Corporate Overview

August 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, including the business of Akcea Therapeutics, Inc., Ionis' majority owned affiliate. 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

Where We Are Today

Our leadership position in RNA-targeted therapeutics **continues to grow** as our technology advances

We have a **large, diverse, expanding, and mature pipeline** that is performing exceptionally well

The Ionis-owned pipeline is now a key priority and will expand substantially; in parallel, we are evolving our commercial strategy

We have the **financial strength** to continue advancing our technology and bring new medicines to the market

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

Positioned for >10 NDAs through 2025; potential for many new commercial medicines

IONIS

Outstanding Pipeline Performance

3

Commercial medicines*

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 (IONIS-HTT$_{Rx}$)
Huntington's disease

AKCEA-APO(a)-L$_{Rx}$ (TQJ230)
Lp(a)-driven CVD

Tofersen (IONIS-SOD1$_{Rx}$)
SOD1 ALS

AKCEA-TTR-L$_{Rx}$
hATTR polyneuropathy

AKCEA-TTR-L$_{Rx}$
ATTR Cardiomyopathy

ION363†
FUS-ALS

AKCEA-APOCIII-L$_{Rx}$†
FCS

≥10

Marketing applications expected through 2025 resulting in many new commercial medicines

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*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

Potential for >10 Marketing Applications through 2025

Anticipated marketing applications resulting in many new commercial medicines

Tofersen
(IONIS-SOD1$_{Rx}$ / BIIB067)
SOD1-ALS

AKCEA-APOCIII-L$_{Rx}$
FCS

Tominersen
(IONIS-HTT$_{Rx}$ / RG6042)
Huntington's disease

AKCEA-TTR-L$_{Rx}$
hATTR polyneuropathy

IONIS-C9$_{Rx}$
(BIIB078)
C9-ALS

IONIS-PKK-L$_{Rx}$
Hereditary angioedema

AKCEA-TTR-L$_{Rx}$
ATTR cardiomyopathy

ION363
FUS-ALS

AKCEA-APOCIII-L$_{Rx}$
Severe hypertriglyceridemia

ION373
Alexander disease

IONIS-GHR-L$_{Rx}$
Acromegaly

Vupanorsen
(AKCEA-ANGPTL3-L$_{Rx}$)
CV/metabolic disease

ION716
Prion diseases

AKCEA-APO(a)-L$_{Rx}$
(TQJ230)
Cardiovascular disease

ION541
Sporadic ALS

IONIS-TMPRSS6-L$_{Rx}$
β-thalassemia

IONIS-HBV$_{Rx}$ / IONIS-HBV-L$_{Rx}$
Hepatitis B virus infection

2021 — **2025** *and beyond*

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Three Transformational Medicines 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 ages[1]

TEGSEDI (inotersen)

A transformative medicine for adult patients with hATTR polyneuropathy[2]

WAYLIVRA (volanesorsen)

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

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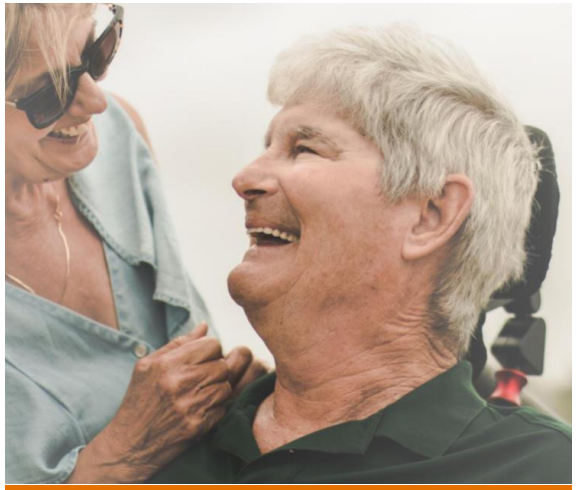
1. Visit www.spinraza.com for more information. 2. Visit www.tegsedi.com for more information. 3. Visit www.waylivra.eu for more information.

Four Medicines Advancing in Phase 3 Development

Tominersen
Huntington's disease
(Roche)

- Potentially **the first** disease-modifying medicine for the **treatment of HD**
- **~ 40K patients in US**[1]



Tofersen
Familial ALS-SOD1
(Biogen)

- **First medicine** demonstrating SOD1 reductions and trends in **slowing disease progression**
- **~1,400 patients** in G7 countries[2]

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

- Demonstrated **robust**, dose-dependent **Lp(a) reductions**[3]
- **>8 million people** worldwide

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

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

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1. Roche data on file. 2. Biogen data on file. G7 countries include the U.S., Germany, the U.K., France, Italy, Spain, and Japan. 3. In patients treated with the high dose in a Phase 2 study in patients with Lp(a)-driven cardiovascular disease, over 6 mos.. Some patients in the Phase 2 study were treated for up to 1 yr.

