



Corporate Overview

November 2020



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

Company Overview

Founded in 1989 to develop a new RNA-targeted drug discovery and development platform

- Located in Carlsbad, CA
- Approximately 500 employees including R&D, manufacturing and G&A

Pipeline of over 40 antisense medicines

Three approved medicines on the market today

Strong intellectual property position covering all aspects of our oligonucleotide therapeutics

2019 Revenue: >\$1BN in total revenue

2019 Cash: >\$2.5BN

Nasdaq: IONS

IONS

Positioned to Achieve our Next Stage of Growth



Moving forward as a **stronger** organization positioned for **accelerated growth**



Building **commercial capabilities** to maximize the value of the **Ionis-owned pipeline**



Advancing our **late- and mid- stage programs**, positioning us for the **next wave of commercial products**



Using our substantial **financial strength** to achieve our goal of **sustained growth**

Financial Strength to Achieve our Goals



Investing broadly in initiatives with the greatest
potential for value creation

Substantial Financial Strength

Continuing to invest in strategic priorities

**Financial position further strengthened through
Akcea acquisition**

**Strong financial results, including revenue growth,
resulting in operating and net income***

On track for revenue and earnings growth next quarter

On track to achieve our 2020 financial guidance

Q3 2020 Financial Performance

On track to achieve 2020 financial guidance

\$160 million in revenue

Driven by growth in commercial and R&D revenue

\$5 million of net income*

Continued financial strength



\$74 million

Continued blockbuster performance

\$2.3 billion of cash

Estimated \$1.8 billion of pro forma cash following Akcea acquisition

Maintaining our 2020 Financial Guidance

Revenue

>\$700 million

Operating Expenses

~\$650-\$690 million*

Meaningfully profitable*

Financial Strength to Support Business Strategy Evolution while Investing in the Pipeline and Technology

- Investing to achieve our goal of substantial growth
 - Advancing the medicines across the pipeline
 - Maximizing the value of all medicines in the pipeline
 - Building commercial capabilities for the Ionis-owned pipeline

Significant financial resources

to invest broadly in initiatives with the greatest potential for value creation

Our Pipeline

A Leading Pipeline in the Industry

Broad, Diverse and Expanding

3

Marketed products*

 **SPINRAZA**
(nusinersen) injection
12 mg/5 mL

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

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

6

Phase 3 studies by YE'20

Tominersen
Huntington's disease

Tofersen
SOD1 ALS

AKCEA-TTR-L_{Rx}
ATTR cardiomyopathy

Pelacarsen
Lp(a)-driven CVD

AKCEA-TTR-L_{Rx}
hATTR polyneuropathy

AKCEA-APOCIII-L_{Rx}[†]
FCS

- Potential for **>10 marketing applications** through 2025
- Achieving success across the **Phase 3, mid-stage and early pipeline**
- Dedicated employees committed to improving the lives of **patients in need**

Transformational Commercial Products for the Treatment of Patients with Rare, Fatal Diseases



SPINRAZA (nusinersen)

The global foundation-of-care for the treatment of spinal muscular atrophy patients of all ages¹



TEGSEDI (inotersen)

A transformative medicine for adult patients with hATTR polyneuropathy²

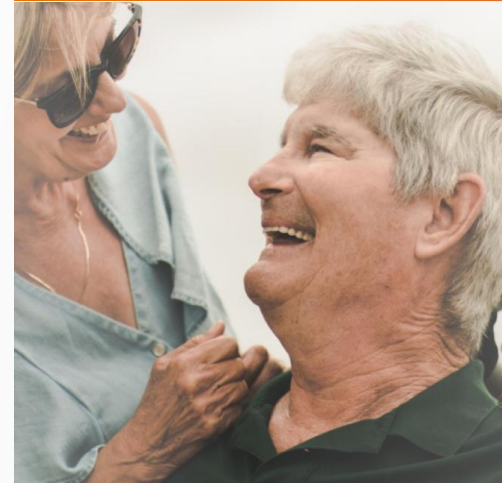


WAYLIVRA (volanesorsen)

