



J.P. Morgan Healthcare Conference

**Presented by Brett P. Monia, Ph.D.
Chief Executive Officer**

January 15, 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, 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, 2018, and its 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 Pharmaceuticals™ is a trademark of Ionis Pharmaceuticals, Inc. Akcea Therapeutics™ is a trademark of Akcea Therapeutics, Inc. TEGSEDI™ is a trademark of Akcea Therapeutics, Inc. WAYLIVRA™ is a trademark of Akcea Therapeutics, Inc. SPINRAZA® is a registered trademark of Biogen.





A commitment
to **science**,
to **medicine**
and to **patients**



Vision

To be the **most successful biotech ever** by changing the world for patients with severe diseases.

- Focus on **innovation and scientific excellence**
- Leverage our **financial strength**
- **Expand** the scope of **antisense technology**
- Substantially and consistently **increase our delivery of transformational medicines** to patients in great need
- Increase and diversify **investments in new technologies**
- **Prioritize growth and our commercialization strategy** for the Ionis-owned pipeline



Where We Are Today



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



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

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The Ionis-owned pipeline is now a key priority, will expand substantially, and investments are underway to develop commercial capabilities

Where We Are Today



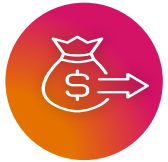
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We have a **large, diverse, expanding, and mature pipeline** that is performing exceptionally well



The Ionis-owned pipeline is now a key priority, will expand substantially, and investments are underway to develop commercial capabilities



We have the **financial strength** to continue advancing our technology and deliver on our pipeline

Continued Financial Strength

We expect to meet or exceed our 2019 guidance

Total Revenue

~\$1 billion

Operating Income

>\$375 million*

Net Income

>\$300 million*

Cash Balance

~\$2.2 billion



*Non-GAAP – please see reconciliation to GAAP in Q319 press release; R&D expense and SG&A expense guidance unchanged

Outstanding Pipeline Performance

Delivering value today and the near-term

3

Commercial medicines

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

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

 **waylivra**[®]
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Phase 3 programs

IONIS-HTT_{Rx} (RG6042)
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

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New **Phase 2 starts** expected in 2020

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New **Phase 2 starts** expected in 2020

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New **Phase 3** starts expected in 2020-2021

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New **Phase 2 starts** expected in 2020

≥5

New **Phase 3** starts expected in 2020-2021

≥10

NDA submissions expected by 2025

IONIS CLINICAL PIPELINE

	MEDICINES	INDICATION	PARTNER	PHASE 1	PHASE 2	PHASE 3
NEUROLOGICAL	IONIS-HTT _{Rx} (RG6042)	Huntington's disease	Roche			
	Tofersen (IONIS-SOD1 _{Rx})	ALS	Biogen			
	IONIS-MAPT _{Rx}	Alzheimer's disease	Biogen			
	IONIS-C9 _{Rx}	ALS	Biogen			
	ION859	Parkinson's disease (Target: LRRK2)	Biogen			
	IONIS-DNM2-2.5 _{Rx}	Centronuclear myopathy	Dynacure			
CARDIOMETABOLIC & RENAL	AKCEA-APO(a)-L _{Rx}	CVD	Akcea / Novartis			
	AKCEA-TTR-L _{Rx}	ATTR cardiomyopathy	Akcea			
	AKCEA-ANGPTL3-L _{Rx}	NAFLD / metabolic disease / CVD	Akcea / Pfizer			
	AKCEA-APOCIII-L _{Rx}	CVD	Akcea			
	IONIS-GCGR _{Rx}	Diabetes	Ionis / Suzhou-Ribo*			
	IONIS-AGT-L _{Rx}	Treatment-resistant hypertension	Ionis			
	IONIS-AZ4-2.5-L _{Rx}	CVD	AstraZeneca			
	IONIS-FXI-L _{Rx}	Clotting disorders	Bayer			
	ION839	NASH	AstraZeneca			
RARE	AKCEA-TTR-L _{Rx}	hATTR polyneuropathy	Akcea			
	AKCEA-APOCIII-L _{Rx}	FCS	Akcea			
	IONIS-GHR-L _{Rx}	Acromegaly	Ionis			
	IONIS-PKK-L _{Rx}	Hereditary angioedema	Ionis			
	IONIS-TMPRSS6-L _{Rx}	β-thalassemia	Ionis			
	IONIS-ENAC-2.5 _{Rx}	Cystic fibrosis	Ionis			
	ION357	Retinitis pigmentosa (Target: RHO)	ProQR			
CANCER	IONIS-AR-2.5 _{Rx}	Prostate cancer	Ionis / Suzhou-Ribo*			
	Danvatirsen	Cancer	AstraZeneca			
OTHER	IONIS-HBV _{Rx} /HBV-L _{Rx}	Hepatitis B virus infection	GSK			
	IONIS-FB-L _{Rx}	Complement mediated diseases	Roche			

