J.P. Morgan Healthcare Conference 2021

Brett P. Monia, Ph.D.
Chief Executive Officer

January 12, 2021

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, including the business of Akcea Therapeutics, Inc., Ionis' wholly owned subsidiary. 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, 2019 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™

2020: A New Beginning

- New leadership, new vision
- Enhanced business model to commercialize Ionis medicines
- Advanced late- and mid-stage pipeline towards market
- Expanded therapeutic scope through technology advancements

2021: Positioned for Growth

Commercial	**Expand wholly owned pipeline** **Prepare markets for Ionis product launches**
Pipeline	**Advance and expand Phase 3 pipeline** **Deliver multiple Phase 2 readouts** **Expand aerosol-delivered clinical pipeline**
Technology	**Advance new LICA chemistry into development** **Expand pipeline with novel genetically validated programs**

IONIS™

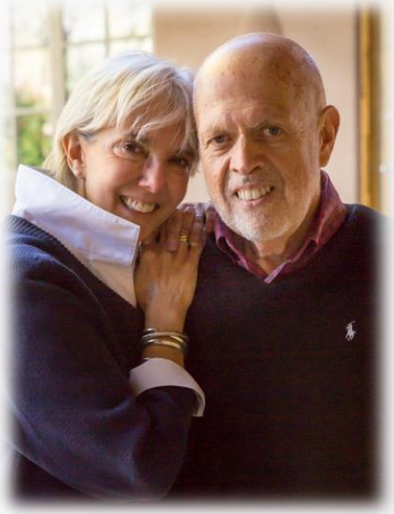
Financial Strength Supports Our Strategic Priorities

Total Revenue[1]	Net Income[1]	2020 YE Cash (Estimated)
> $700M	Meaningfully profitable	~ $2B

On track to meet 2020 financial guidance[1]

1. Expected 2020 results. Non-GAAP – please see reconciliation to GAAP in 3Q20 earnings release

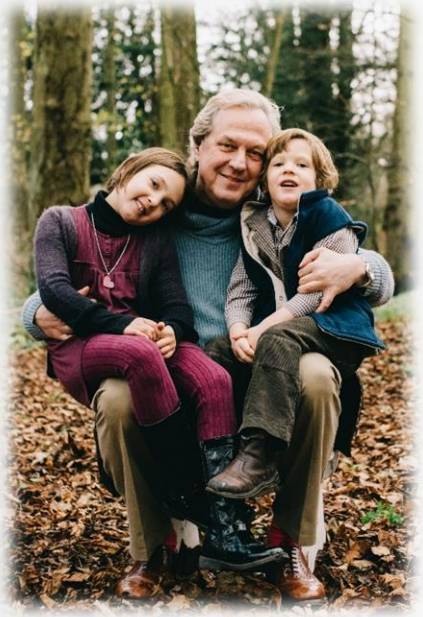
Pioneering New Markets and Changing Standards of Care



