



Corporate Overview

April 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, 2020, which is 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 Pharmaceuticals™ is a trademark of Ionis Pharmaceuticals, Inc. Akcea Therapeutics® is a registered trademark of Akcea Therapeutics, Inc. TEGSEDI® is a trademark of Akcea Therapeutics, Inc. WAYLIVRA® is a registered trademark of Akcea Therapeutics, Inc. SPINRAZA® is a registered trademark of Biogen.

Company Overview

Created new biotechnology industry sector focused on RNA-targeted therapeutics

Pipeline of medicines addressing neurological disease, cardiovascular disease and other select therapeutic areas

Three first-in-class marketed products

Strong intellectual property position covering all aspects of oligonucleotide therapeutics

2020 Revenue: \$729M

2020 Cash: ~\$2B

Employees: 757

Nasdaq: IONS

The IONIS logo is displayed in a vibrant pink color on a wall made of light-colored, rectangular stone tiles. The logo is positioned above two large, dark grey planters filled with red flowers. The background of the slide features a blurred image of a modern building entrance with large glass windows and a stone wall.

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: Investing for Growth

Commercial

Advancing the wholly owned pipeline
Building commercial capabilities

Pipeline

Advancing and expanding the late-stage pipeline
Advancing towards data from up to six Phase 2 and 3 studies
Expanding aerosol-delivered clinical pipeline

Technology

Developing new LICA chemistry
Expanding the pipeline with novel genetically validated programs

Achieved 2020 Guidance and Strengthened the Business

2021 Focused on Investments to Drive Future Revenue Growth

Achieved 2020 financial guidance*

**Further strengthened and streamlined the business
through Akcea and Sobi transactions**

**Well capitalized with the financial strength
to achieve our strategic goals**

2020 Financial Results

Achieved Financial Guidance While Managing COVID-19 Challenges

\$729 million in revenue

Half from commercial revenues

\$111 million of net income*

Continued financial strength



>\$2 billion

Continued blockbuster performance

\$1.9 billion of cash

Enabling increasing investment in three key value-driving areas

2021 Financial Guidance Reflects Focus on Wholly Owned Medicines

Revenue

>\$600 million

Operating Expenses

\$675-\$725 million*

Net Loss

<\$75 million*

Investing in our Strategic Priorities to Drive Future Revenue and Earnings Growth

Ionis' Antisense Technology...

