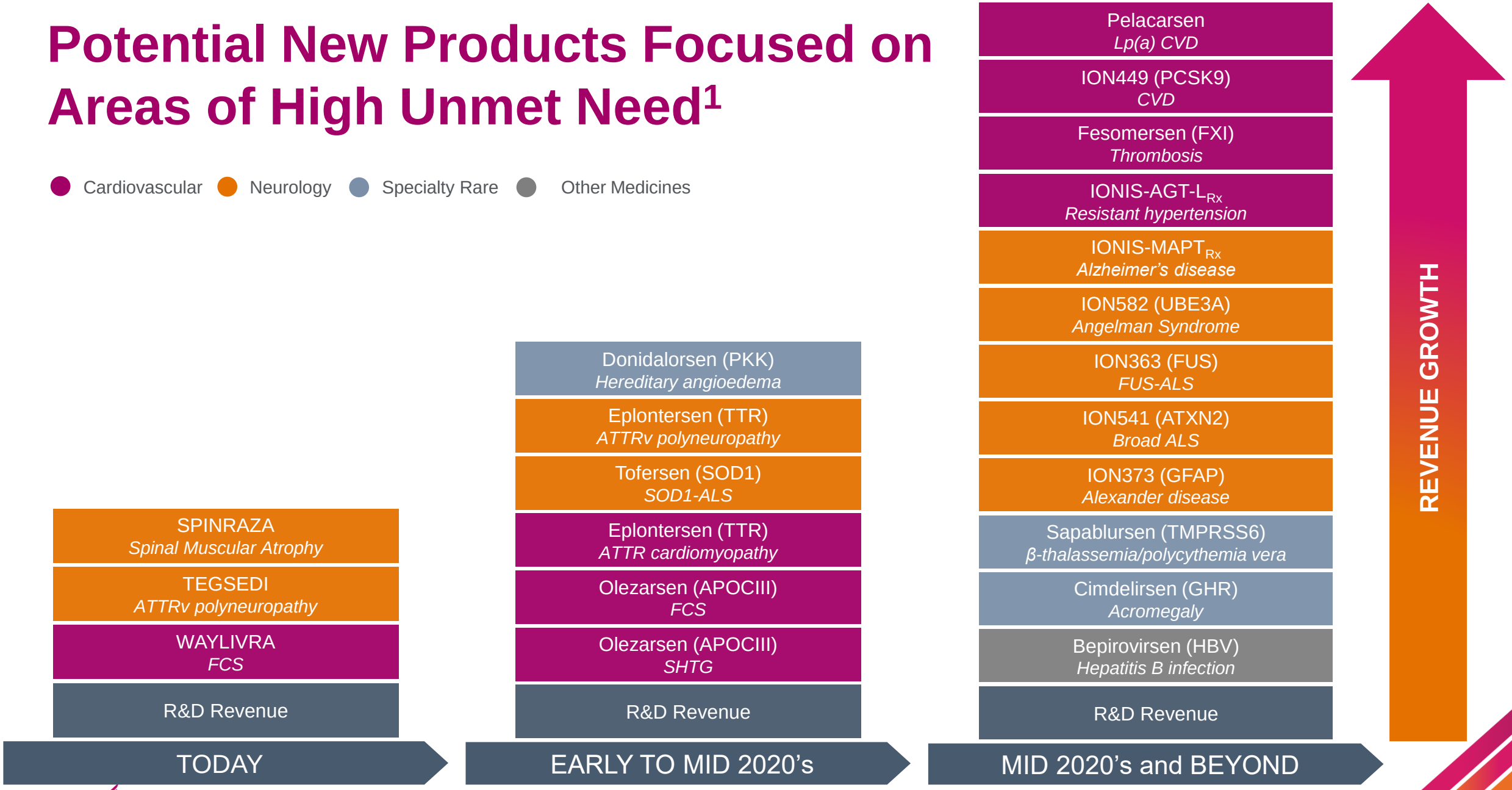
Eplontersen	ATTR cardiomyopathy			Cost-sharing & royalty bearing
Olezarsen (APOCIII)	SHTG			Global
Pelacarsen	Lp(a) CVD			Milestones & up to low 20% royalties
Donidalorsen (PKK)	Hereditary angioedema			Global
ION363 (FUS)	FUS/ALS			Global
Tofersen	SOD1-ALS			Milestones & up to mid-teen royalties
ION449 (PCSK9)	CVD			Milestones & up to low teen royalties
Fesomersen (FXI)	Clotting disorders			Milestones & up to high 20% royalties
IONIS-AGT-L_{Rx}	Treatment-resistant hypertension			Global
ION373 (GFAP)	Alexander disease			Global
Tominersen	Huntington's disease			Milestones & up to mid-teen royalties
IONIS-$MAPT_{Rx}$	Alzheimer's disease			Milestones & up to mid-teen royalties
ION541 (ATXN2)	Broad ALS			Milestones & up to mid-teen royalties
ION260 (ATXN3)	SCA3			Milestones & up to mid-teen royalties
ION464 (SNCA)	MSA & Parkinson's disease			Milestones & up to mid-teen royalties
ION859 (LRRK2)	Parkinson's disease			Milestones & up to mid-teen royalties
ION582 (UBE3A)	Angelman syndrome			Milestones & up to mid-teen royalties
Sapablursen (TMPRSS6)	b-thalassemia/polycythemia vera			Global
Cimdelirsen (GHR)	Acromegaly			Global

