Corporate Overview

August 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.

In this presentation, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries.

IONIS™

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

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

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

Revised 2021 Financial Guidance

Reflects Bicycle Therapeutics Transaction

Revenue	Revised Operating Expenses	Revised Net Loss
>$600 million	$710-$750 million*	<$110 million*
Unchanged	Prior: $675-$725 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

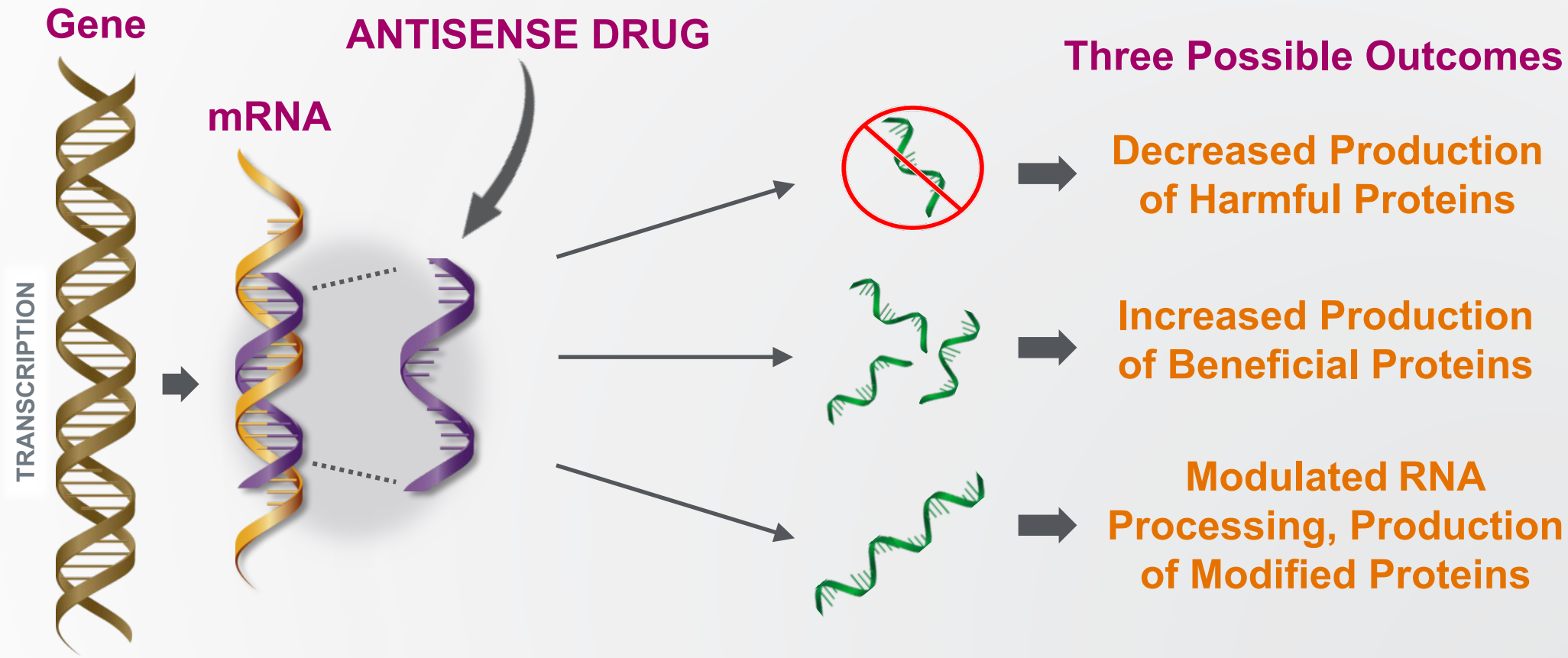
SQ, IT, IV, inhaled, intra-ocular

Works Broadly Throughout the Body

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

IONIS™

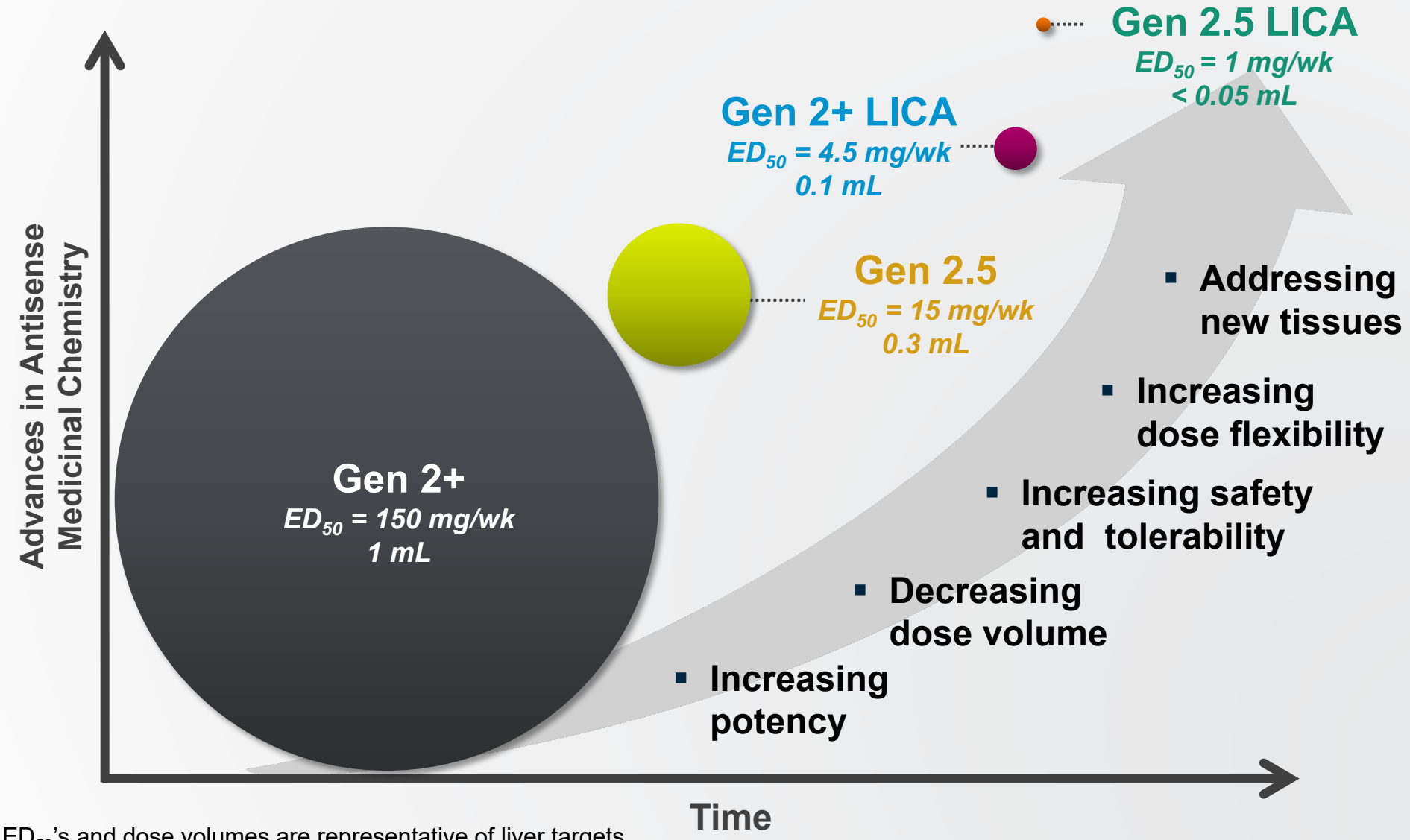
Antisense Technology: Versatility to Modulate All RNA