Works on All Types of RNA

mRNA, Long non-coding RNA, Toxic RNA, MicroRNA

Works Through Many Different Mechanisms

Decrease or increase protein production, alter splicing, decrease toxic RNAs

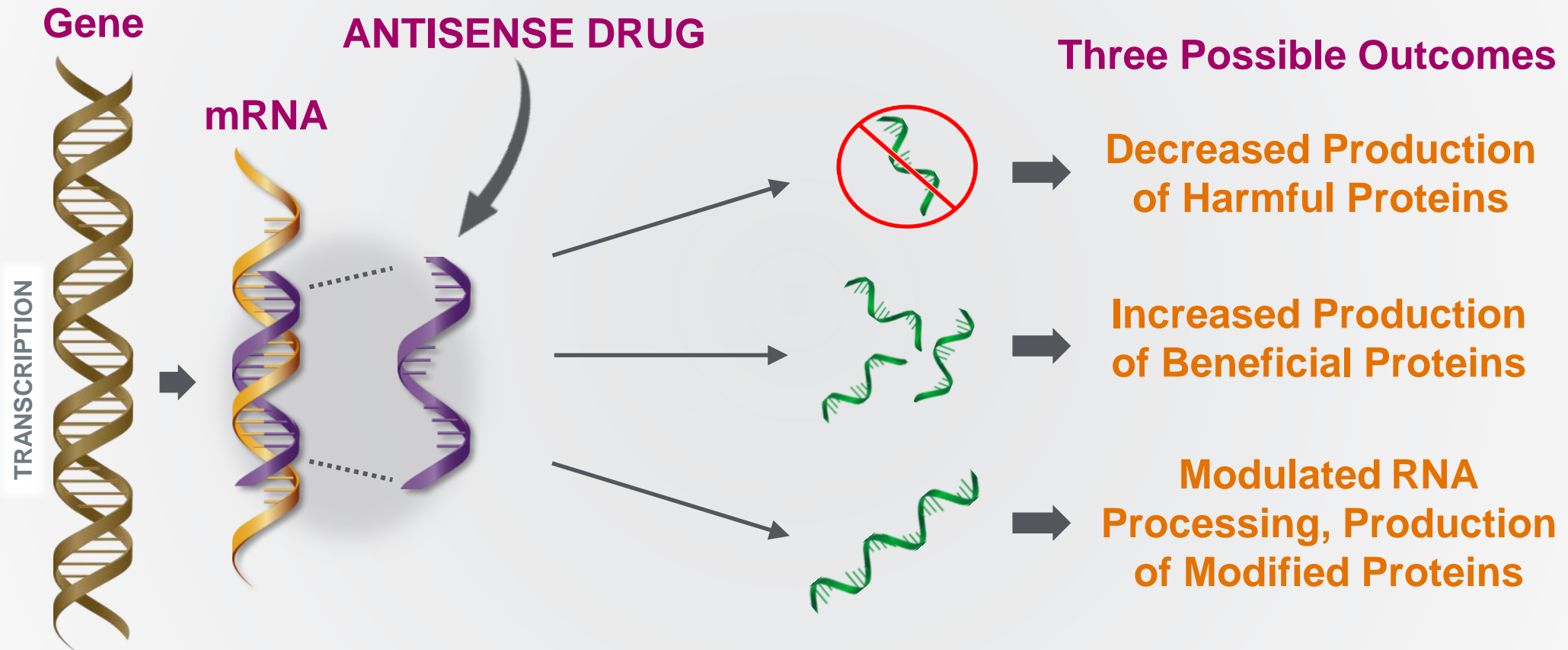
Works by Many Routes of Administration

SQ, IT, IV, inhaled, intra-ocular

Works Broadly Throughout the Body

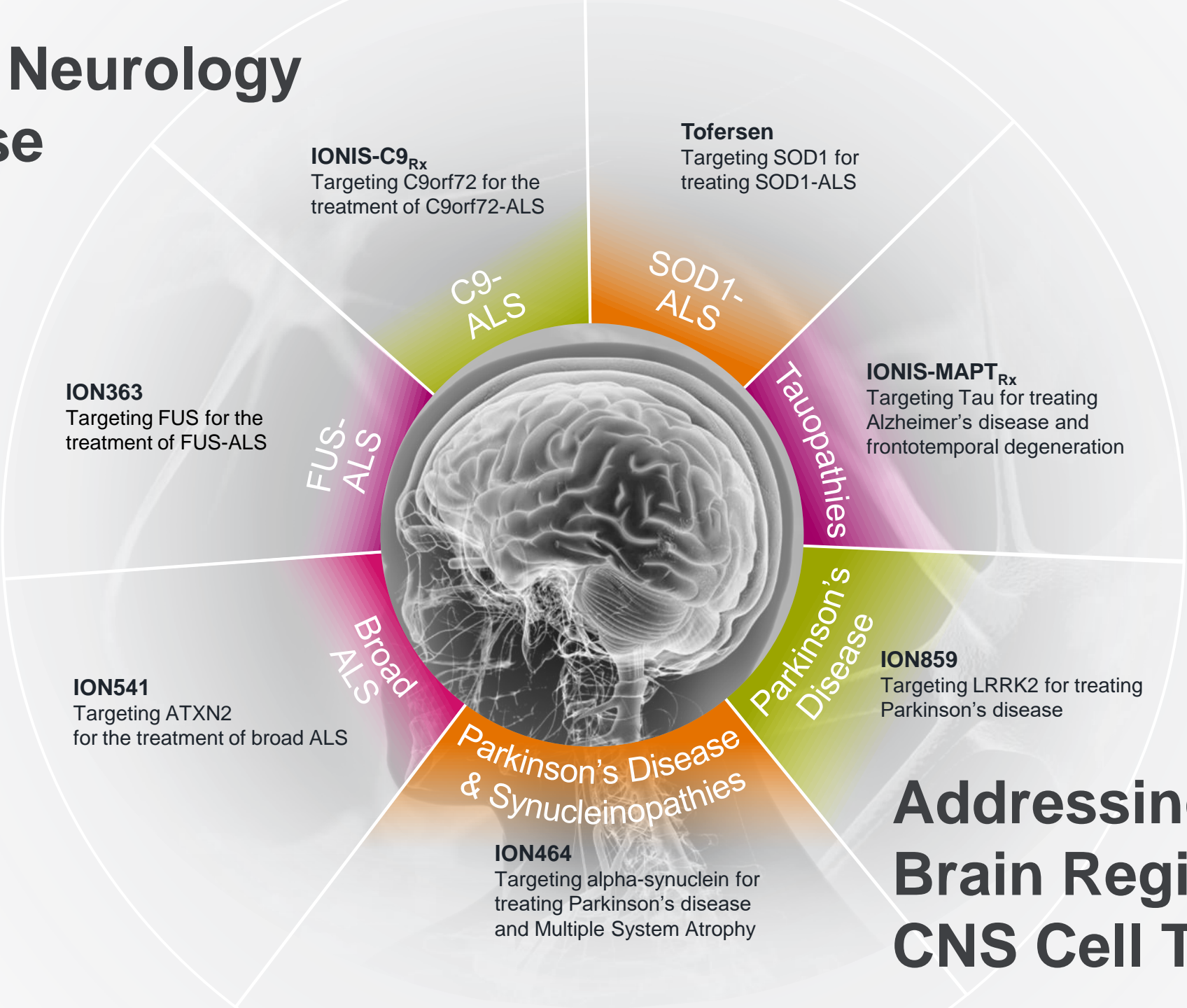
Liver, muscle, brain, spinal cord, eye, cancer cells, fat, kidney, heart, lung