TTR Amyloidosis

Spinal Muscular Atrophy

Familial Chylomicronemia Syndrome



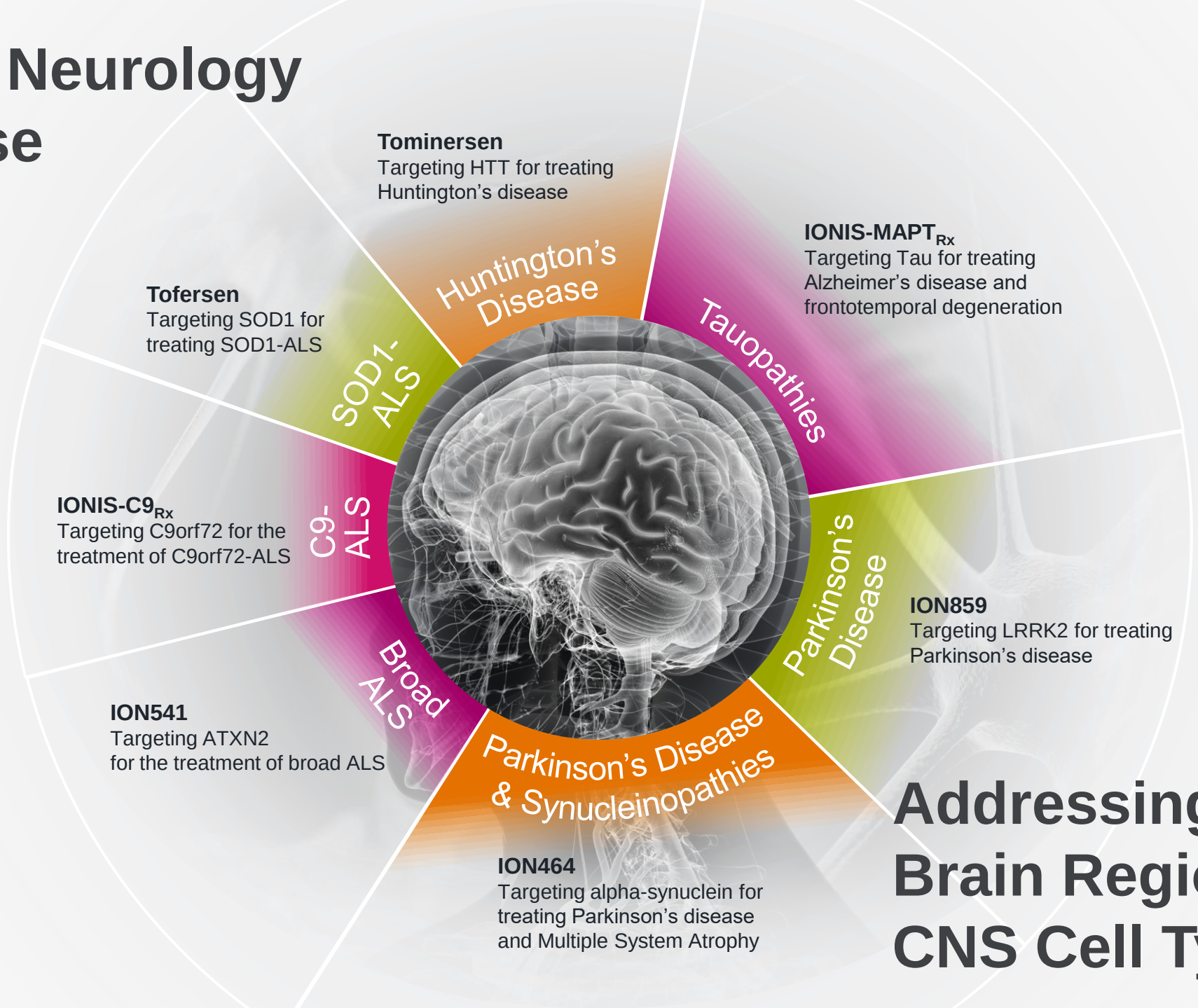
Huntington's Disease

Lp(a) CVD Risk Reduction

ALS

IONIS™

Leading Neurology Franchise



Tominersen
Targeting HTT for treating Huntington's disease

IONIS-MAPT$_{Rx}$
Targeting Tau for treating Alzheimer's disease and frontotemporal degeneration

Tofersen
Targeting SOD1 for treating SOD1-ALS

IONIS-C9$_{Rx}$
Targeting C9orf72 for the treatment of C9orf72-ALS

ION859
Targeting LRRK2 for treating Parkinson's disease

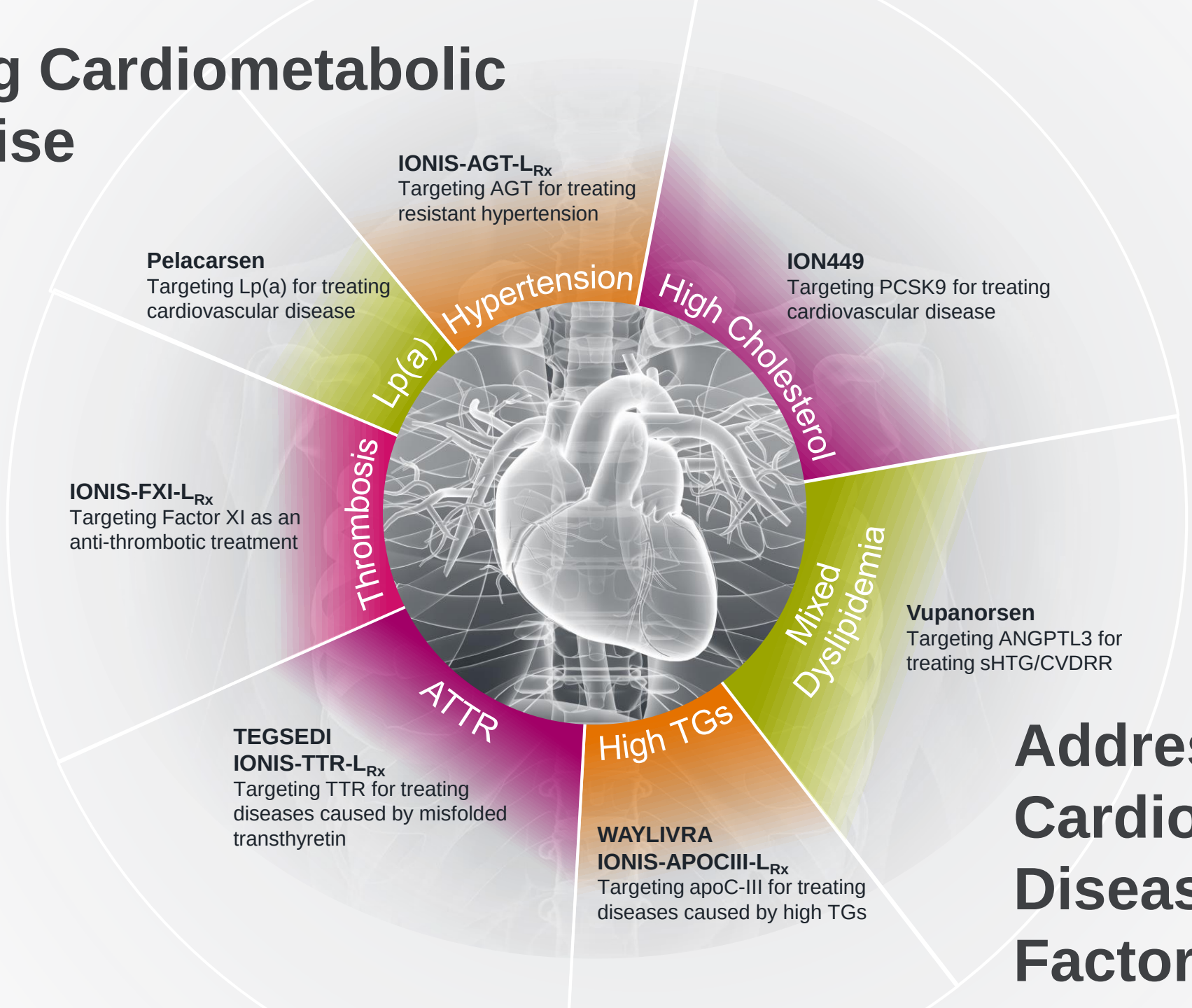
ION541
Targeting ATXN2 for the treatment of broad ALS