Result = Medicines with Transformational Potential

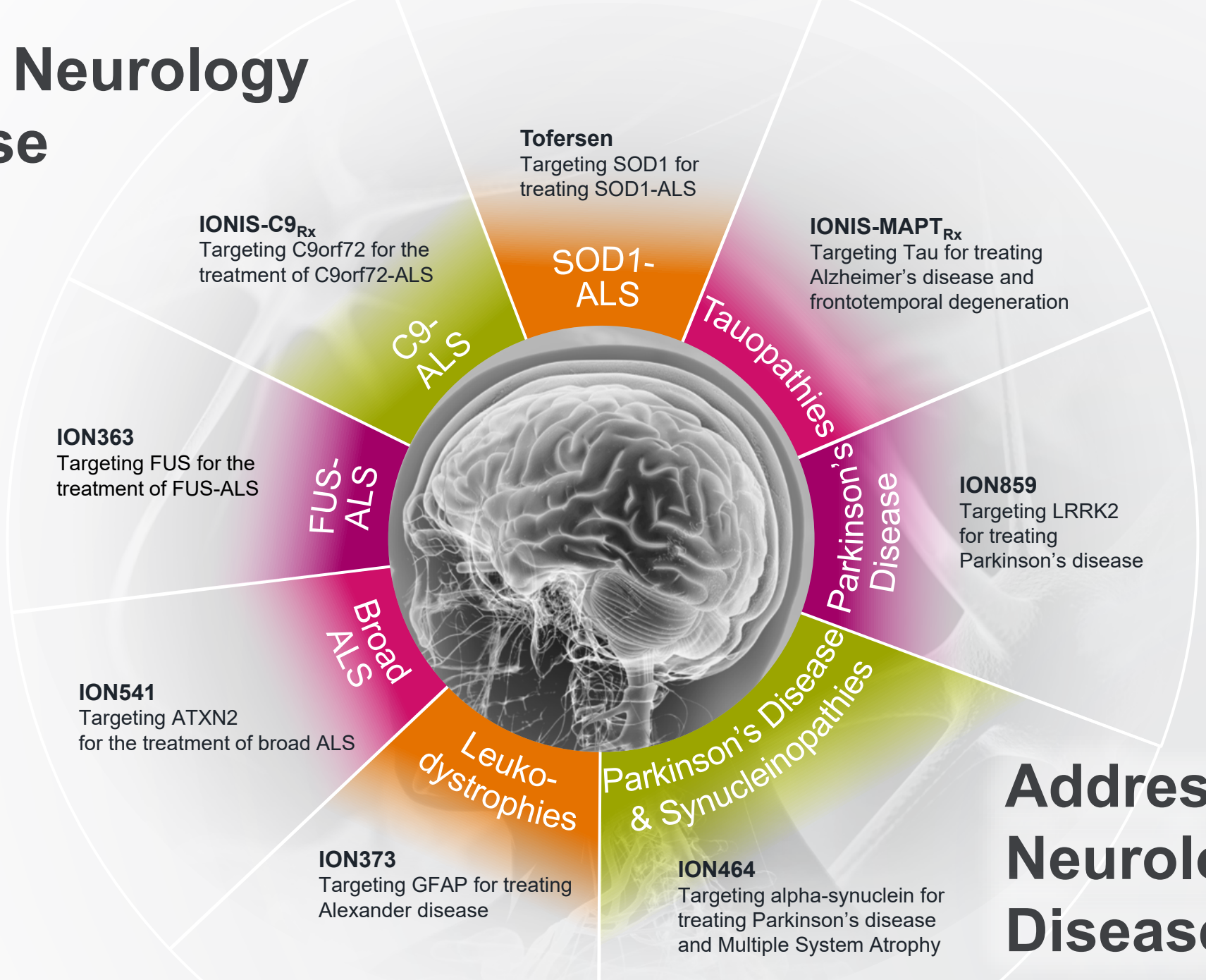
IONIS™

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



ED_{50}'s and dose volumes are representative of liver targets

Leading Neurology Franchise



Tofersen
Targeting SOD1 for treating SOD1-ALS

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

ION363
Targeting FUS for the treatment of FUS-ALS

ION541
Targeting ATXN2 for the treatment of broad ALS

ION373
Targeting GFAP for treating Alexander disease

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

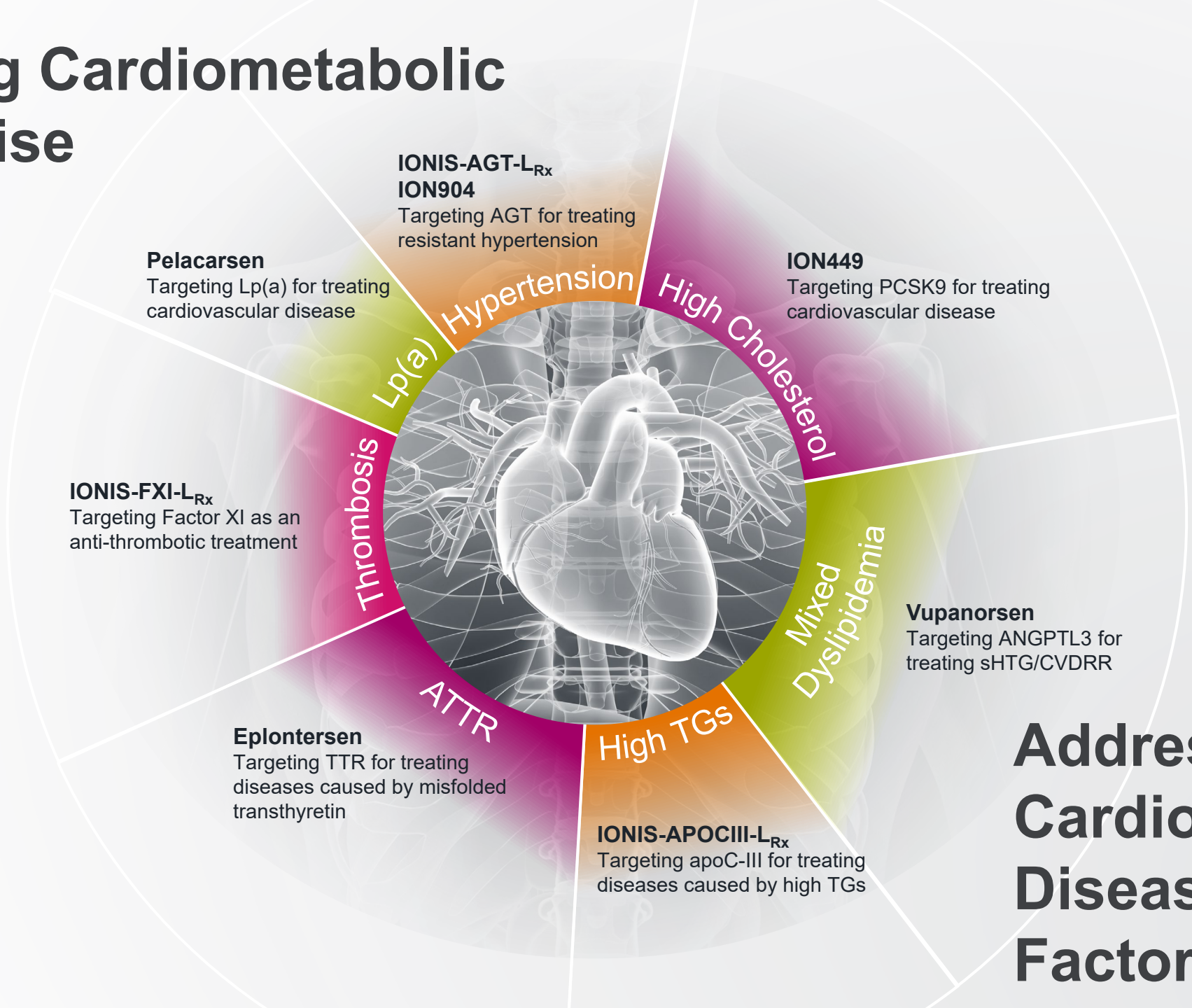
IONIS-MAPT$_{Rx}$
Targeting Tau for treating Alzheimer's disease and frontotemporal degeneration

ION859
Targeting LRRK2 for treating Parkinson's disease

Addressing Major Neurological Diseases

IONIS™

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

Eplontersen
Targeting TTR for treating diseases caused by misfolded transthyretin

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

Addressing Major Cardiovascular Disease Risk Factors

IONIS™

Pioneering New Markets & Changing Standards of Care

Advancing Phase 3 Pipeline

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

IONIS™

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[1]

DATA READOUTS			H1	H2
PKK-L_{Rx}	Phase 2	Hereditary Angioedema (top-line data)	✓	
AGT-L_{Rx}	Phase 2	Hypertension	✓	
Tominersen	Phase 3	Huntington's disease	✓	
ENAC-2.5$_{Rx}$	Phase 2	Cystic Fibrosis	✓	
MAPT$_{Rx}$	Phase 1/2	Alzheimer's Disease		✓
Tofersen	VALOR Phase 3	SOD1-ALS		●
Vupanorsen	Phase 2b	sHTG/CVD risk reduction		●
PKK-L_{Rx}	Phase 2	Hereditary Angioedema (full data)		●
GHR-L_{Rx}	Phase 2 + OLE	Acromegaly		●
KEY STUDY INITIATIONS			**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		●

● Wholly owned ● Partnered

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

IONIS™

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™


IONIS™
A Force for Life