2021 Annual Meeting of Stockholders Corporate Presentation

June 2021

Changes to the Ionis Board of Directors (1 of 2)

Departures

Stanley T. Crooke, M.D., Ph.D.
Ionis Founder and Executive Chairman
30 Years of Ionis Leadership

Breaux B. Castleman
8 Year Board Member
Audit Committee

Changes to the Ionis Board of Directors (2 of 2)

Joseph Loscalzo, M.D., Ph.D.
Appointed Chairman
Seven years Ionis Board Member

Allene M. Diaz
New Board Member

Joseph H. Wender
Lead Independent Director

Spencer R. Berthelsen, M.D.	Frederick T. Muto, Esq.
Joan E. Herman	Peter W. Reikes
Joseph Klein, III	Michael Hayden, C.M., O.B.C., M.B., Ch.B., Ph.D., F.R.C.P.(C), F.R.S.C.
B. Lynne Parshall, Esq.	
Brett P. Monia, Ph.D.	

IONIS™

Forward Looking Language Statement

This presentation includes forward-looking statements regarding our business, financial guidance and the therapeutic and commercial potential of SPINRAZA® (nusinersen), TEGSEDI® (inotersen), WAYLIVRA® (volanesorsen) and Ionis' technologies and 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 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 these 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™

Ionis Today and the Future:

Continuing to Lead in the Discovery & Development of RNA-Targeted Therapeutics

Built Upon 30 Years of Innovation

Launching a new business model; building our commercial capabilities; expanding our wholly owned pipeline

Expanding and enhancing the scope of our drug discovery capabilities

Expanding our mid/late-stage pipeline to deliver on our goal of 12+ marketed medicines in 2026

Achieving Our Strategic Goals

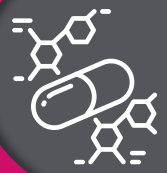
Evolving Business Model/ Excellence in Commercialization

- ✓Reacquired Akcea
- ✓Established distribution agreements w/Sobi for TEGSEDI & WAYLIVRA
- ✓Building commercial capabilities & wholly owned pipeline
- ✓Expanding R&D & manufacturing capacity

Expanding and Enhancing the Scope of Our Drug Discovery Capabilities

- ✓Strengthened genomics capabilities through new partnerships
- ✓Strengthened targeted delivery (“LICA”) capabilities
- ✓Launched additional initiatives to accelerate expansion of existing platform and creation of new complementary platforms

12+ Marketed Medicines in 2026



- 6 ongoing Phase 3 studies
- Tofersen Phase 3 read out Fall 2021
- More Phase 3 starts in 2H2021 and 2022
- ≥ 1 Phase 3 readout each year through 2026

IONIS™

Two Leading Therapeutic Franchises

Neurological

Addressing major neurological diseases

3 ongoing Phase 3 studies

11 medicines in clinical development

3 wholly owned medicines in clinical development

SPINRAZA® (nusinersen) injection 12 mg/5 mL

Tegsedi® (inotersen) injection 284 mg/1.5 mL

Cardiometabolic

Addressing major cardiovascular disease risk factors

3 ongoing Phase 3 studies

14 medicines in clinical development

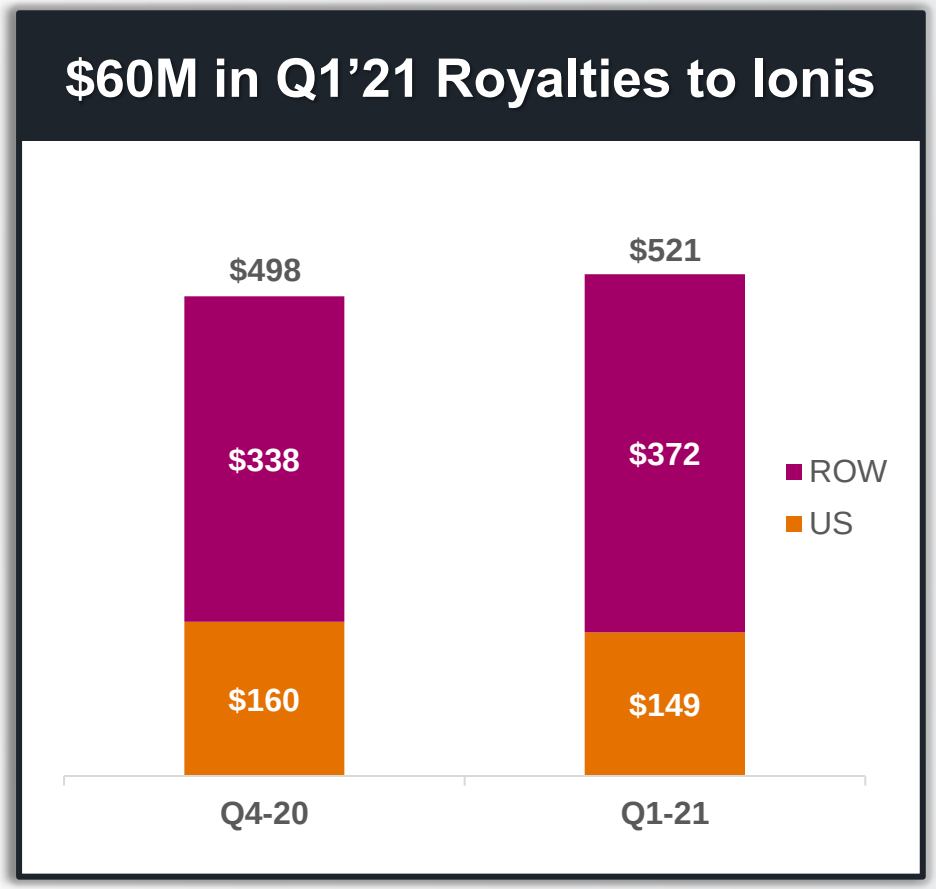
6 wholly owned medicines in clinical development

waylivra™ (volanesorsen sodium) Injection 300mg in 1.5mL

IONIS™

SPINRAZA® (nusinersen) injection 12 mg/5 mL

Continued Blockbuster Performance with $521M in Q1 2021 Sales



- **>11,000 patients on SPINRAZA worldwide[1,2]**
- **>60,000 SMA patients in markets where Biogen has a commercial presence[3]**
- **Ongoing commitment to improving outcomes for SMA patients of all ages**
  - **DEVOTE study:** designed to evaluate the potential for increased efficacy with higher dose SPINRAZA[4]
  - **RESPOND study:** dosing underway in SMA patients with suboptimal response to gene therapy[5]