ION464
Targeting alpha-synuclein for treating Parkinson's disease and Multiple System Atrophy

Addressing All Major Brain Regions & CNS Cell Types

IONIS™

Leading Cardiometabolic Franchise



IONIS-AGT-L_{Rx}
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
IONIS-TTR-L_{Rx}
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

IONIS™

Two Leading Therapeutic Franchises

Neurological

Addressing all major brain regions and CNS cell types

3 ongoing Phase 3 studies

8 medicines in clinical development

5 wholly owned medicines

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

12 medicines in clinical development

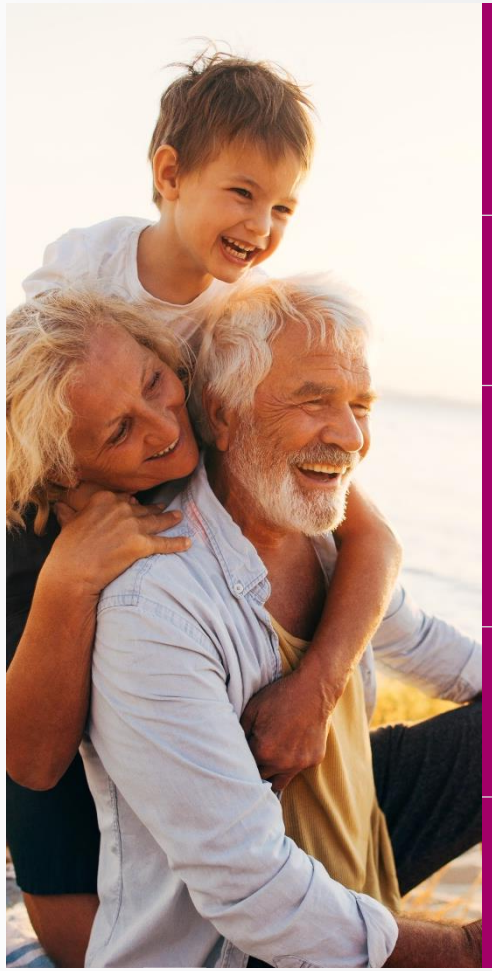
7 wholly owned medicines

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

IONIS™

Pioneering New Markets & Changing Standards of Care

Multi-Billion Dollar Opportunities



		Prevalence[1]	Phase 3 Data
Tofersen	**SOD1-ALS** Biogen	**~ 1.4K patients** in G7 countries	2021
Tominersen	**Huntington's disease** Roche	**~ 80K patients** in major markets	2022
IONIS-TTR-L_{Rx}	**hATTR polyneuropathy** **ATTR cardiomyopathy** Wholly owned	**> 250K patients** worldwide	2022 (PN) 2024 (CM)
IONIS-APOCIII-L_{Rx}	**FCS** Wholly owned	**~ 3-5K patients** worldwide	2023
Pelacarsen	**Lp(a) CVDRR** Novartis	**> 8M patients** worldwide	2024