Antisense Technology: Versatility to Modulate All RNA



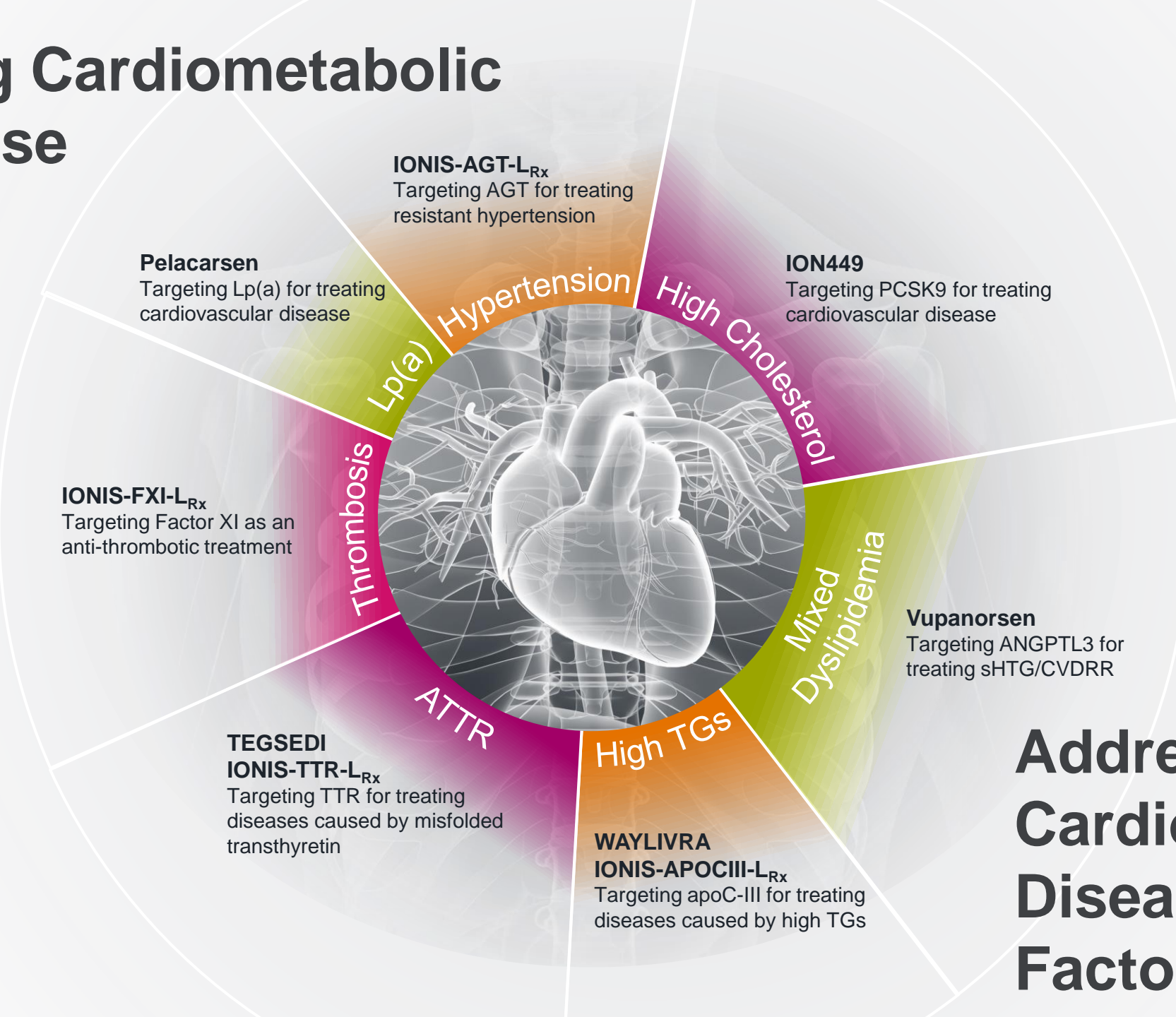
**Result = Medicines with
Transformational Potential**