Source: Biogen Q1 2021 Financial Results and Business Update; 1. Includes patients from post-marketing, EAP and clinical settings; 2. As of March 31, 2021; 3. Biogen estimate, data on file; 4. DEVOTE study: clinicaltirals.org/NCT04089566 5. RESPOND study: clinicaltrials.org/NCT04488133;

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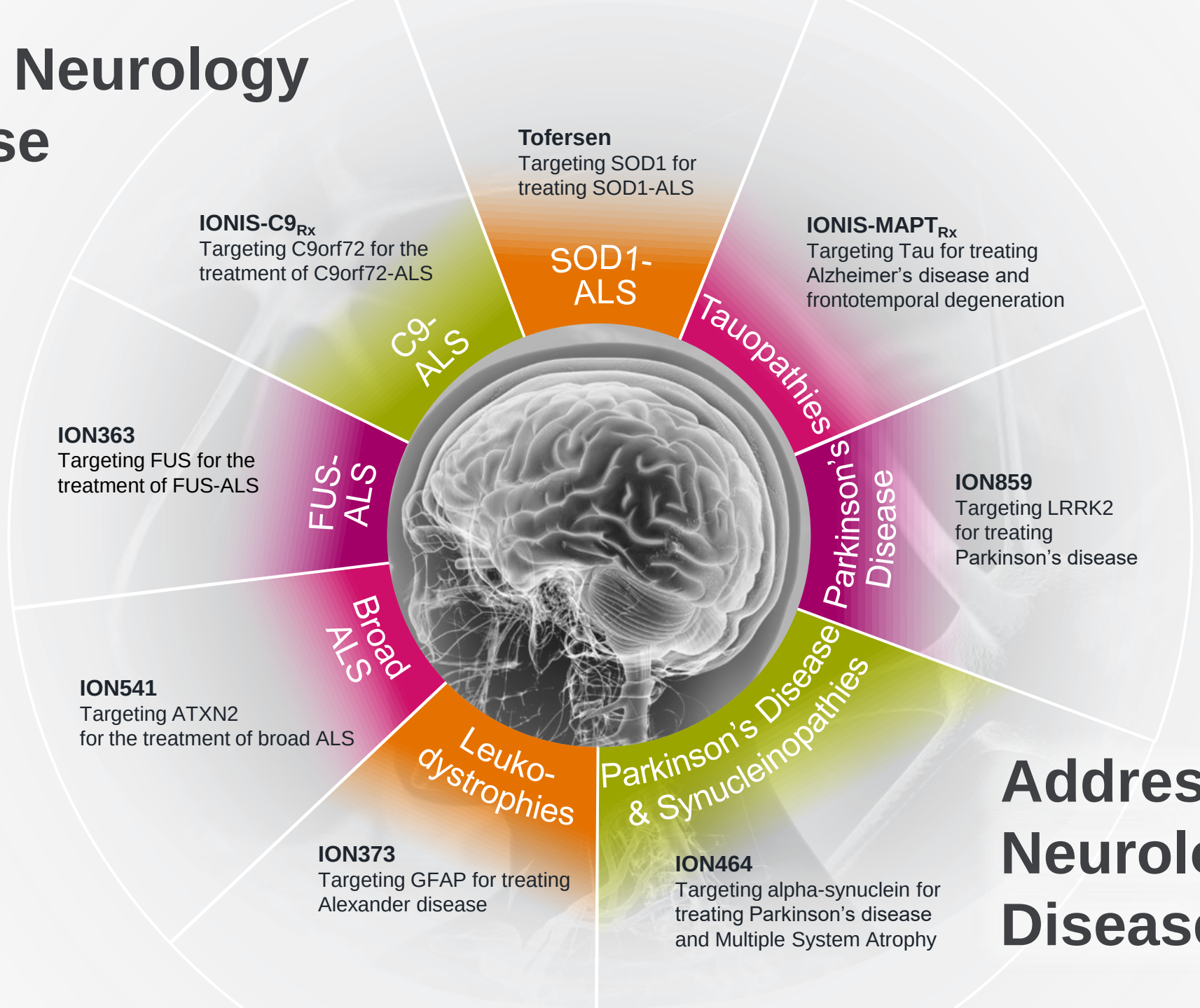
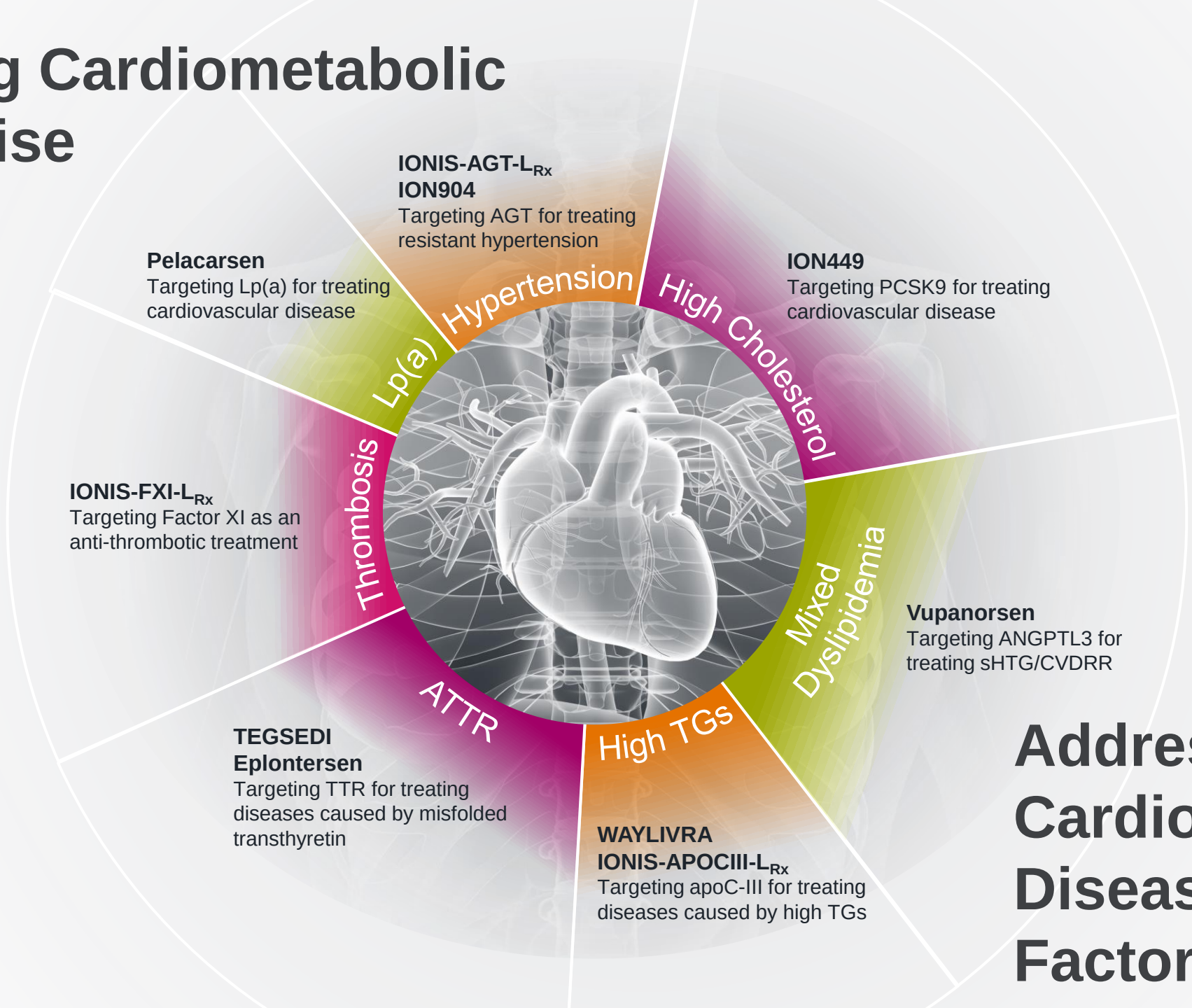
Leading Neurology Franchise