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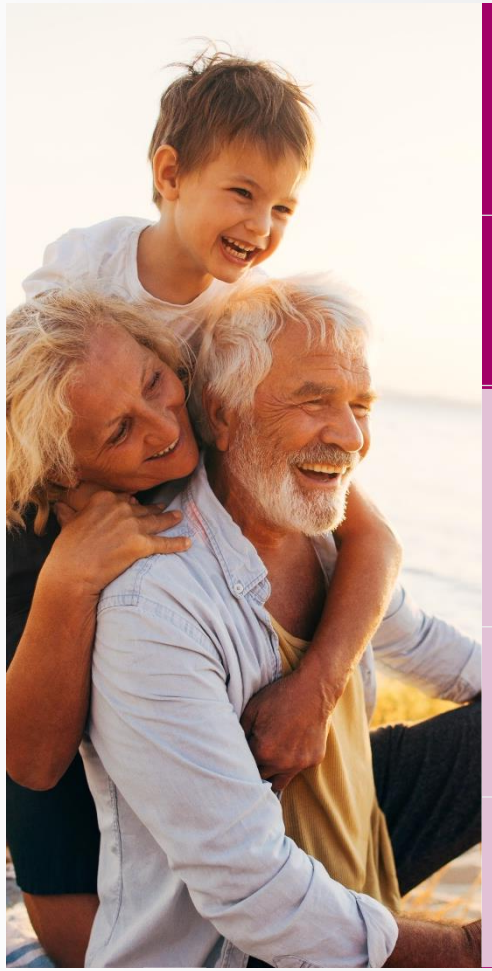
1. Market data on file.
ALS, amyotrophic lateral sclerosis. FCS, familial chylomicronemia syndrome. hATTR, hereditary transthyretin amyloidosis. CVDRR, cardiovascular disease risk reduction. TG, triglyceride.

Pioneering New Markets & Changing Standards of Care

Multi-Billion Dollar Opportunities



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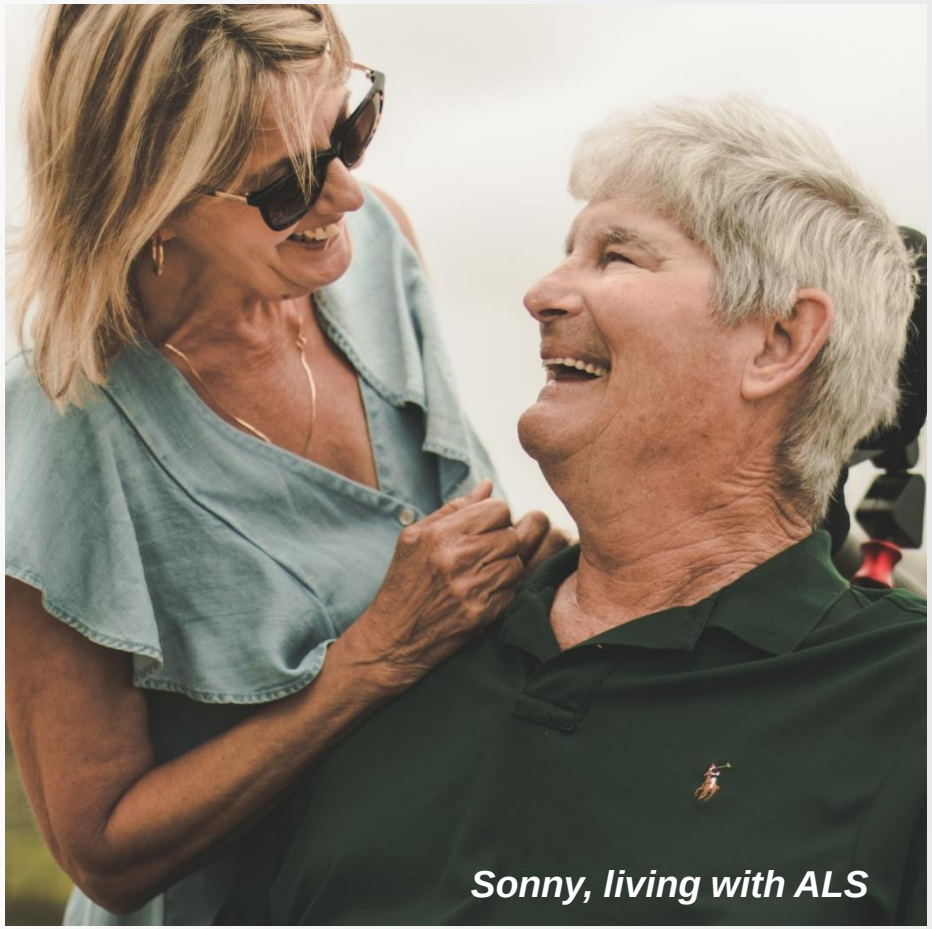
Amyotrophic Lateral Sclerosis

