



Corporate Overview
October 2020



Forward Looking Language Statement

This presentation includes forward-looking statements regarding our business, financial guidance and the therapeutic and commercial potential of TEGSEDI® (inotersen), WAYLIVRA® (volanesorsen) and Ionis' technologies and products in development, including Ionis' cardiovascular franchise. 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™ 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




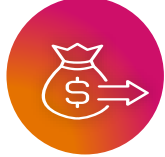
2019 Revenue: >\$1BN in total revenue

2019 Cash: >\$2.5BN

Nasdaq: IONS

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 shows a modern building entrance with large glass windows and a stone wall, with two large planters containing red flowers in the foreground.

Where we are Today

-  Advancing our **late-stage pipeline**, positioning us for the **next wave of commercial growth**
-  Building **commercial capabilities**, augmented by capabilities integrated from Akcea, to maximize the value of the growing and advancing **lonis-owned pipeline**
-  Investing in new **technologies** to **complement** our **drug discovery platform**
-  Using our substantial **financial strength** to achieve our goal of exponential growth

Financial Strength to Achieve our Goals



Investing broadly in initiatives with the greatest
potential for value creation

Delivering Strong 2020 Financial Results

1H 2020

\$279M

Revenue

\$174M

Commercial Revenues

Driven by SPINRAZA royalties of \$138M

\$2.3B

Cash

Enabling investment across the business to drive value creation

FY 2020

Reaffirmed
2020 financial guidance

>\$700M

Revenue

~\$650M-\$690M

Operating Expenses

Meaningfully Profitable

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

- Focused on investing broadly across the business
 - Maximizing the value of all medicines in the pipeline
 - Building commercial capabilities for the Ionis-owned pipeline
 - Integrating Akcea commercial infrastructure
 - Investing in complementary technologies

Significant financial resources

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

Our Pipeline



Broad, Diverse and Expanding

A Leading Pipeline in the Industry

Broad, Diverse and Expanding

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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

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Phase 3 studies by YE'20

Tominersen (IONIS-HTT_{Rx})
Huntington's disease

Tofersen (IONIS-SOD1_{Rx})
SOD1 ALS

AKCEA-TTR-L_{Rx}
ATTR cardiomyopathy

Pelacarsen (AKCEA-APO(a)-L_{Rx})
Lp(a)-driven CVD

AKCEA-TTR-L_{Rx}
hATTR polyneuropathy

AKCEA-APOCIII-L_{Rx}[†]
FCS

- **>40 medicines** advancing in preclinical through Phase 3 development
- Potential for **>10 marketing applications** through 2025
- Pipeline addresses **diverse therapeutic areas significantly underserved**
- 15 LICA medicines in development, many addressing **broad patient populations**
- Leading pipeline for **cardiovascular** and **neurological diseases**

IONIS[™]

*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

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

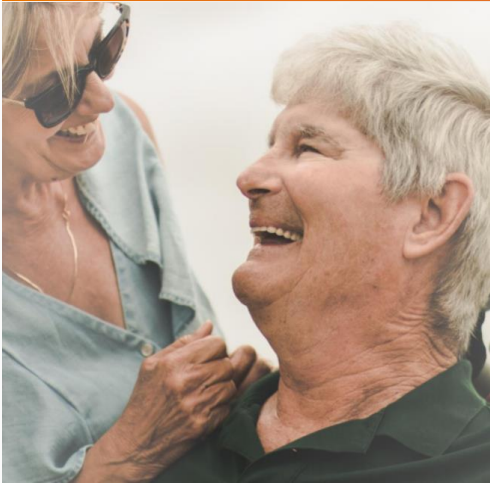


WAYLIVRA (volanesorsen)

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

Five Phase 3 Medicines with Data Expected through 2024

DATA EXPECTED 2021 - 2024



Tofersen
Familial ALS-SOD1
(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 / Akcea</i>			
	Vupanorsen	CVD	Pfizer			
	AKCEA-APOCIII-L _{Rx}	CVD	<i>Ionis / Akcea</i>			
	IONIS-FB-L _{Rx}	Nephropathy	Roche			
	IONIS-AGT-L _{Rx}	Treatment-resistant hypertension	<i>Ionis</i>			
	IONIS-FXI-L _{Rx}	Clotting disorders	Bayer			
	IONIS-AZ4-2.5-L _{Rx}	CVD	AstraZeneca			
	ION532	Kidney disease	AstraZeneca			
METABOLIC	IONIS-GHR-L _{Rx}	Acromegaly	<i>Ionis</i>			
	AKCEA-APOCIII-L _{Rx}	FCS	<i>Ionis / Akcea</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 / Akcea</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			
	ION541	Broad ALS	Biogen			
	ION464	Multiple system atrophy	Biogen			
						*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			

Potential for >10 Marketing Applications through 2025

Positioned for multiple 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 we are Stronger than Ever

- On track to achieve 2020 guidance and well-capitalized
- Executing on our ambitious agenda
- Building our commercial capabilities
- Dedicated employees committed to serving patients in need



IONIS™

IONIS: A FORCE FOR LIFE