A transformative medicine for patients with Familial Chylomicronemia Syndrome (FCS)³

Five Phase 3 Medicines for Patients with Significant Unmet Need

Significant Market Opportunities



Tofersen
SOD1-ALS
(Biogen)

- **First medicine** demonstrating SOD1 reductions and trends in **slowing disease progression**
- **~1,400 patients** in G7 countries¹



Tominersen
Huntington's disease
(Roche)

- Potentially **the first** disease-modifying medicine for the **treatment of HD**
- **~ 40K patients** in US²



TTR-L_{Rx}
TTR amyloidosis
(Ionis-owned)

- **Robust TTR reductions** with positive safety and tolerability profile demonstrated
- **>250K patients** worldwide



APOCIII-L_{Rx}
FCS, CVD
(Ionis-owned)

- Demonstrated **robust** dose-dependent **TG reductions**³
- **>8 million patients** worldwide



Pelacarsen
Lp(a)-driven CVD
(Novartis)

- Demonstrated **robust**, dose-dependent **Lp(a) reductions**
- **>8 million patients** worldwide

IONIS CLINICAL PIPELINE

	Medicines	Indication	Partner	Phase 1	Phase 2	Phase 3
CARDIO-RENAL	Pelacarsen	CVD	Novartis			
	AKCEA-TTR-L _{Rx}	ATTR cardiomyopathy	<i>Ionis</i>			
	Vupanorsen	CVD	Pfizer			
	AKCEA-APOCIII-L _{Rx}	CVD	<i>Ionis</i>			
	IONIS-FB-L _{Rx}	Nephropathy	Roche			
	IONIS-AGT-L _{Rx}	Treatment-resistant hypertension	<i>Ionis</i>			
	IONIS-FXI-L _{Rx}	Clotting disorders	Bayer			
	ION449	CVD	AstraZeneca			
	ION532	Kidney disease	AstraZeneca			
METABOLIC	IONIS-GHR-L _{Rx}	Acromegaly	<i>Ionis</i>			
	AKCEA-APOCIII-L _{Rx}	FCS	<i>Ionis</i>			
	IONIS-GCGR _{Rx}	Diabetes	<i>Ionis</i> [†]			
	ION839	NASH	AstraZeneca			
	ION224	NASH	<i>Ionis</i>			
NEUROLOGICAL	Tofersen	SOD1-ALS	Biogen			
	Tominersen	Huntington's disease	Roche			
	AKCEA-TTR-L _{Rx}	hATTR polyneuropathy	<i>Ionis</i>			
	IONIS-C9 _{Rx} [*]	C9-ALS	Biogen			
	IONIS-MAPT _{Rx} [*]	Alzheimer's disease	Biogen			
	ION859	Parkinson's disease	Biogen			
	IONIS-DNM2-2.5 _{Rx} [*]	Centronuclear myopathy	Dynacure			
	ION464	Multiple system atrophy & Parkinson's disease	Biogen			
	ION541 [*]	ALS	Biogen			
				*Currently in a Phase 1/2 study primarily to evaluate this medicine's safety profile. <i>Ionis</i> categorizes this medicine as Phase 2 because current evaluation is in patients, not healthy volunteers. This study may be categorized by partners or on regulatory sites, such as clinicaltrials.gov, as a Phase 1 study.		
				† Licensed to Suzhou-Ribo in China		

IONIS CLINICAL PIPELINE - CONTINUED

	MEDICINES	INDICATION	PARTNER	PHASE 1	PHASE 2	PHASE 3
INFECTIOUS	IONIS-HBV _{Rx}	Hepatitis B virus infection	GSK			
CANCER	IONIS-AR-2.5 _{Rx}	Prostate cancer	<i>Ionis</i> [†]			
	Danvatirsen	Cancer	<i>Ionis</i>			
	ION736*	Cancer	AstraZeneca			
OPHTHALMOLOGY	IONIS-FB-L _{Rx}	Complement mediated diseases	Roche			
	ION357*	Retinitis pigmentosa	ProQR			
PULMONOLOGY & ALLERGY	IONIS-ENAC-2.5 _{Rx}	Cystic fibrosis	<i>Ionis</i>			
	IONIS-PKK-L _{Rx}	Hereditary angioedema	<i>Ionis</i>			
HEME	IONIS-TMPRSS6-L _{Rx}	β-thalassemia	<i>Ionis</i>			
OTHER	ION253	GI Autoimmune disease	Janssen			