Addressing Major Neurological Diseases

Leading Cardiometabolic Franchise



IONIS-AGT-L_{Rx}
ION904
Targeting AGT for treating resistant hypertension

Pelacarsen
Targeting Lp(a) for treating cardiovascular disease

ION449
Targeting PCSK9 for treating cardiovascular disease

IONIS-FXI-L_{Rx}
Targeting Factor XI as an anti-thrombotic treatment

Vupanorsen
Targeting ANGPTL3 for treating sHTG/CVDRR

TEGSEDI
Eplontersen
Targeting TTR for treating diseases caused by misfolded transthyretin

WAYLIVRA
IONIS-APOCIII-L_{Rx}
Targeting apoC-III for treating diseases caused by high TGs

Addressing Major Cardiovascular Disease Risk Factors

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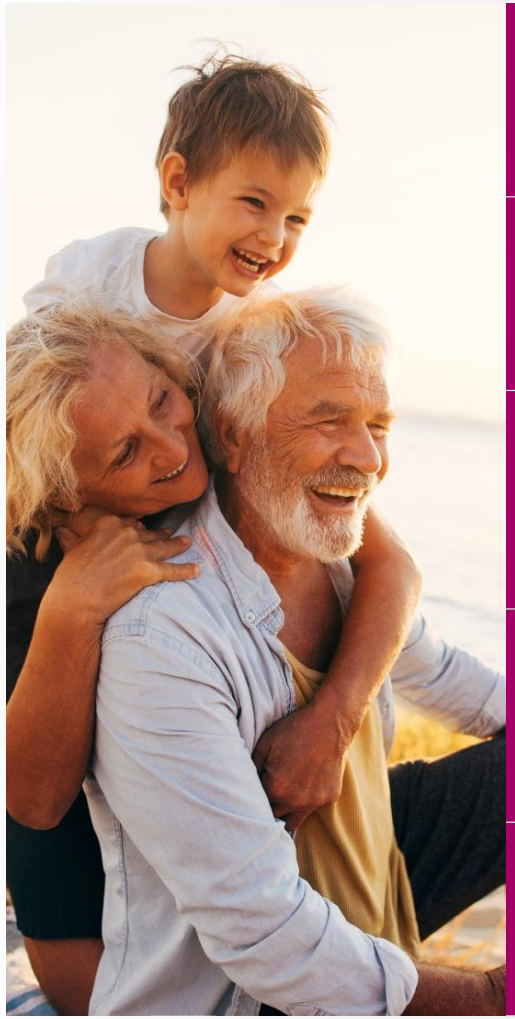
Phase 3 Studies

Pioneering New Markets & Changing Standards of Care

Advancing Phase 3 Pipeline



		Prevalence[1]	Phase 3 Data[2]
Tofersen	**SOD1-ALS** Biogen	**~ 1.4K patients** in G7 countries	Fall 2021
ION363	**FUS-ALS** Wholly owned	**~ 350 patients** in G7 countries	2024
Eplontersen (IONIS-TTR-L_{Rx})	**hATTR polyneuropathy** **ATTR cardiomyopathy** Wholly owned	**> 250K patients** worldwide	2022 (PN) 2024 (CM)
IONIS-APOCIII-L_{Rx}	**FCS** **sHTG** Wholly owned	**~ 3-5K patients** worldwide **> 3M patients** U.S.	2023 (FCS) 2024 (sHTG)
Pelacarsen	**Lp(a) CVDRR** Novartis	**> 8M patients** worldwide	2024