Leading Neurology Franchise



Addressing All Major Brain Regions & CNS Cell Types

Leading Cardiometabolic Franchise



Addressing Major
Cardiovascular
Disease Risk
Factors

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



Cardiometabolic

Addressing major cardiovascular disease risk
factors

3 ongoing Phase 3 studies

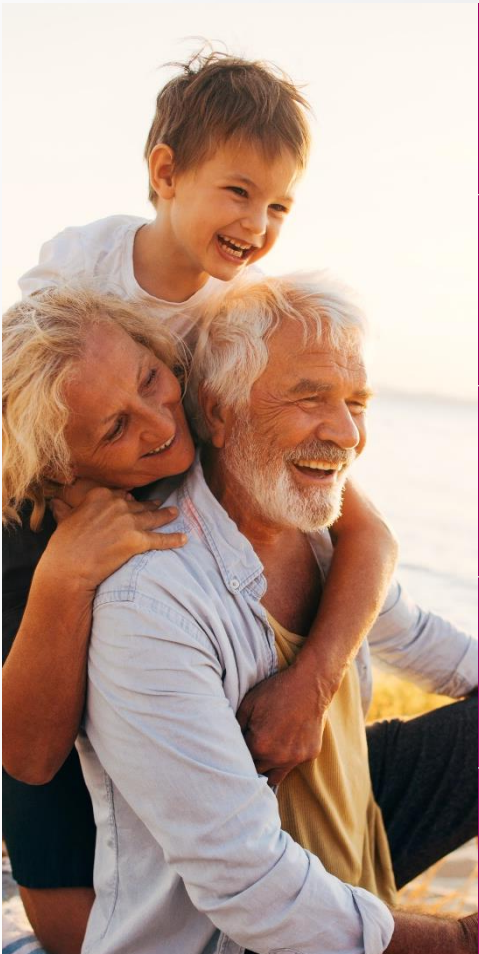
12 medicines in clinical development

7 wholly owned medicines



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	2021
	ION363	FUS-ALS Wholly owned	~ 350 patients in G7 countries	2024
	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