IONIS CLINICAL PIPELINE

	MEDICINES	INDICATION	PARTNER	PHASE 1	PHASE 2	PHASE 3
CARDIO-RENAL	**AKCEA–APO(a)-L_{Rx}**	CVD	Akcea / Novartis			
	AKCEA–TTR-L_{Rx}	ATTR cardiomyopathy	Akcea			
	Vupanorsen (AKCEA-ANGPTL3-L_{Rx})	CVD	Akcea / Pfizer			
	AKCEA-APOCIII-L_{Rx}	CVD	Akcea			
	IONIS-FB-L_{Rx}	Nephropathy	Roche			
	IONIS-AGT-L_{Rx}	Treatment-resistant hypertension	Ionis			
	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	Ionis			
	AKCEA-APOCIII-L_{Rx}	FCS	Akcea			
	IONIS-GCGR$_{Rx}$	Diabetes	Ionis*			
	ION839	NASH	AstraZeneca			
	ION224	NASH	Ionis			
NEUROLOGICAL	**Tofersen (IONIS-SOD1$_{Rx}$)**	ALS	Biogen			
	Tominersen (IONIS-HTT$_{Rx}$)	Huntington's disease	Roche			
	AKCEA-TTR-L_{Rx}	hATTR polyneuropathy	Akcea			
	IONIS-C9$_{Rx}$	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	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	Ionis*			
	Danvatirsen	Cancer	Ionis			
	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	Ionis			
	IONIS-PKK-L$_{Rx}$	Hereditary angioedema	Ionis			
HEME	**IONIS-TMPRSS6-L$_{Rx}$**	β-thalassemia	Ionis			
OTHER	**ION253**	GI Autoimmune disease	Janssen			

*Licensed to Suzhou-Ribo in China

IONIS-OWNED PIPELINE

	MEDICINES	INDICATION	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3
CARDIO-RENAL	**AKCEA–TTR-L_{Rx}**	ATTR cardiomyopathy				
	AKCEA-APOCIII-L_{Rx}	CVD				
	IONIS-AGT-L_{Rx}	Treatment-resistant hypertension				
	ION547	Cardiometabolic disease				
	ION904	Cardiometabolic disease				
METABOLIC	**IONIS-GHR-L_{Rx}**	Acromegaly				
	AKCEA-APOCIII-L_{Rx}	FCS				
	IONIS-GCGR$_{Rx}$*	Diabetes				
	ION224	NASH				
NEUROLOGICAL	**AKCEA-TTR-L_{Rx}**	hATTR polyneuropathy				
	ION363	ALS				
	ION716	Prion disease				
	ION283	Lafora disease				
	ION373	Alexander disease				
CANCER	**IONIS-AR-2.5$_{Rx}$***	Prostate Cancer				
	ION929	Cancer				
	ION251	Multiple myeloma				
	ION674*	Lymphomas				
PULMONARY & ALLERGY	**IONIS-ENAC-2.5$_{Rx}$**	Cystic fibrosis				
	IONIS-PKK-L_{Rx}	Hereditary angioedema				
	ION663	Pulmonary disease				
HEME	**IONIS-TMPRSS6-L_{Rx}**	β-thalassemia				

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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

IONIS

Ionis is Cracking the Code in Neurological Diseases

SPINRAZA
Spinal muscular atrophy

ATTR amyloidosis
TEGSEDI for hATTR polyneuropathy
AKCEA-TTR-L_{Rx} for all major forms

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

Alzheimer's disease
IONIS-$MAPT_{Rx}$

Amyotrophic lateral sclerosis
Tofersen (IONIS-$SOD1_{Rx}$), IONIS-$C9_{Rx}$,
ION541 (Sporadic), ION363 (FUS)

Parkinson's disease
ION859

Centronuclear myopathy
IONIS-$DNM2\text{-}2.5_{Rx}$

Alexander disease
ION373

Prion disease
ION716

Lafora disease
ION283

Multiple System Atrophy
ION464

Angelman syndrome
ION581

Severe epilepsies
Multiple Programs

Leukodystrophies

Myotonic dystrophy

Spinocerebellar ataxias

Spinal and Bulbar muscle atrophy

Charcot-Marie-Tooth

Multiple sclerosis

Severe pain

And many more in research stage

Investing in the Technology to Increase our Leadership Position

INVESTMENTS	IMPACT
Improved Drug Candidate Selection Processes	• Improved drug discovery efficiency • Improved overall drug performance
Human Genomics Investments	• Novel target identification • Improved drug discovery efficiency (e.g. patient selection, biomarkers, disease natural history) • Increased probability for clinical success
New Routes of Delivery	• Even more patient convenience (e.g. oral) • Opens up new target organs/cell types (e.g. pulmonary, ocular)
Medicinal Chemistry (e.g. LICA)	• Even more patient convenience (e.g. monthly, quarterly dosing) • Opens up new target organs/cell types (e.g. cardiac, muscle, immune) • Enhanced overall safety and efficacy performance

Q2 2020 Financial Performance

On track to achieve 2020 financial guidance

$146 million in revenue

Driven by commercial revenue growth

$8 million of net income*

An increase compared to Q1

SPINRAZA® (nusinersen) injection 12 mg/5 mL

$72 million**

Continued blockbuster performance

>$2.3 billion of cash

Substantial financial resources to execute on ambitious agenda

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*Non-GAAP – please see reconciliation to GAAP in Q2'20 press release; **SPINRAZA royalty tier resets at the beginning of each year

Maintaining our 2020 Financial Guidance

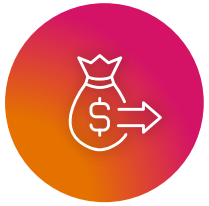
Revenue	Operating Expenses
>$700 million	~$650-$690 million*

Meaningfully profitable*

*Non-GAAP – please see reconciliation to GAAP in Q2'20 press release

Ionis Continues to Lead the Way in RNA-targeted Therapeutics

Growing leadership position



Strong financial position

Rapidly advancing pipeline

Rapidly advancing technology

Expanding Ionis-owned pipeline & evolving commercial strategy

Incredible momentum supporting even greater productivity

IONIS™

A Force for Life