A fatal disease with a tremendous unmet medical need


Sonny, living with ALS

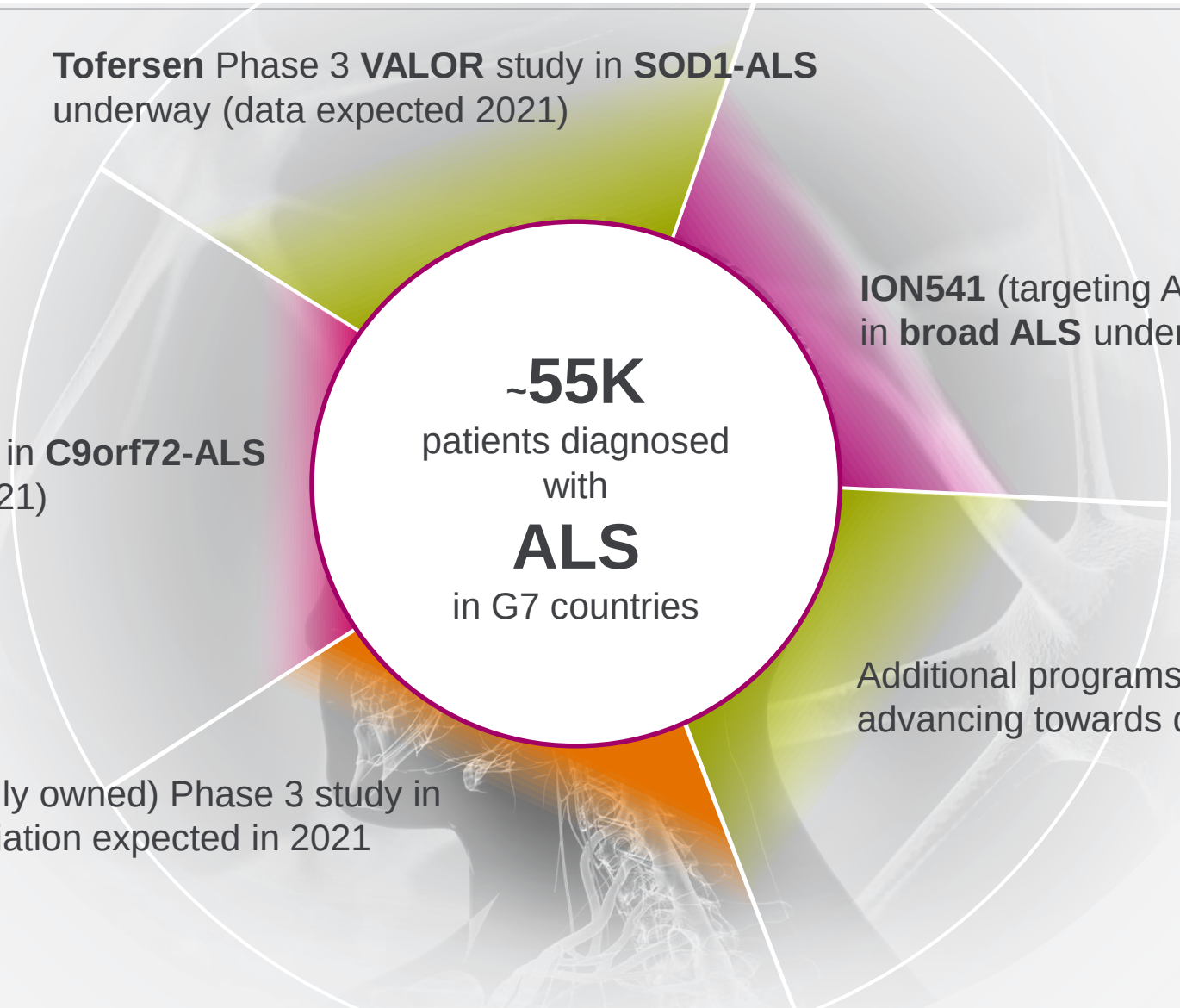
- **Fatal disease** characterized by **motor neuron** degeneration resulting in **paralysis** and **respiratory failure**
- **Rapidly progressing**, with average **survival of 3-5 years** from symptom onset

~ 55K patients in G7 countries[1]

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

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

We Are Committed to Treating All Forms of ALS



Tofersen Phase 3 **VALOR** study in **SOD1-ALS** underway (data expected 2021)

ION541 (targeting ATXN2) Phase 1/2 study in **broad ALS** underway

Additional programs for **all forms of ALS** advancing towards development

ION363 (wholly owned) Phase 3 study in **FUS-ALS** initiation expected in 2021

IONIS-C9$_{Rx}$ Phase 1/2 study in **C9orf72-ALS** underway (data expected 2021)

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Pioneering New Markets

Tofersen[1]