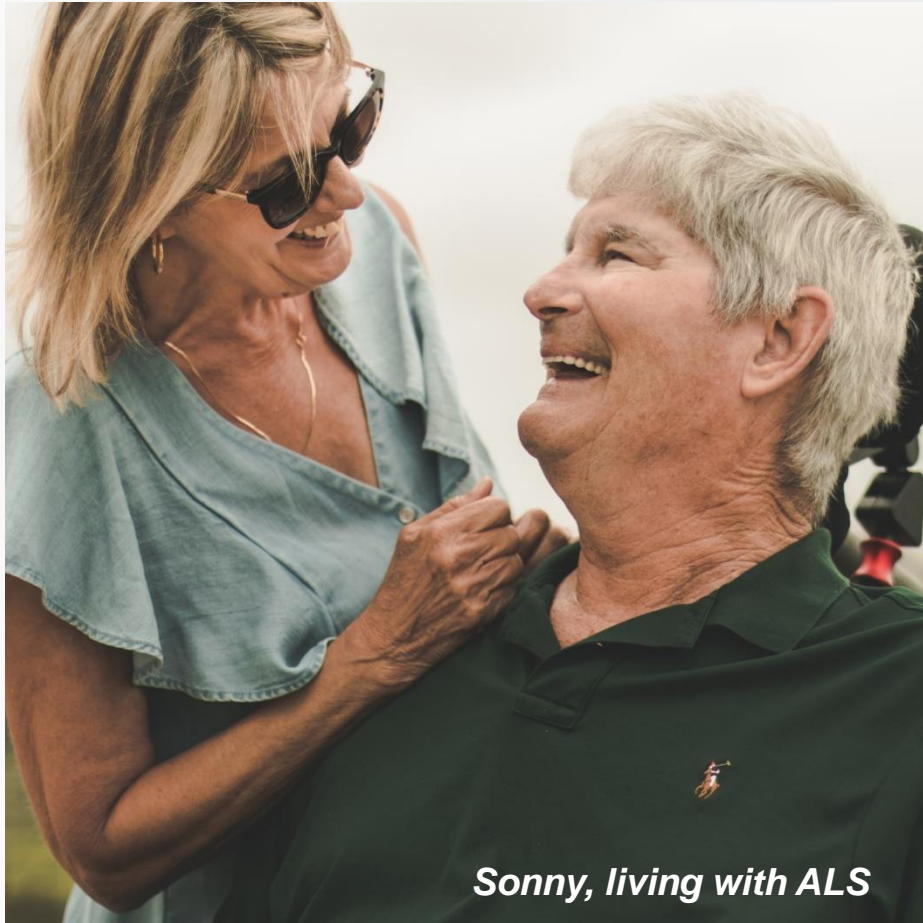


1. Market data on file. 2. Timing of partnered program catalysts based on partners' most recent publicly available disclosures