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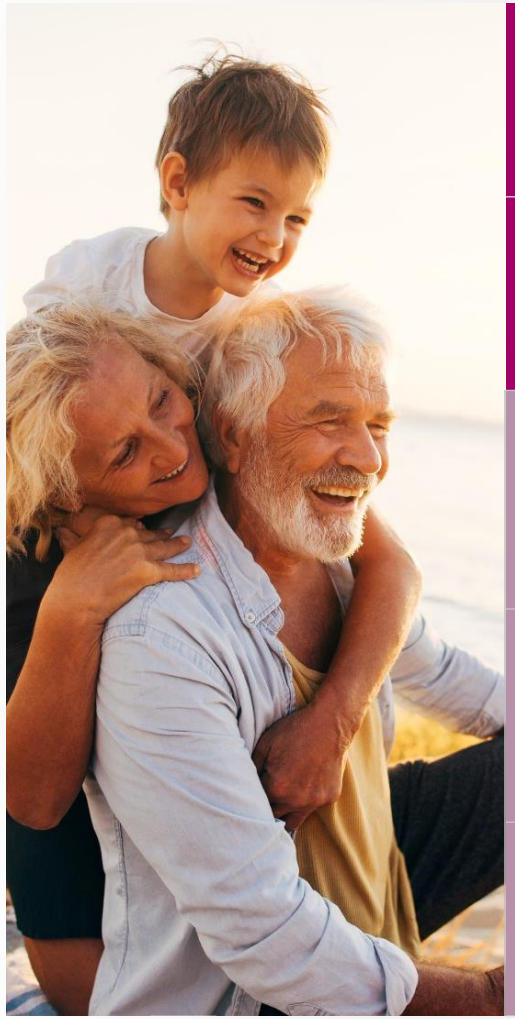
1. Market data on file. 2. Data timing expectations are based on current estimates and are subject to change. Partnered program timelines are based on partners' most recent public disclosures.
ALS, amyotrophic lateral sclerosis. FCS, familial chylomicronemia syndrome. hATTR, hereditary transthyretin amyloidosis. CVDRR, cardiovascular disease risk reduction.

Pioneering New Markets & Changing Standards of Care

Advancing Phase 3 Pipeline



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Tofersen for the treatment of SOD1-ALS

Pioneering New Markets

Sonny, living with ALS

IONIS

Amyotrophic Lateral Sclerosis

A fatal disease with a tremendous unmet medical need

- **Severe neuromuscular disease** characterized by motor neuron degeneration resulting in **functional decline, paralysis** and **respiratory deterioration**
- **Rapidly progressive** with average **survival** of **3-5 years** from symptom onset
- **Genetic** and **broad ALS** programs underway with Ionis and Biogen

~ 55K
patients in G7 countries[1]

- Genetic ALS (e.g. SOD1, C9, FUS): ~15%
- ALS with no known genetic cause: ~85%

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1. Market data on file, G7 countries include the U.S., Germany, the U.K., France, Italy, Spain, and Japan.

SOD1-ALS: Molecular Pathology

Mutant SOD1 toxic gain of function

- **Mutant superoxide dismutase type 1** (SOD1) protein misfolds, aggregates and **causes** ALS through **toxic gain of function** in neurons and glia
- **2nd** most common **genetic** form of ALS
- **Over 100 mutations** have been identified in the SOD1 gene
  - Some mutations cause a rapidly progressing form of the disease
- **Tofersen targets** the **root cause** of SOD1 ALS

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Tofersen for the Treatment of SOD1-ALS

First investigational medicine to demonstrate trends in slowing disease progression

Prevalence	High Unmet Need	First In Class Product Profile Potential
~ 1.4K	Fatal	Transformational
SOD1-ALS patients in G7 countries[1]	Severe motor neuron disease with no disease modifying treatments	Demonstrated a slowing of decline of clinical function in Phase 1/2 study of tofersen

1. Market data on file

Pioneering New Markets

Tofersen[1]

First of four medicines targeting ALS

Projected Phase 3 Data
Fall 2021

- **Targets the root cause** of SOD1-ALS, mutant superoxide dismutase type 1 protein
- Demonstrated **robust reductions** in SOD1 in patients with trends in **slowing disease** progression[2]
- **Next** potential **commercial medicine**
- Phase 3 **VALOR** study **fully enrolled**
- Phase 3 **ATLAS** study in **presymptomatic** SOD1-ALS patients underway

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1. Partnered with Biogen. 2. Based on results from Phase 1/2

ION363 for the treatment of FUS-ALS

Pioneering New Markets

In honor of Jaci Hermstad

IONIS™

ION363 (FUS-ALS)

Caused by mutations in the Fused in Sarcoma (FUS) gene – no effective treatment

- **3rd** most common **genetic** form of ALS
  - ~25% incidence of SOD1-ALS
- **FUS-ALS** is a **fast-progressing** form of ALS
  - Good genotype-phenotype correlation
- **FUS mutations** cause motor **neuron degeneration** through a **toxic gain of function** mechanism
  - FUS is an RNA binding protein
  - Mutant FUS protein aggregates in the cytoplasm

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Pioneering New Markets

ION363

First wholly owned medicine in development for ALS

Projected Phase 3 Data
2024

- **Targets the root cause** of FUS-ALS, mutant FUS
- Prevented **motor neuron loss** in a mouse model of **FUS-ALS**
- Several FUS-ALS patients **previously treated** with **ION363** in an investigator sponsored compassionate use study
- **Innovative** pivotal study designed to achieve an **accelerated path** to the **market**
- Phase 3 study **underway**

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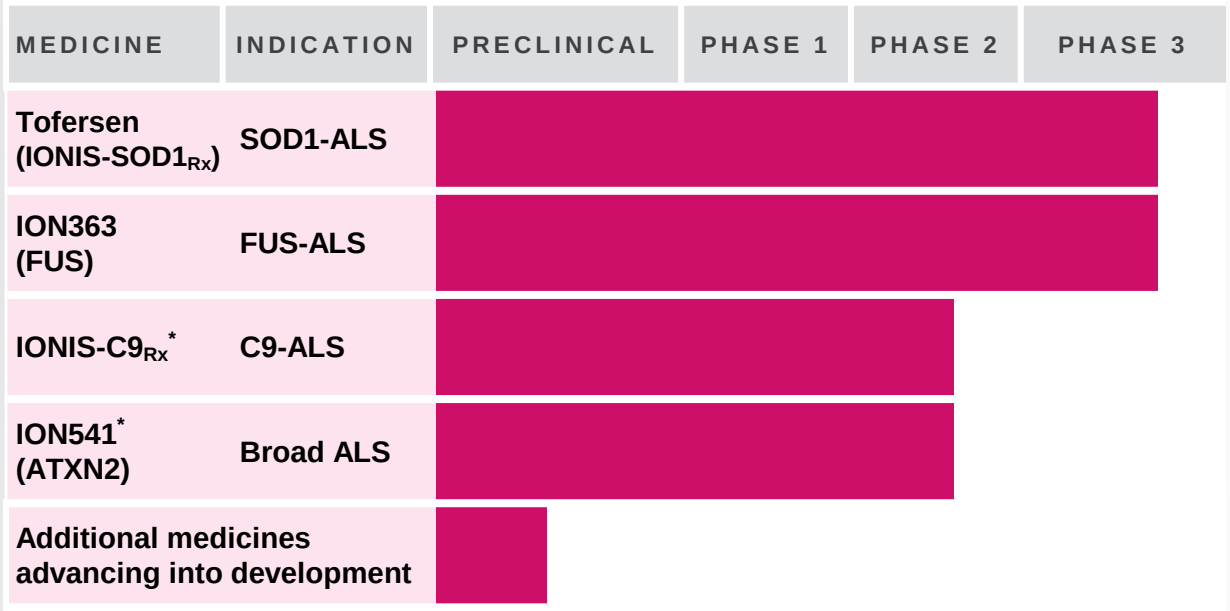
Committed to Treating All Forms of ALS

