



Corporate Overview

October 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. 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](http://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 light-colored stone wall. The letters are bold and three-dimensional, with a slight shadow effect. The background of the slide is a photograph of a modern building entrance with a stone wall and large glass windows. In the foreground, there are two large grey planters filled with red flowers. The overall scene is bright and professional.

# H1 2021 Financial Results

**\$237 million in revenue**

Driven by commercial revenues

**\$81 million net loss\***

Reflects strategy to drive growth



**\$132 million**

In royalties to Ionis

**\$2.1 billion of cash**

Financial strength to achieve strategic priorities

# Revised 2021 Financial Guidance

Reflects Bicycle Therapeutics Transaction

**Revenue**

>\$600 million

Unchanged

**Revised  
Operating Expenses**

\$710-\$750 million\*

Prior: \$675-\$725 million

**Revised  
Net Loss**

<\$110 million\*

Prior: <\$75 million

## Reaffirming 2021 Revenue Guidance



\*Non-GAAP – please see Financial Impacts of Akcea Acquisition and Restructured Commercial Operations and reconciliation to GAAP in Q2'21 press release

# 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*

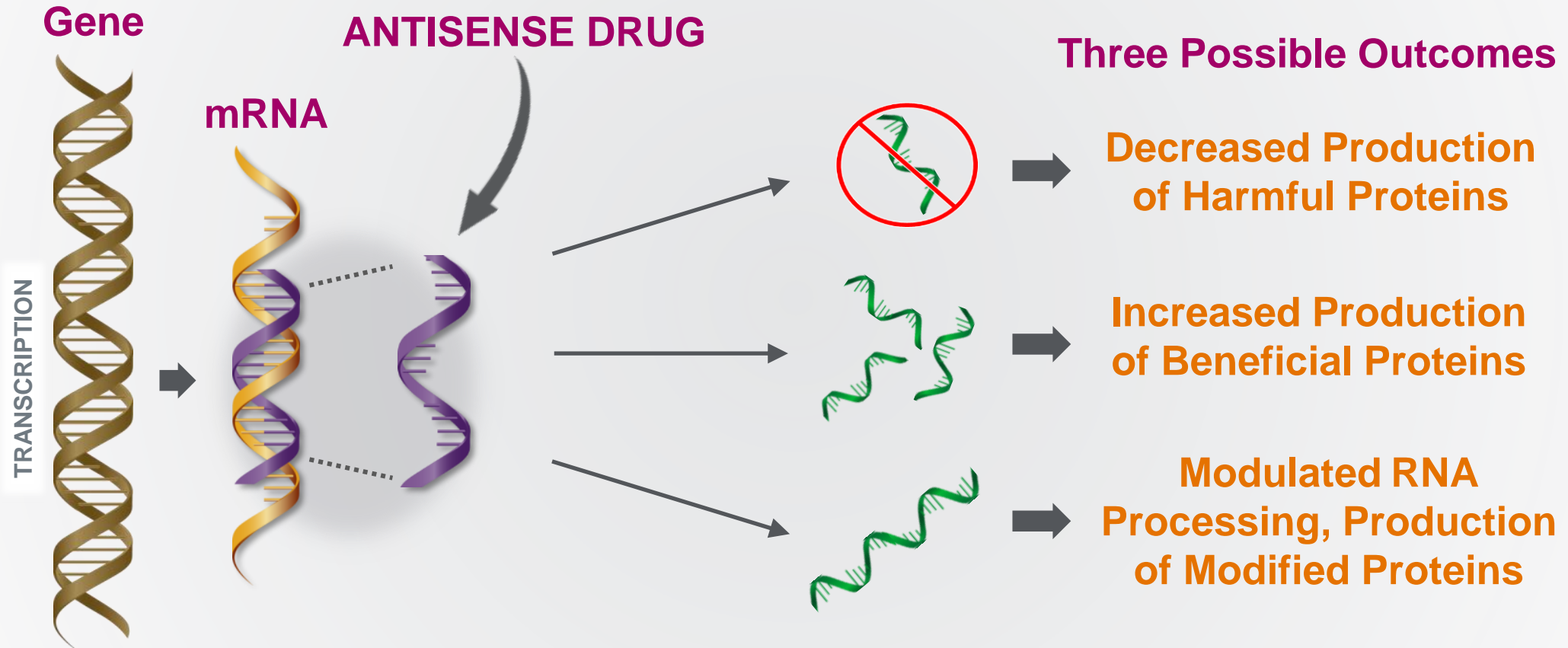
## Works by Many Routes of Administration