First of four medicines targeting ALS

Projected Phase 3 Data
2021

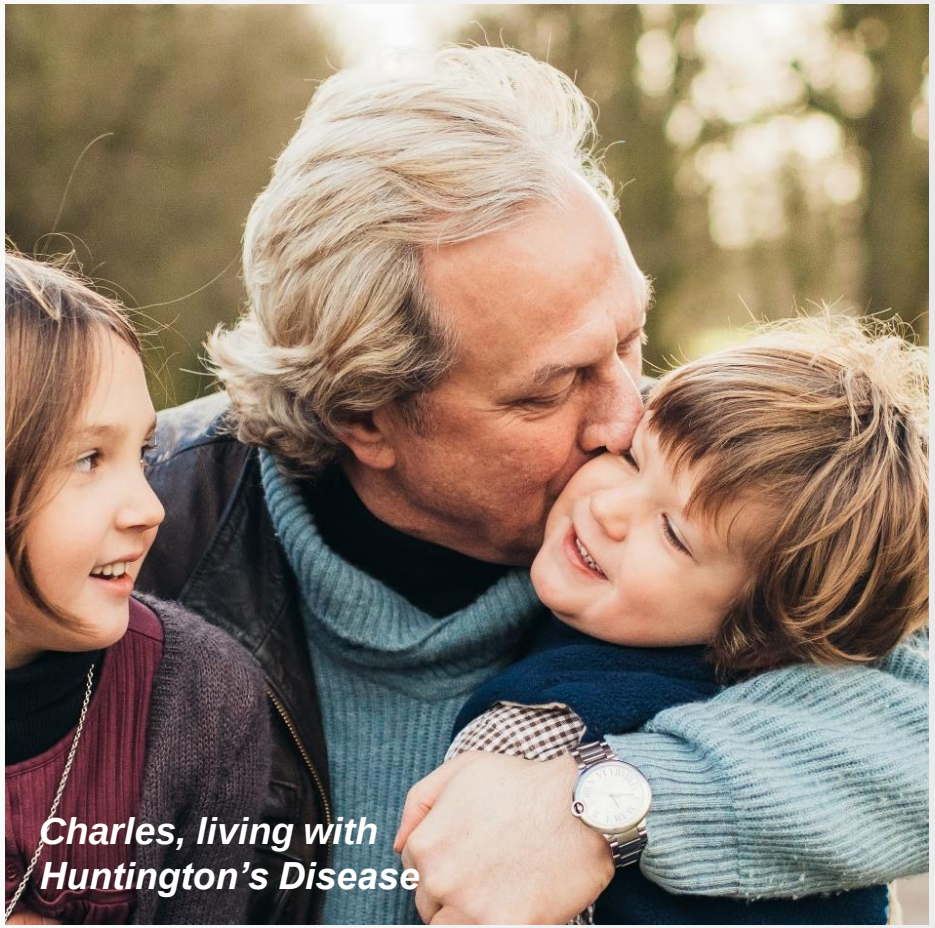
- Phase 3 **VALOR** study **fully enrolled**
- **Next** potential **commercial medicine**
- Phase 3 **ATLAS** study in **presymptomatic** SOD1-ALS patients expected to start in 2021
- Demonstrated **robust reductions** in SOD1 with trends in **slowing disease** progression[2]

IONIS™

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

Huntington's Disease

A rare, genetic, fatal neurological disease



- **Described** as suffering from **ALS, Parkinson's** and **Alzheimer's** – simultaneously[1]
- **Genetic** disease – **devastation continues** across multiple generations
- **Slowly progressing disease – death 15-20 years** from symptom onset

~ 80K symptomatic patients in major markets[2]

- **> 5x** more presymptomatic patients[1]

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1. The Huntington's Disease Society of America. 2. US, FR, DE, IT, ES, GB (source: Roche/Genentech)

Pioneering New Markets

Tominersen[1]

Potentially first disease modifying medicine for Huntington's disease

Projected Phase 3 Data
2022

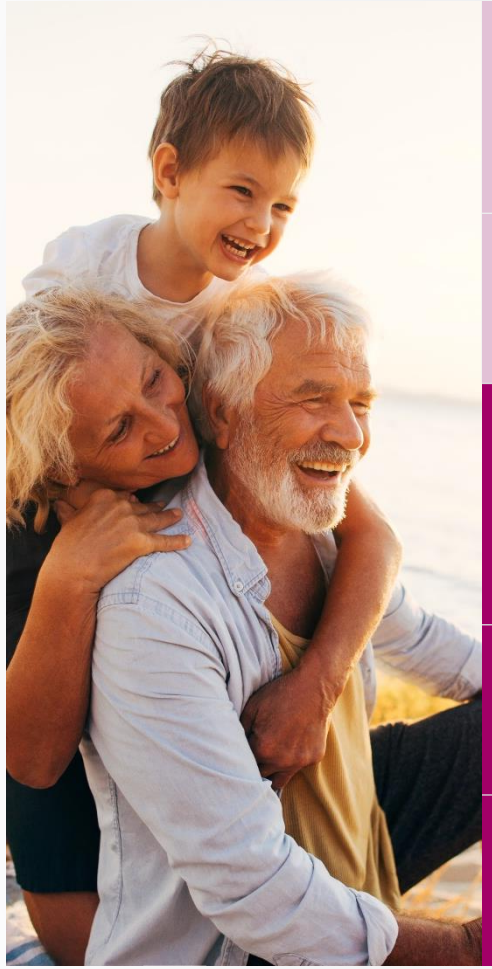
- GENERATION HD1 Phase 3 study **fully enrolled**
- **Targets the root cause** of Huntington's disease, the mutant huntingtin protein
- **PRIME** designation in EU
- Demonstrated **robust** and **sustained reductions** in **mutant huntingtin protein**[2] in patients