- Tofersen: **Phase 3 VALOR** study underway in SOD1-ALS (data expected Fall 2021)
- ION363: Phase 3 study with **Ionis-owned** program targeting **FUS** in FUS-ALS underway
- IONIS-$C9_{Rx}$: **Phase 1/2 study ongoing** in **C9-ALS** (data expected 1H 2022)
- ION541: **Phase 1/2 study ongoing** targeting **ATXN2** in **broad ALS population**
- Additional programs advancing

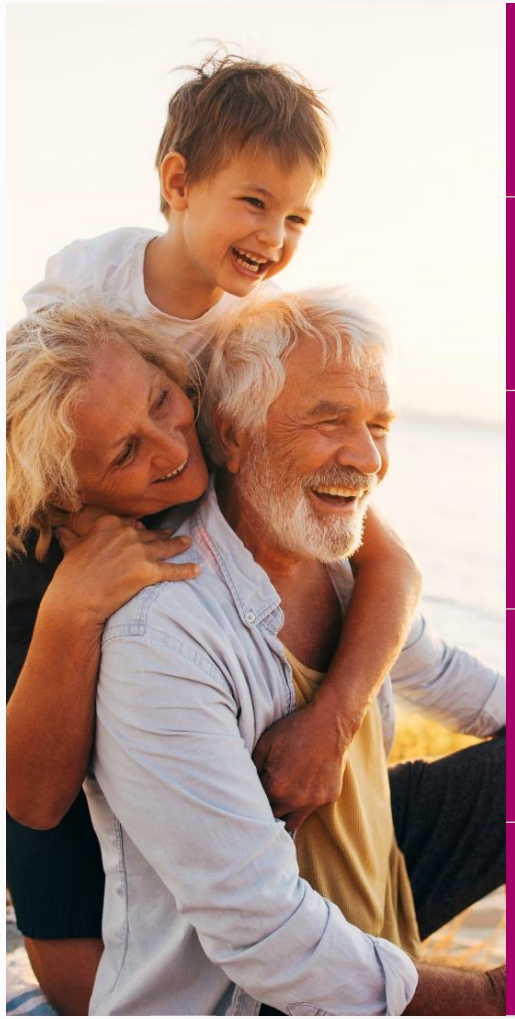
Multiple ALS Medicines in Development



* Ionis categorizes patient studies to establish safety profile as Phase 1/2 and in healthy volunteers as Phase 1. Certain studies in this presentation that are categorized as Phase 1/2 may be categorized differently by outside parties.

Pioneering New Markets & Changing Standards of Care

Advancing Phase 3 Pipeline



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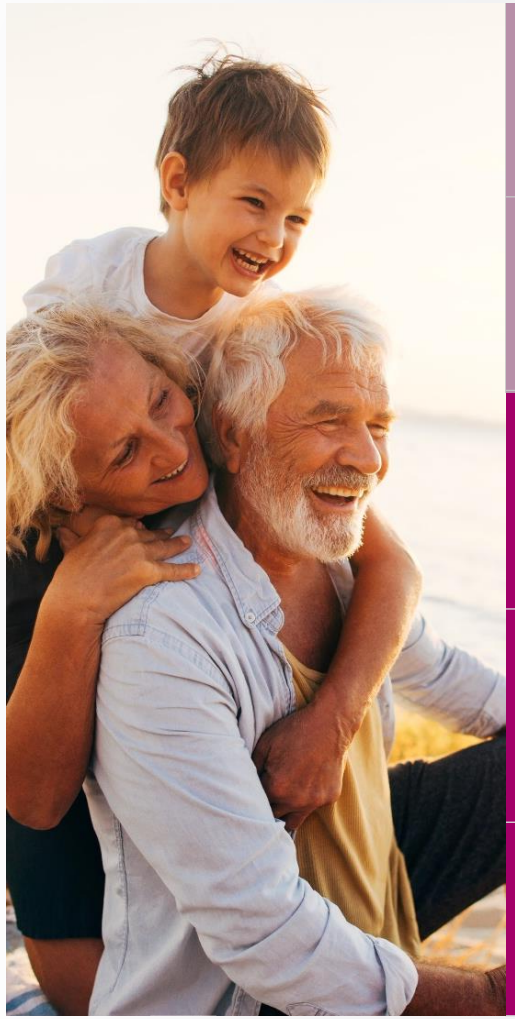
Pioneering New Markets & Changing Standards of Care

Advancing Phase 3 Pipeline



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Eplontersen
(IONIS-TTR-L_{Rx})