*SQ, IT, IV, inhaled, intra-ocular*

## Works Broadly Throughout the Body

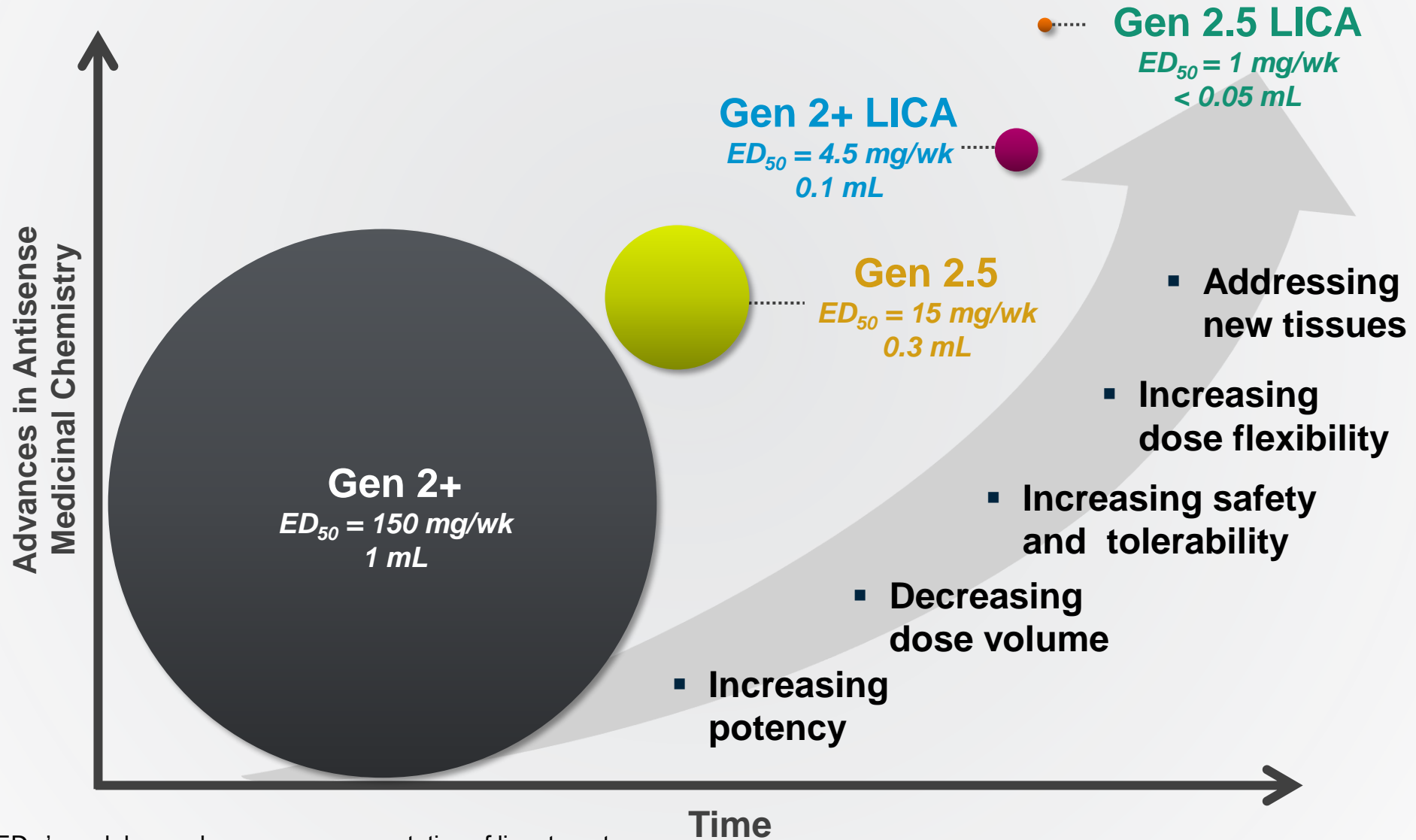
*Liver, brain, spinal cord, eye, kidney, pancreas, cancer cells, fat, lung*