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

Amyotrophic Lateral Sclerosis

A fatal disease with a tremendous unmet medical need

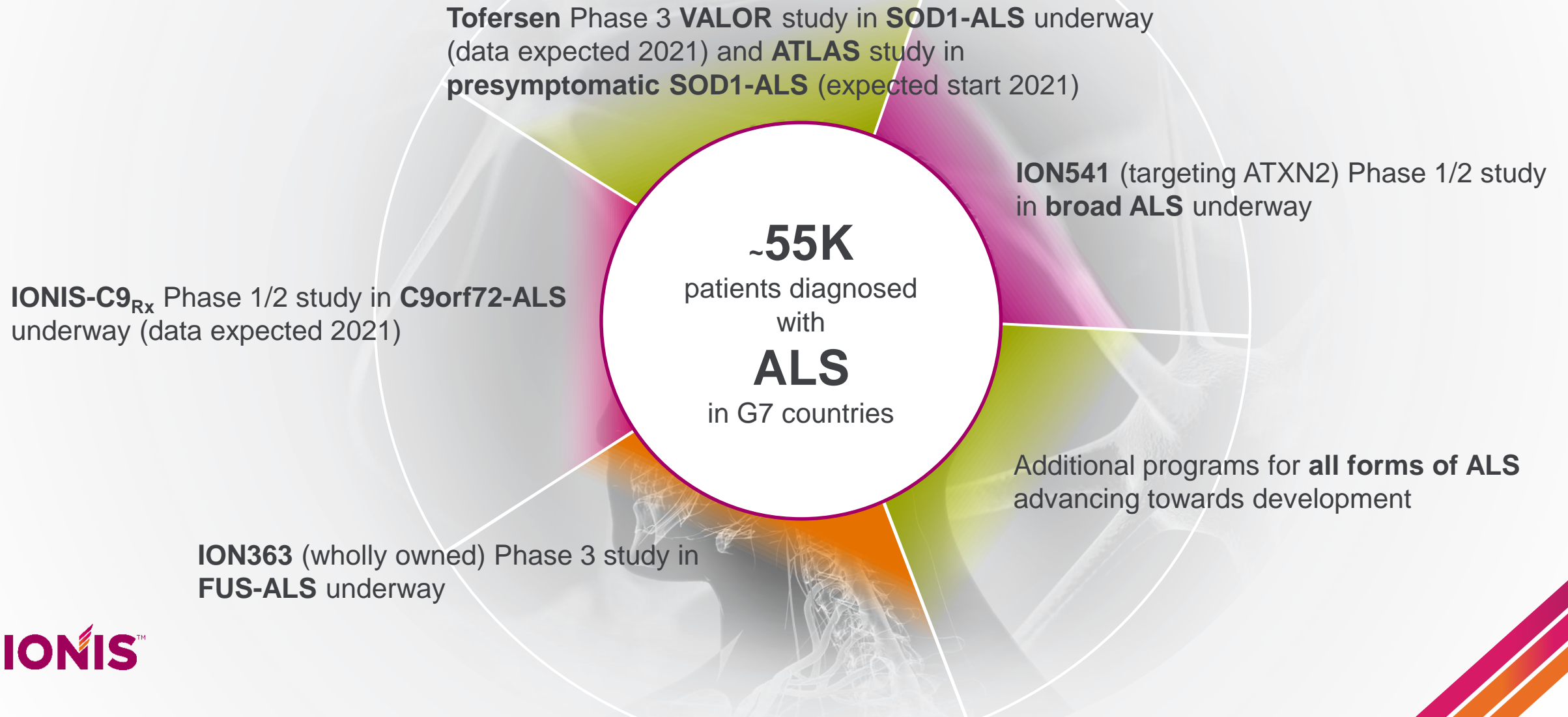


- **Fatal disease** characterized by **motor neuron** degeneration resulting in **paralysis** and **respiratory failure**
- **Rapidly progressing**, with average **survival of 3-5 years** from symptom onset

~ 55K patients in G7 countries¹

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

We Are Committed to Treating All Forms of ALS



Pioneering New Markets

Tofersen¹

*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
- **Targets the root cause** of SOD1-ALS, mutant superoxide dismutase type 1 protein
- Demonstrated **robust reductions** in SOD1 with trends in **slowing disease** progression²

ION363

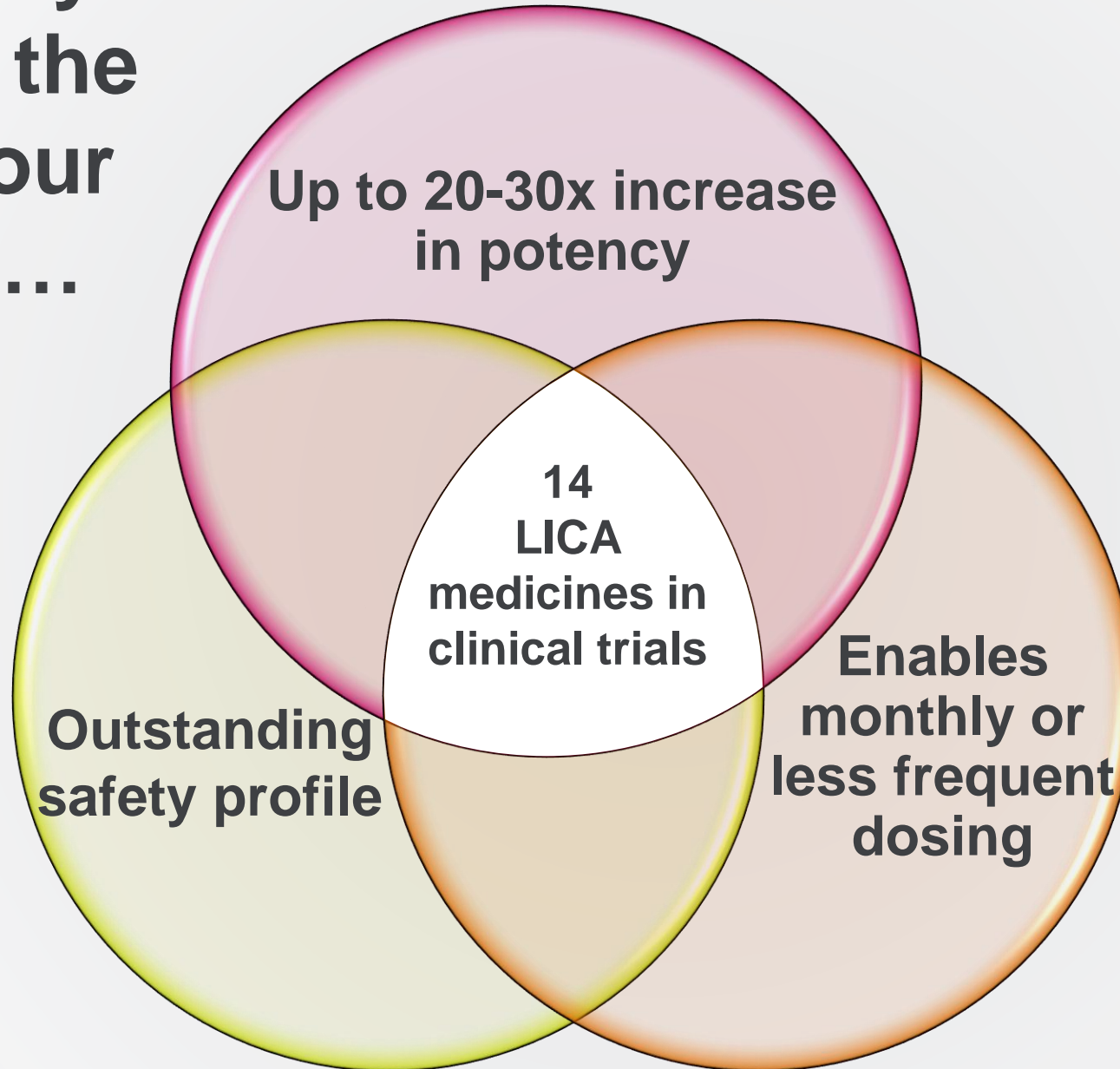
*First wholly owned medicine
in development for ALS*