IONIS™

1. Partnered with Roche. 2. Based on results from Phase 1/2 and open label extension studies

Pioneering New Markets & Changing Standards of Care

Multi-Billion Dollar Opportunities



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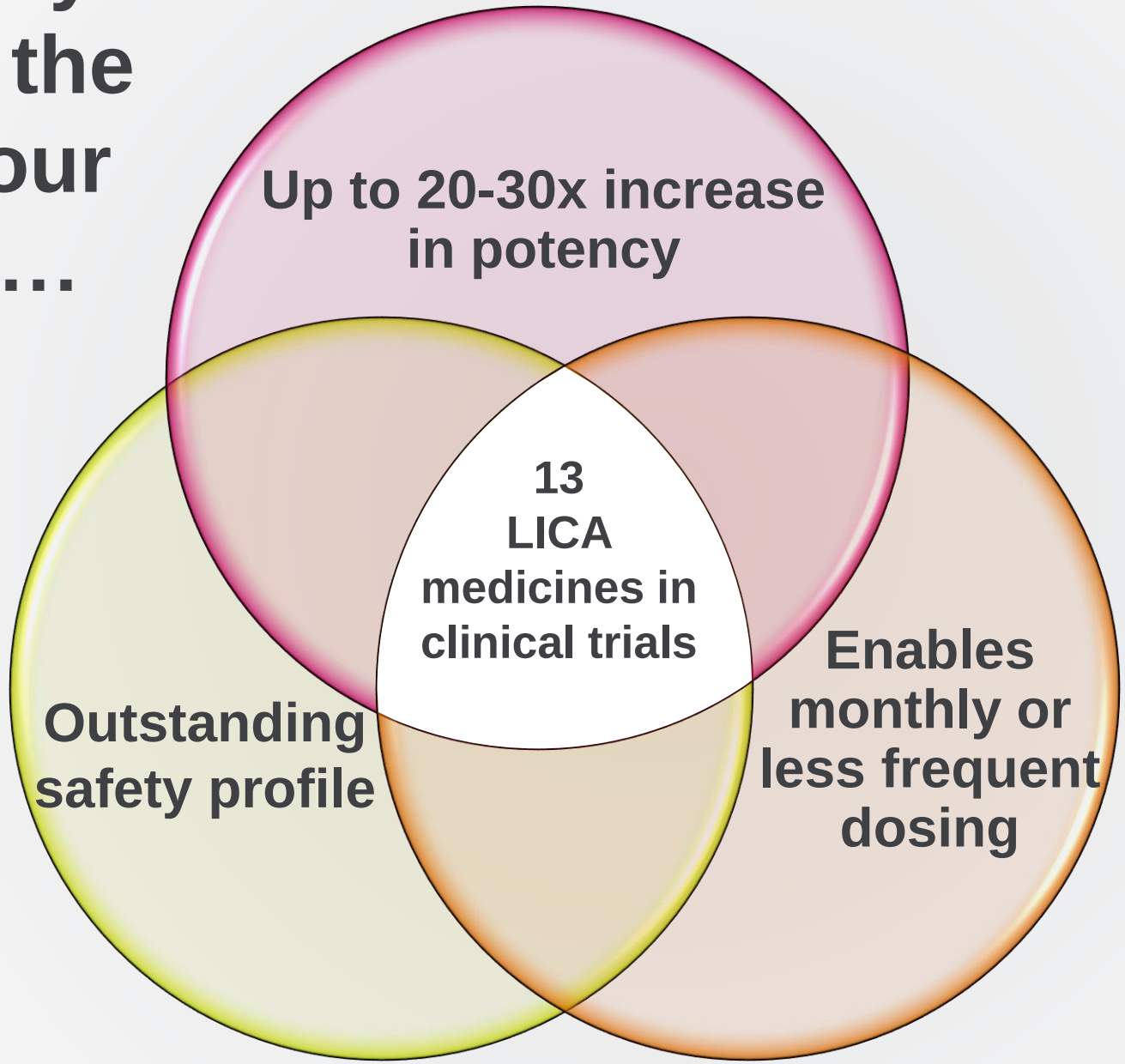
LICA Greatly Enhances the Profile of our Medicines…



…Continues to Deliver Value to Patients Today

IONIS™

TTR Amyloidosis (ATTR)

A devastating 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

> 250K patients worldwide[1,2]

- ~ 50K hATTR polyneuropathy
- > 200K ATTR cardiomyopathy

IONIS™

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.

Changing Standards of Care

IONIS-TTR-L_{Rx}

Potential to be foundational therapy for hATTR polyneuropathy and ATTR cardiomyopathy

Projected Phase 3 Data
2022 polyneuropathy
2024 cardiomyopathy

- Two ongoing Phase 3 studies: **NEURO-TTRansform** and **CARDIO-TTRansform** outcome study
- An Ionis next-generation **high-potency LICA medicine**
- **Robust target reductions** demonstrated in Phase 1 study

IONIS™

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	Severe High Triglycerides (> 500 mg/dl)	High Triglycerides (150 – 500 mg/dl)
~ 3-5K **patients** globally[1]	> 10M **patients** globally[2]	~ 50M **patients** globally[2]

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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

Projected Phase 3 Data
2023

Changing Standards of Care

- Phase 3 **FCS BALANCE** study actively recruiting
- **Initiating second Phase 3 study** in broader indication in 2021
- **Robust triglyceride reductions** demonstrated in Phase 2 study