# Antisense Technology: Versatility to Modulate All RNA



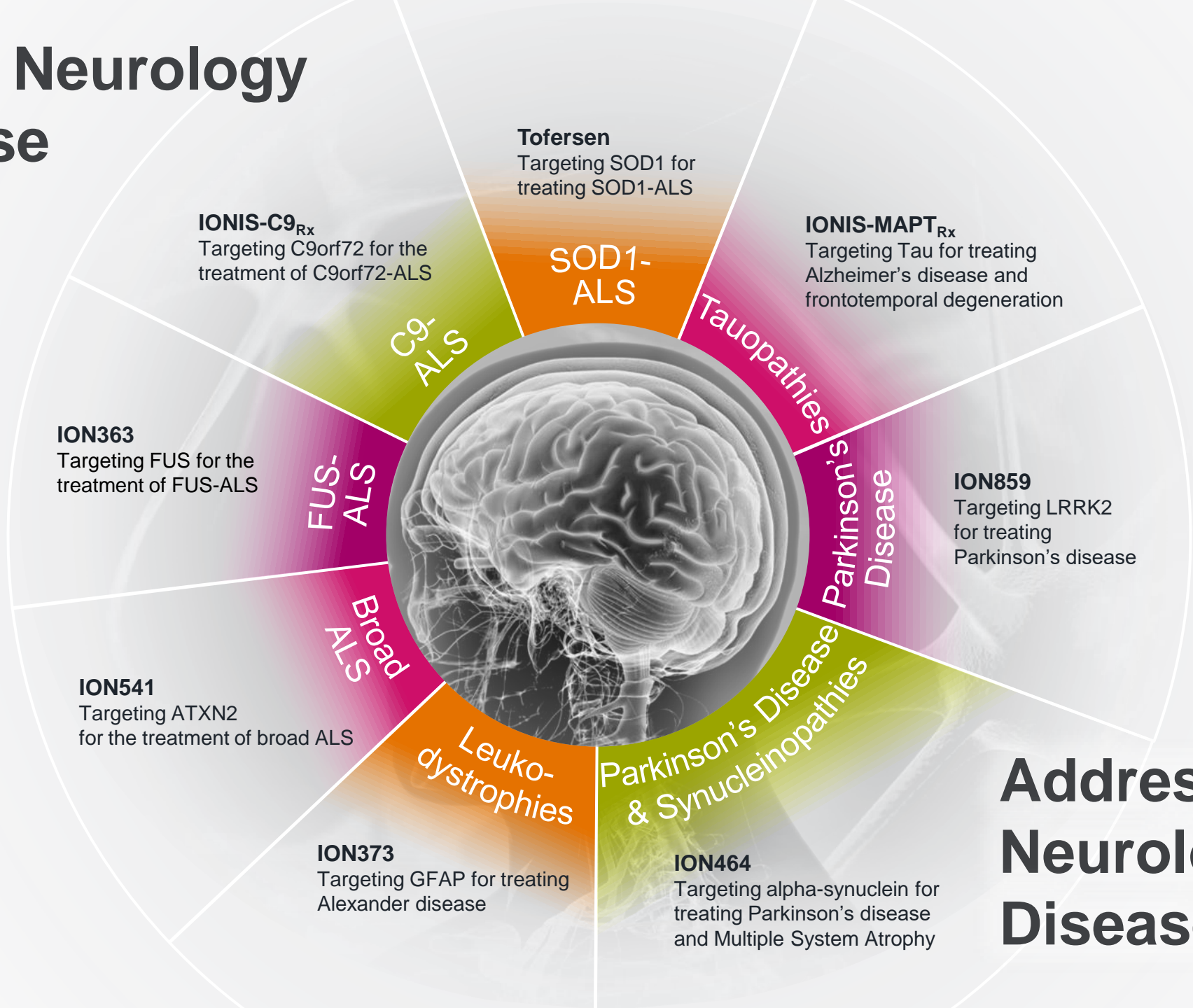
**Result = Medicines with  
Transformational Potential**