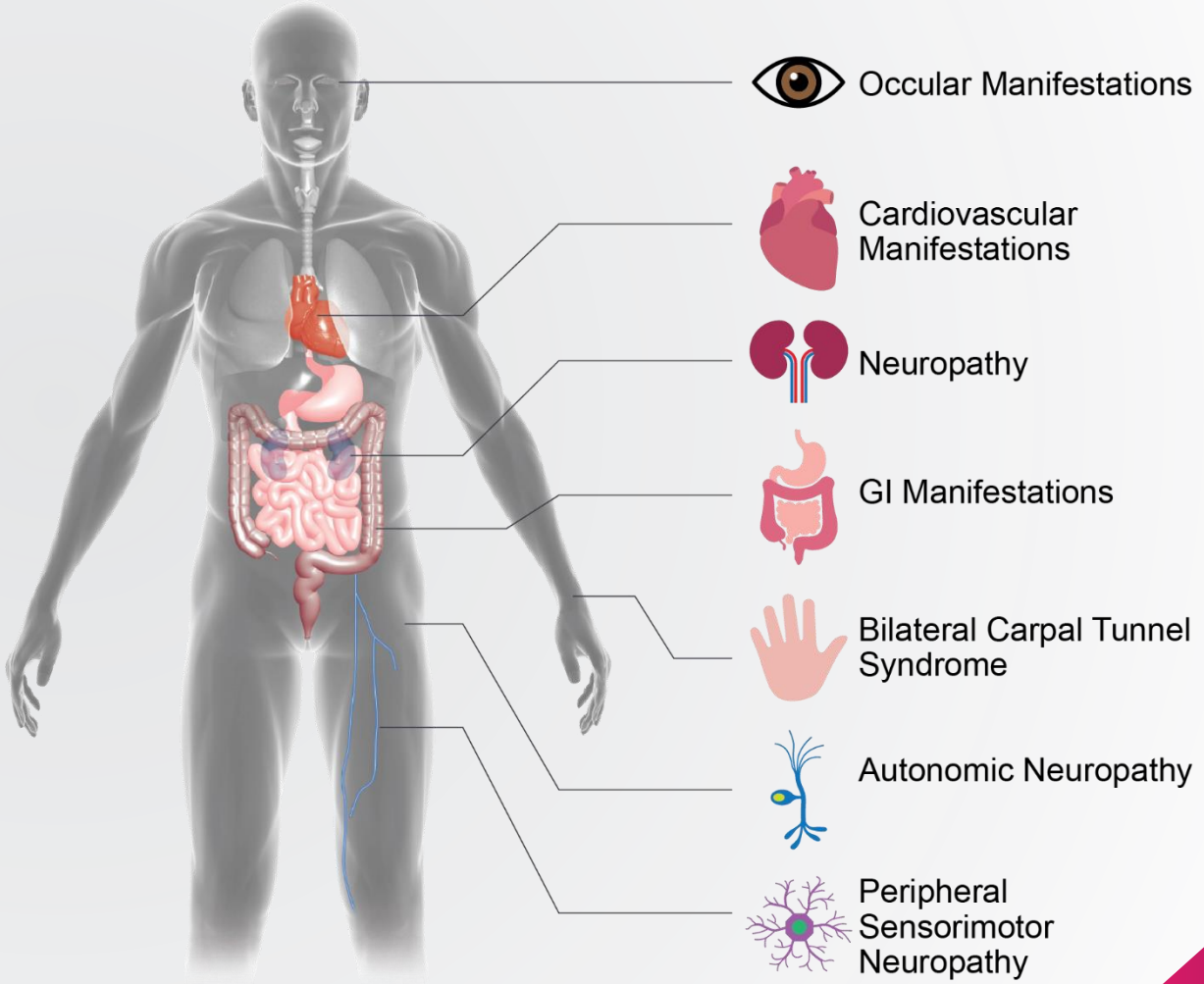
Changing the Standard of Care

Clay, living with ATTR

TTR Amyloidosis (ATTR)

A devastating and fatal disease

- Characterized by the formation of **TTR amyloid deposits** leading to multi-organ failure[1,2]
- Patients suffer from multi-organ failure, dominated by progressive **polyneuropathy** and **cardiomyopathy**
- Progressive disease resulting in a **rapid decline** in **quality of life and death**
  - 3-15 year life expectancy for polyneuropathy[3] patients
  - 2-5 year life expectancy for cardiomyopathy[4] patients



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

Potentially changing the standard of care for all forms of amyloidosis

Prevalence	High Unmet Need	Product Profile Potential to Change the Standard of Care
> 250K	**Often Fatal**	**Transformational**
ATTR patients globally[1]	Progressive disease resulting in a rapid decline in quality of life	Largest CM outcomes trial in TTR amyloidosis

1. Ionis data on file

Eplontersen

Expanding our ATTR franchise

- Eplontersen utilizes our highly advanced **LICA** chemistry, providing high **potency** with attractive **convenience** and **tolerability**
- **Targets** TTR: **the root cause** of TTR amyloidosis
- **Robust** target **reduction** and **positive safety** profile demonstrated in healthy volunteers
  - > 90% demonstrated in Phase 1 healthy volunteer study
  - **Favorable safety** and **tolerability** observed

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Changing Standards of Care

Eplontersen

Potential foundational therapy for hATTR polyneuropathy and ATTR cardiomyopathy

Projected Phase 3 Data
2022 polyneuropathy
2024 cardiomyopathy

- **Targets the root cause** of TTR amyloidosis, mutant TTR protein
- An Ionis next-generation **high-potency LICA medicine**
- **Robust target reductions** demonstrated in Phase 1 study
- Two ongoing Phase 3 studies actively recruiting: **NEURO-TTRansform** and **CARDIO-TTRansform** outcome study

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IONIS-APOCIII-L$_{Rx}$

Changing the Standard of Care

Fred, living with FCS

Severe Diseases Driven by Elevated Triglycerides

- **Elevated triglyceride levels are associated with major medical issues**
  - Increased CVD risk
  - Acute, potentially fatal pancreatitis
- **Apolipoprotein C-III (apoC-III)**
  - Key regulator of triglycerides
  - Independent cardiovascular risk factor
- **Potential best-in-class mechanism for TG-related cardiometabolic disease management**

Familial Chylomicronemia Syndrome (FCS) (> 1,000 mg/dl)	Severe High Triglycerides (sHTG) (> 500 mg/dl)	High Triglycerides (150 – 500 mg/dl)
~ 3-5K **patients** globally[1]	**> 3M** **patients** In the U.S.[2]	**~ 50M** **patients** globally[2]

1. Ionis data on file. 2. Ford, MD, MPH et al., Arch Intern Med. 2009;169(6):572-578

IONIS-APOCIII-L_{Rx}

One product, multiple indications targeting elevated triglycerides

Prevalence

~ 3-5K

FCS patients globally[1]