IONIS™

Cardiovascular Disease Driven by Elevated Lipoprotein(a)

A major untreated cardiovascular disease risk factor

- Lp(a) levels are **genetically determined** at birth
- **Elevated Lp(a) levels cause cardiovascular disease** through multiple mechanisms
- **No approved** therapies

Lp(a) Driven CVD

> 8M patients worldwide[1]

1. Novartis data on file

Pioneering New Markets

Pelacarsen[1]

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

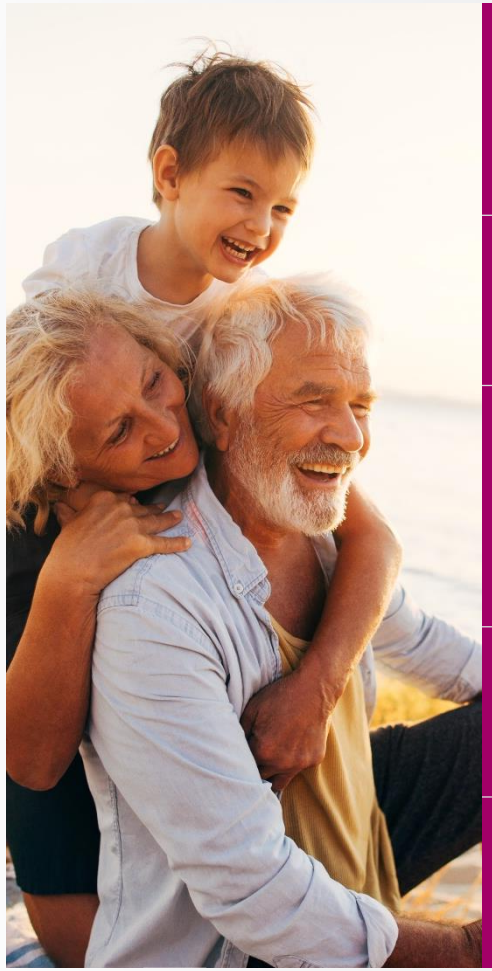
- Phase 3 **Lp(a)HORIZON** outcome study actively recruiting
- Granted **Fast Track** Designation by the FDA
- **98% of patients** achieved Lp(a) levels below CVD risk threshold[2,3]

Projected Phase 3 Data
2024

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

Pioneering New Markets & Changing Standards of Care

Multi-Billion Dollar Opportunities



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Waves of Medicines from Pipeline…

12+

Marketed products in 2026

Wholly owned Other

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

Partnered Other

HBV_{Rx} (Hep B)

Wholly owned Cardio

TTR-L_{Rx} (ATTR-CM)
APOCIII-L_{Rx} (FCS)
APOCIII-L_{Rx} (TG diseases)
AGT-L_{Rx} (RHTN)
GHR-L_{Rx} (Acromegaly)

Partnered Cardio

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

Wholly owned Neuro

TTR-L_{Rx} (hATTR-PN)
ION716 (Prion)
ION373 (Alexander)
ION363 (FUS-ALS)
ION283 (Lafora)

Partnered Neuro

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

SPINRAZA® (nusinersen) injection 12 mg/5 mL

Tegsedi® (inotersen) injection 284 mg/1.5 mL

waylivra® (volanesorsen) injection 285 mg/1.5 mL

…Position Ionis to Deliver Double-Digit Revenue Growth

Value-Driving Pipeline Catalysts in 2021

DATA READOUTS			H1	H2
GHR-L_{Rx}	Phase 2	Acromegaly	●	
ENAC-2.5$_{Rx}$	Phase 1/2	Cystic Fibrosis	●	
PKK-L_{Rx}	Phase 2	Hereditary Angioedema	●	
	Phase 2	Severe COVID-19*	●	
Tominersen	OLE & NHS	Huntington's Disease	●	●
Tofersen	VALOR Phase 3	SOD1-ALS		●
Vupanorsen	Phase 2b	Dyslipidemia		●
$C9_{Rx}$	Phase 1/2	C9-ALS		●
$MAPT_{Rx}$	Phase 1/2	Alzheimer's Disease		●

KEY STUDY INITIATIONS			H1	H2
SPINRAZA	RESPOND Phase 4	SMA, Suboptimal gene therapy response	●	
ION363	Phase 3	FUS-ALS	●	
Tofersen	ATLAS Phase 3	Presymptomatic SOD1-ALS		●
APOCIII-L_{Rx}	Phase 3	Second indication		●
AGT-L_{Rx}	Phase 2b	Resistant hypertension		●
	Phase 2b	Heart failure with reduced ejection fraction		●
ENAC-2.5$_{Rx}$	Phase 2	Cystic Fibrosis with rare mutations		●

IONIS™

* Investigator initiated study in Brazil

● Wholly owned ● Partnered

Positioned to Transform the Lives of Patients and Drive Substantial Growth

Advancing pipeline & technology

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

Substantial **Financial strength** to invest in our strategic priorities

Ionis: A Force for Life