# Advances in Antisense Technology Have Substantially Improved the Utility of Antisense Drugs





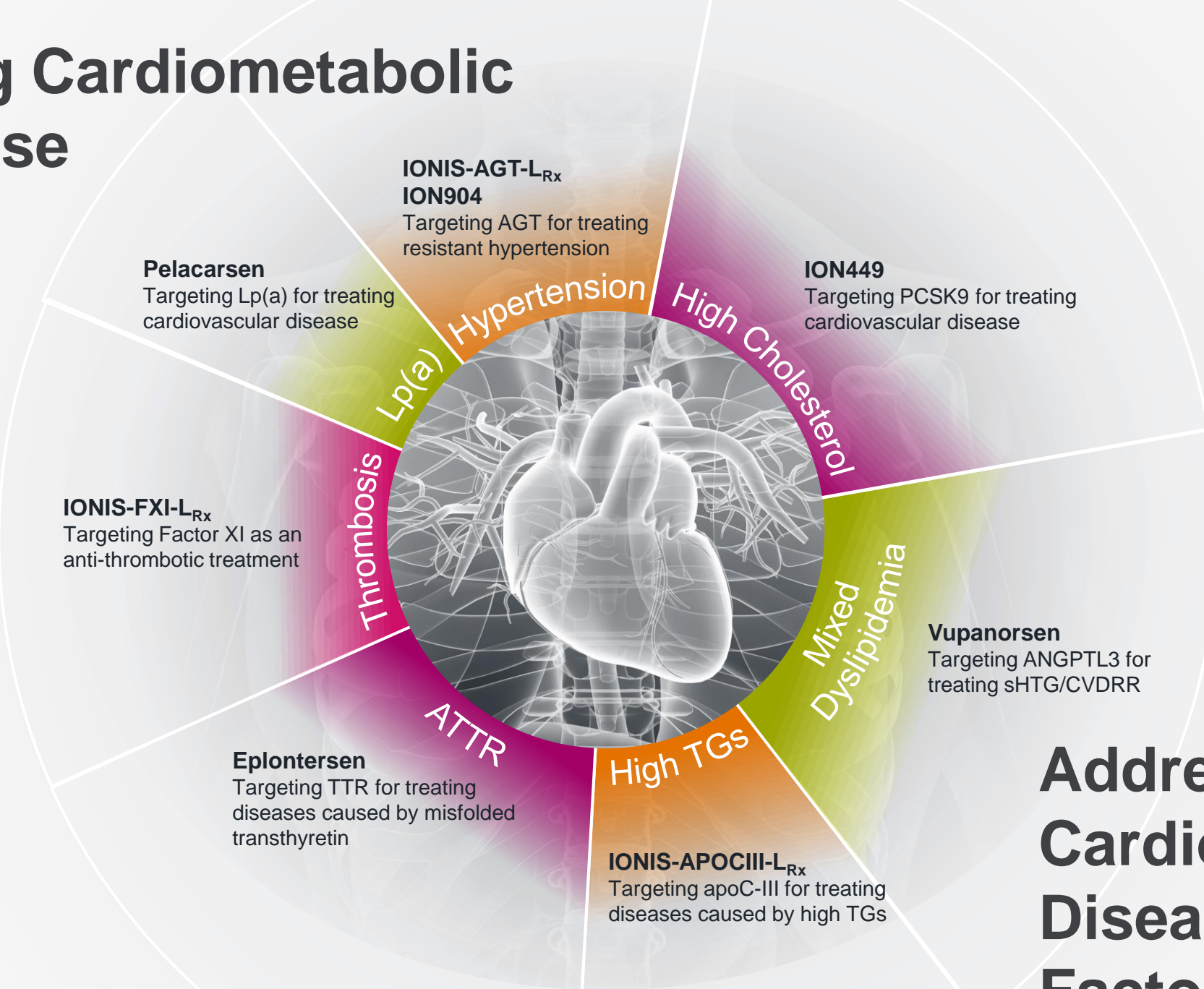
# Leading Neurology Franchise



## Addressing Major Neurological Diseases



# Leading Cardiometabolic Franchise



## Addressing Major Cardiovascular Disease Risk Factors



# Pioneering New Markets & Changing Standards of Care

## Advancing Phase 3 Pipeline



		Phase 3 Data <sup>1</sup>	Prevalence <sup>2</sup>
<b>Tofersen</b>	<b>SOD1-ALS</b> Biogen	2021	~ 1.4K patients in G7 countries
<b>Eplontersen</b>	<b>hATTR polyneuropathy</b> Wholly owned	2022	> 50K patients worldwide
<b>IONIS-APOCIII-L<sub>Rx</sub></b>	<b>FCS</b> Wholly owned	2023	~ 3-5K patients worldwide
<b>Pelacarsen</b>	<b>Lp(a) CVDRR</b> Novartis	2024	> 8M patients worldwide
<b>Eplontersen</b>	<b>ATTR cardiomyopathy</b> Wholly owned	2024	> 200K patients worldwide
<b>ION363</b>	<b>FUS-ALS</b> Wholly owned	2024	~ 350 patients in G7 countries
<b>IONIS-APOCIII-L<sub>Rx</sub></b>	<b>sHTG</b> Wholly owned	2024	> 3M patients U.S.



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

# Key 2021 Pipeline Events<sup>1</sup>

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

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



• Wholly owned • Partnered

# 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**



**IONIS™**

**A Force for Life**