> 3M

sHTG patients in the U.S.[1]

High Unmet Need

FCS

High risk of unpredictable & potentially fatal acute pancreatitis

sHTG

High risk of CVD & type 2 diabetes

Best In Class Product Profile Potential

Transformational

Potential best in class TG reductions with patient-friendly monthly SC administration

1. Ionis data on file

Changing Standards of Care

IONIS-APOCIII-L_{Rx}

One product, multiple indications targeting elevated triglycerides

- **Robust triglyceride reductions** demonstrated in Phase 2 study
- Phase 3 **FCS BALANCE** study actively recruiting
- Phase 3 **severe hypertriglyceridemia** (sHTG) study start planned for 2H 2021

Projected Phase 3 Data
2023 (FCS)
2024 (sHTG)

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Michael, living with Lp(a) driven Cardiovascular Disease

Pelacarsen

(IONIS-APO(a)-L_{Rx})

Pioneering New Markets

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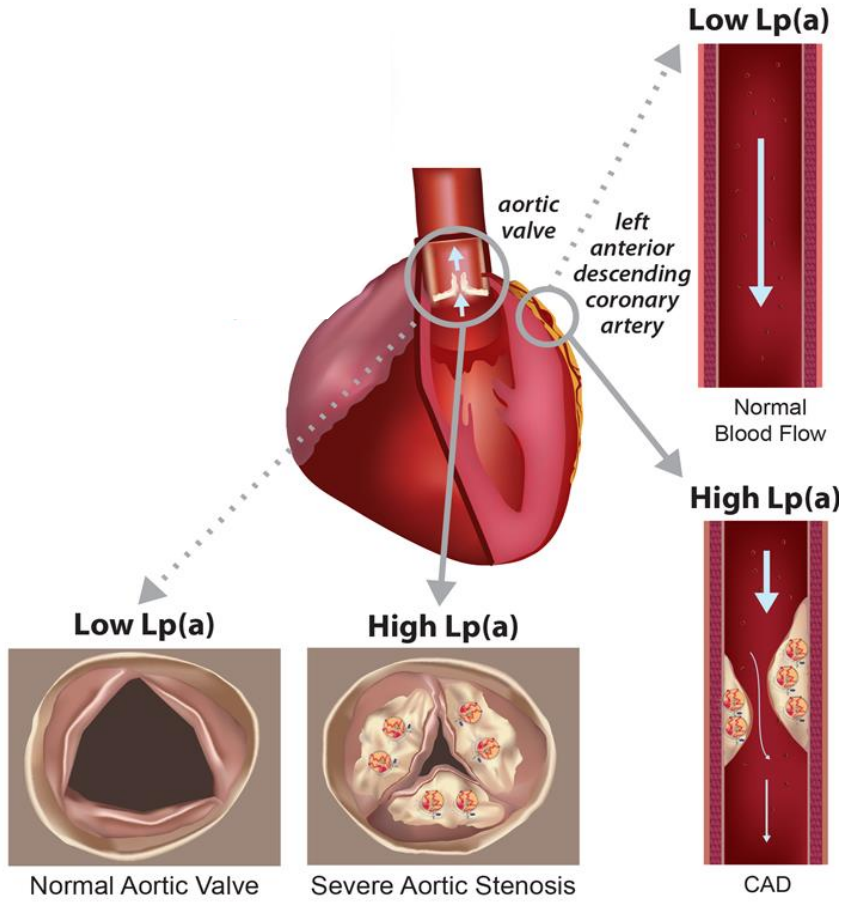
Lipoprotein(a)

A highly prevalent untreated risk factor for cardiovascular disease

- Lp(a) levels are **genetically determined** at birth
- Elevated Lp(a) levels **cause cardiovascular disease** through multiple mechanisms
- Elevated levels are recognized as a **major untreated cardiovascular risk factor**
- **No approved** pharmacological therapies



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Pelacarsen

Potential first in class profile for Lp(a) driven cardiovascular disease

Prevalence	High Unmet Need	First In Class Product Profile Potential
> 8M	**Often Fatal**	**Transformational**
People worldwide with Lp(a) driven CVD[1]	Genetic cause of coronary artery disease, heart attack, stroke and peripheral arterial disease	Expected to be first disease modifying treatment for Lp(a) driven CVD

1. Ionis data on file

Pioneering New Markets

Pelacarsen[1]

Expected to be first disease modifying treatment for Lp(a) driven cardiovascular disease

Projected Phase 3 Data
2024

- **Targets the root cause** of Lp(a)-driven cardiovascular disease
- **98% of patients** achieved Lp(a) levels below CVD risk threshold in Phase 2 study[2,3]
- Granted **Fast Track** Designation by the FDA
- Phase 3 **Lp(a)HORIZON** cardiovascular outcome study actively enrolling

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1. Partnered with Novartis. 2. ≤ 50 mg/dL is considered below the threshold for risk of CVD events. 3. Results of Phase 2 study

IONIS-PKK-L_{Rx}

Changing the Standard of Care

Hereditary Angioedema is Characterized by Unpredictable and Painful Attacks that are Potentially Fatal