IONIS

Cardiovascular Neurology Specialty Rare

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

Cardiovascular · Neurology · Specialty Rare · Other Medicines



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

Building on our Technology Leadership in RNA-Targeted Therapeutics

INVESTMENTS	IMPACT
Medicinal chemistry	• Extended dosing intervals • Enhanced therapeutic profile • Being incorporated into new medicines • Lifecycle management for existing medicines (e.g. Spinraza follow-on)

New targeted delivery strategies (LICA); *e.g., muscle, pancreas, lung*	• Enable new disease areas
	  • Neuromuscular disease
	  • Heart failure
	  • Metabolic diseases

New routes of delivery	• Opens up new target organs/cell types (e.g., pulmonary) • Strengthens leadership position

IONIS

Key 2022 Pipeline Events[1]

REGULATORY FILINGS			H1	H2
Eplontersen (TTR)	ATTRv polyneuropathy	NDA filing		●
DATA READOUTS			**H1**	**H2**
Tominersen (HTT)	Phase 3 post hoc	Huntington's disease	✓	
Donidalorsen (PKK)	Phase 2	Hereditary angioedema (HAE)	✓	
ION449 (PCSK9)	Phase 2b	Cardiovascular disease (CVD)	✓	
IONIS-C9$_{Rx}$ (BIIB078)	Phase 1/2	C9-Amyotrophic lateral sclerosis (ALS)	✓	
Tofersen	Phase 3 OLE	SOD1-ALS	●	
Eplontersen (TTR)	Phase 3	ATTRv polyneuropathy	●	
IONIS-AGT-L$_{Rx}$	Phase 2b	Treatment-resistant hypertension (TRH)		●
Fesomersen (FXI)	Phase 2b	Thrombosis		●
Bepirovirsen (HBV)	Phase 2b	Hepatitis B virus (HBV) infection		●
Donidalorsen (PKK)	Phase 2 OLE	HAE		●
Cimdelirsen (GHR)	Phase 2	Acromegaly (monotherapy)		●
STUDY INITIATIONS			**H1**	**H2**
Sapablursen (TMPRSS6)	Phase 2	Polycythemia vera	✓	
ION904 (AGT)	Phase 2	Uncontrolled hypertension (HTN)	✓	
IONIS-MAPT$_{Rx}$ (BIIB080)	Phase 2	Alzheimer's disease		●
ION717 (PRNP)	Phase 1/2	Prion disease		●
TECHNOLOGY ADVANCEMENTS			**H1**	**H2**
SMA	Advance follow-on program		✓	
Muscle LICA	Advance into preclinical development (IND-supporting)			●
MsPA Backbone	Advance into preclinical development (IND-supporting)			●

1. Partnered program events based on partners' most recent publicly available disclosures

● Wholly owned ● Partnered ✓ Achieved ● Expected

Financial Strength to Drive Substantial Growth

Strong Financial Foundation

- Well capitalized with **>$2 billion in cash**[1]
- **Multiple sources of revenue** with diverse margin profiles

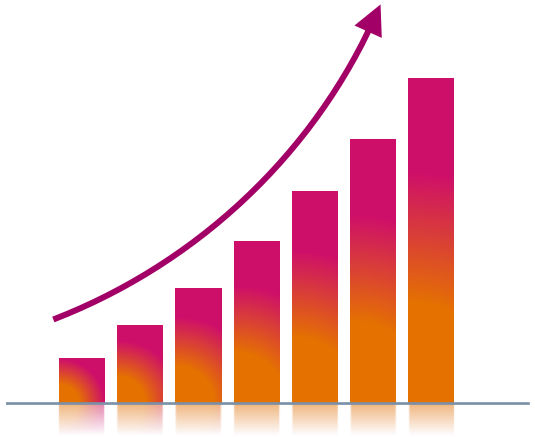
+

Accelerating Investments

- **Building** the Ionis commercial portfolio
- **Expanding** and diversifying our technology
- **Advancing** new medicines to the market

=

Substantial Growth



1. As of March 31, 2022.

Thoughtful Corporate Responsibility in Everything We Do

Inaugural Corporate Responsibility Report Published in December 2021

Ionis: a Leading, Fully Integrated Biotechnology 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**

Full integration of **research, development & commercial** organizations

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

Sustained delivery of transformational medicines

IONIS

IONIS®

A Force for Life

Please stand by
The live Q&A session will begin momentarily

To ask a question,
simply type your question in the “Ask a Question” box below
and click Send