*Currently in a Phase 1/2 study primarily to evaluate this medicine’s safety profile. Ionis categorizes this medicine as Phase 2 because current evaluation is in patients, not healthy volunteers. This study may be categorized by partners or on regulatory sites, such as clinicaltrials.gov, as a Phase 1 study. † Licensed to Suzhou-Ribo in China

Potential for >10 Marketing Applications through 2025

Should result in a large number of new marketed products, driving significant revenue growth

			ION363 <i>FUS-ALS</i>	IONIS-FXI-L _{Rx} <i>ESRD</i>
			AKCEA-APOCIII-L _{Rx} <i>Severe hypertriglyceridemia</i>	ION541 <i>Sporadic ALS</i>
			ION373 <i>Alexander disease</i>	IONIS-TMPRSS6-L _{Rx} <i>β-thalassemia</i>
			IONIS-GHR-L _{Rx} <i>Acromegaly</i>	IONIS-HBV _{Rx} <i>Hepatitis B virus infection</i>
		AKCEA-APOCIII-L _{Rx} <i>FCS</i>	IONIS-C9 _{Rx} <i>C9-ALS</i>	Vupanorsen <i>Cardiovascular disease</i>
		Tominersen <i>Huntington's disease</i>	IONIS-PKK-L _{Rx} <i>Hereditary angioedema</i>	ION716 <i>Prion diseases</i>
Tofersen <i>SOD1-ALS</i>	AKCEA-TTR-L _{Rx} <i>hATTR polyneuropathy</i>		AKCEA-TTR-L _{Rx} <i>ATTR cardiomyopathy</i>	Pelacarsen <i>Cardiovascular disease</i>

2021

2025 and beyond

Technology



Advancing and broadening the reach of our technology

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, IM, enema, inhaled, intra-ocular, oral

Works Broadly Throughout the Body

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

Increasing our Leadership Position in RNA-targeted Therapeutics

INVESTMENTS

**New Chemistries
(e.g. LICA)**

New Routes of Delivery

Human Genomics Investments

New Technology Platforms

IMPACT

- Expanded target organs/cell types (e.g. cardiac, muscle, immune)
 - Enhanced delivery to CNS, kidney, lung, etc.
-
- Increased convenience (e.g. oral)
 - Expanded target organs/cell types (e.g. pulmonary, ocular)
-
- Novel target identification and improved discovery efficiency
 - Increased probability for clinical success with more defined patient pop.
-
- Expand reach of antisense with complementary technology
 - Invest in new drug discovery platforms

Conclusion



Ionis is stronger than ever

Today, Ionis is Stronger than Ever

3

Marketed products*



6

Phase 3 studies by YE'20

Tominersen
Huntington's disease

Tofersen
SOD1 ALS

AKCEA-TTR-L_{Rx}
ATTR cardiomyopathy

Pelacarsen
Lp(a)-driven CVD

AKCEA-TTR-L_{Rx}
hATTR polyneuropathy

AKCEA-APOCIII-L_{Rx}[†]
FCS

- Financially strong, on track to achieve **2020 financial guidance**
- Stronger, more efficient business following **Akcea acquisition**
- Potential for **>10 marketing applications** through 2025
- Achieving success across the **Phase 3, mid-stage and early pipeline**
- Dedicated employees committed to improving the lives of **patients in need**



*In 1Q 2021, Biogen plans to initiate the Phase 4 RESPOND study of SPINRAZA in patients with suboptimal response to gene therapy clinicaltrials.org/NCT04488133. Biogen is also conducting the DEVOTE study of a higher dose of SPINRAZA clinicaltrials.gov/NCT04089566. † P3 study start by YE 2020



IONIS™

IONIS: A FORCE FOR LIFE