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

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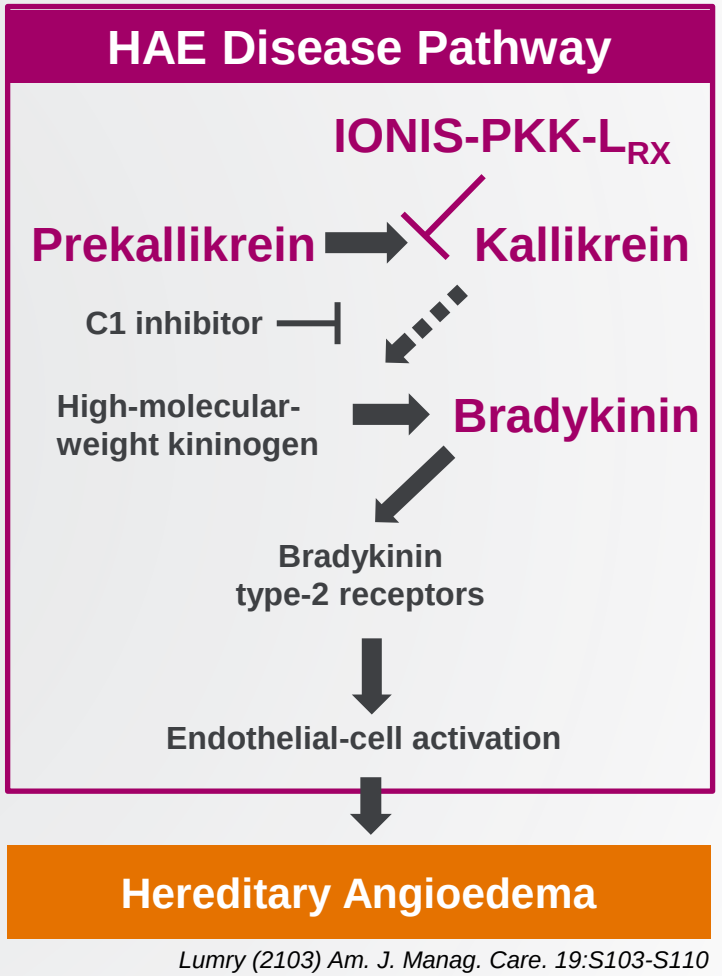
Hereditary Angioedema is a Rare, Severe Disease Driven by Overactivity of the Prekallikrein Pathway

- Hereditary Angioedema (HAE) is caused by **insufficient or dysfunctional C1-Inhibitor** resulting in:
  - Overactivity of the Prekallikrain (PKK) pathway
  - Excessive bradykinin production
  - Severe swelling, characteristic of HAE

- **IONIS-PKK-L_{Rx}** is a LICA-medicine designed to **block the production of PKK**, thereby reducing production of bradykinin – the cause of HAE



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IONIS-PKK-L_{Rx}

Potential to change standard of care for the treatment of HAE

Prevalence	High Unmet Need	Best In Class Product Profile Potential
> 20K	**Potentially Fatal**	**Transformational**
Patients in the United States and Europe suffering from HAE[1]	Significant need for safe, better tolerated, and more convenient therapy for prevention of potentially fatal HAE attacks	Potential best in class reductions in HAE related attacks with monthly SC administration

1. Ionis data on file

IONIS-PKK-L_{Rx} Demonstrated Significant Reductions in HAE Attack Rate in Phase 2 Study

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

Phase 3 planning underway

IONIS™

IONIS-PKK-L$_{Rx}$

Potential best in class medicine for prevention of HAE attacks

Phase 3
Planning Underway

Changing Standard of Care

- **Targets** the pathway at the **root cause of HAE**
- Designed as a convenient **prophylactic treatment** for prevention of HAE attacks
- Utilizes Ionis' next-generation **LICA chemistry with high potency, attractive tolerability and convenience**
- Phase 2 profile supports a potential **Best-In-Class medicine** for HAE

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2021 Planned Pipeline Events

Key 2021 Pipeline Events

DATA READOUTS[1]			H1	H2
PKK-L_{Rx}	Phase 2	Hereditary Angioedema (top-line data)	✓	
AGT-L_{Rx}	Phase 2	Hypertension	✓	
Tominersen[2]	Phase 3	Huntington's disease	✓	
ENAC-2.5$_{Rx}$	Phase 2	Cystic Fibrosis	✓	
GHR-L_{Rx}	Phase 2 + OLE	Acromegaly		●
PKK-L_{Rx}	Phase 2	Hereditary Angioedema (full data)		●
MAPT$_{Rx}$	Phase 1/2	Alzheimer's Disease		●
Vupanorsen	Phase 2b	sHTG/CVD risk reduction		●
Tofersen	VALOR Phase 3	SOD1-ALS		●
KEY STUDY INITIATIONS[1]			**H1**	**H2**
SPINRAZA	RESPOND Phase 4	SMA, Suboptimal gene therapy response	✓	
Tofersen	ATLAS Phase 3	Presymptomatic SOD1-ALS	✓	
ION363	Phase 3	FUS-ALS	✓	
AGT-L_{Rx}	Phase 2b	Resistant hypertension	✓	
AGT-L_{Rx}	Phase 2	Heart failure with reduced ejection fraction	✓	
ION373	Phase 2/3	Alexander disease	✓	
ION224	Phase 2b	NASH	●	
APOCIII-L_{Rx}	Phase 3	Second TG indication (sHTG)		●
ION582	Phase 1/2	Angelman syndrome		●

1. Timing of partnered program catalysts based on partners' most recent publicly available disclosures
2. Dosing stopped in Phase 3 GENERATION HD1 Study, paused in GEN-EXTEND OLE study. GEN-PEAK and Roche HD Natural History study continuing

● Wholly owned ● Partnered

IONIS™

12+ Marketed Medicines Projected in 2026

SPINRAZA® (nusinersen) injection 12 mg/5 mL

Tegsedi® (inotersen) injection 284 mg/1.5 mL

waylivra® (volanesorsen) injection 285 mg/1.5 mL

Wholly owned Neuro

Eplontersen (hATTR-PN)
ION716 (Prion)
ION373 (Alexander)
ION363 (FUS-ALS)
ION283 (Lafora)

Partnered Neuro

Tofersen (SOD1-ALS)
$C9_{Rx}$ (C9-ALS)
ION541 (Broad ALS)

Wholly owned Cardio

Eplontersen (ATTR-CM)
APOCIII-L_{Rx} (FCS)
APOCIII-L_{Rx} (sHTG)
AGT-L_{Rx} (RHTN)

Partnered Cardio

Pelacarsen (Lp(a) CVDRR)
Vupanorsen (sHTG/CVDRR)
FXI-L_{Rx} (ESRD)
ION449 (PCSK9)

Wholly owned Other

TMPRSS6-L_{Rx} (β-thal)
PKK-L_{Rx} (HAE)
GHR-L_{Rx} (Acromegaly)

Partnered Other

HBV_{Rx} (Hep B)

Well Positioned for Accelerated Growth

Advancing pipeline & technology

Pioneering new markets & **Changing** standards of care

Financial strength to invest in areas with the greatest **value-driving potential**

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A force for life

Q&A

Please standby as we compile your questions. Thanks for your patience.