**Projected Phase 3 Data
2024**

Pioneering New Markets

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

LICA Greatly Enhances the Profile of our Medicines...



...Continues to Deliver Value to Patients Today

TTR Amyloidosis (ATTR)

A devastating and fatal disease



Chuck, living with hATTR

- 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 polyneuropathy³ patients
 - 2-5 year life expectancy for cardiomyopathy⁴ patients

> 250K patients worldwide^{1,2}

~ 50K hereditary ATTR

> 200K wild type ATTR

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**
- **Targets the root cause** of TTR amyloidosis, mutant TTR protein
- **Robust target reductions** demonstrated in Phase 1 study

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**

~ 3-5K
patients globally¹

**Severe High
Triglycerides
(> 500 mg/dl)**

> 10M
patients globally²

**High
Triglycerides
(150 – 500 mg/dl)**

~ 50M
patients globally²

Changing Standards of Care

IONIS-APOCIII-L_{Rx}

*One product, multiple indications
targeting elevated triglycerides*

**Projected Phase 3 Data
2023**

- 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

Cardiovascular Disease Driven by Elevated Lipoprotein(a)

A major untreated cardiovascular disease risk factor

*Michael, living with
Lp(a)-driven CVD*



- 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 worldwide¹

Pioneering New Markets

Pelacarsen¹

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

**Projected Phase 3 Data
2024**

- 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}

Regular cadence of Phase 3 data...

 **SPINRAZA**[®]
(nusinersen) injection
12 mg/5 mL

 **Tegsedi**[®]
(inotersen) injection
284 mg/1.5 mL

 **waylivra**[®]
(volanesorsen) injection
265 mg/1.5 mL

Wholly owned Neuro

TTR-L_{Rx} (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

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

Partnered Cardio

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

Wholly owned Other

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

Partnered Other

HBV_{Rx} (Hep B)

...Positions Ionis
for 12+ marketed
products in 2026

Value-Driving Catalysts in 2021

DATA READOUTS ¹			H1	H2
PKK-L _{Rx}	Phase 2	Hereditary Angioedema	✓	
GHR-L _{Rx}	Phase 2	Acromegaly	●	
ENAC-2.5 _{Rx}	Phase 2	Cystic Fibrosis	●	
AGT-L _{Rx}	Phase 2	Hypertension	●	
MAPT _{Rx}	Phase 1/2	Alzheimer's Disease		●
Vupanorsen	Phase 2b	Dyslipidemia		●
C9 _{Rx}	Phase 1/2	C9-ALS		●
Tofersen	VALOR Phase 3	SOD1-ALS		●
KEY STUDY INITIATIONS ¹			H1	H2
SPINRAZA	RESPOND Phase 4	SMA, Suboptimal gene therapy response	✓	
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	Alexander disease	●	
ION224	Phase 2b	NASH	●	
Tofersen	ATLAS Phase 3	Presymptomatic SOD1-ALS		●
APOCIII-L _{Rx}	Phase 3	Second indication		●
ENAC-2.5 _{Rx}	Phase 2	Cystic Fibrosis with rare mutations		●

1. Timing of partnered program catalysts based on partners' most recent publicly available disclosures

Accelerating our Next Stage of Growth

Advancing
pipeline
&
technology

Pioneering new
markets
&
Changing
standards of care

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



Ionis: A Force for Life