*China rights only

Ionis Pre-clinical Pipeline Continues to Grow

	MEDICINES	INDICATION	PARTNER
NEUROLOGICAL	ION581	Angelman syndrome	Biogen
	ION260	Neurodegenerative disease	Biogen
	ION283	Lafora disease	Ionis
	ION373	Alexander disease	Ionis
	ION541	Neurodegenerative disease	Biogen
	ION464	Multiple system atrophy	Biogen
	ION716	Prion disease	Ionis
RARE	ION663	Pulmonary disease	Ionis
CARDIOMETABOLIC & RENAL	ION547	Cardiometabolic disease	Ionis
	ION904	Cardiometabolic disease	Ionis
	ION224	NASH	Ionis
	ION532	Chronic kidney disease	AstraZeneca

	MEDICINES	INDICATION	PARTNER
CANCER	ION929	Cancer	Ionis / Suzhou-Ribo*
	ION537	Cancer	MD Anderson
	ION251	Multiple myeloma	Ionis
	ION674	Lymphomas	Ionis / Suzhou-Ribo*
	ION736	Cancer	AstraZeneca
OTHER	ION253	GI Autoimmune disease	Janssen

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10
New **medicines** entered
pipeline in **2019**

5
New **Phase 1** starts
in **2019**

≥5
New **medicines** to enter
pipeline in **2020**

≥5
New **Phase 1** starts
in **2020**

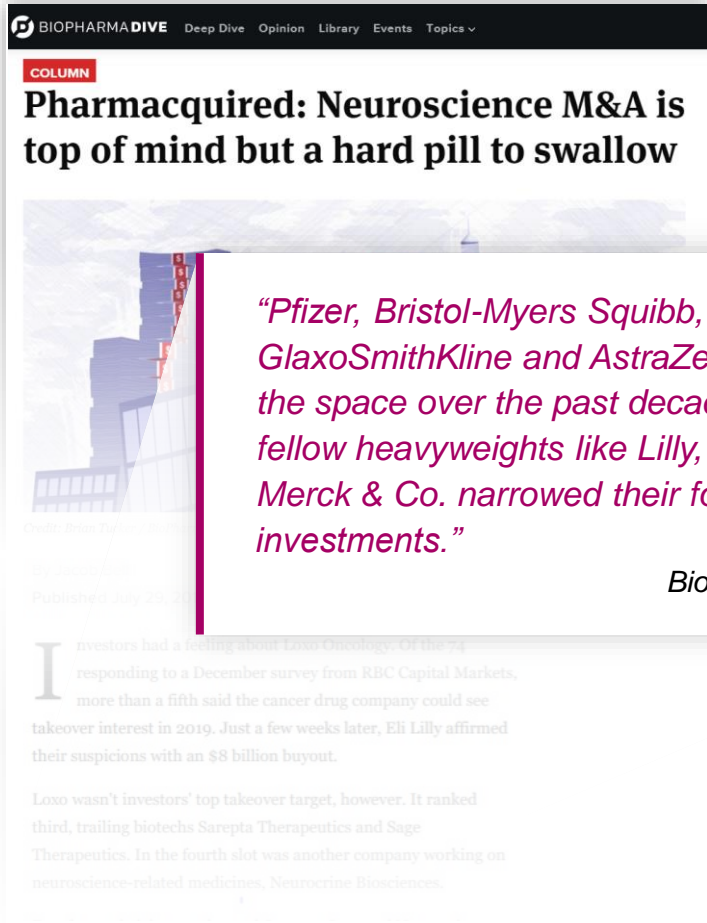
The Ionis Neurological Disease Pipeline

CRACKING THE CODE



Cracking the Code on Neurological Diseases

Big pharma has either exited or been forced to acquire



“Pfizer, Bristol-Myers Squibb, GlaxoSmithKline and AstraZeneca all exited the space over the past decade, while fellow heavyweights like Lilly, Sanofi and Merck & Co. narrowed their focus and investments.”

BiopharmaDive 7/19

Cracking the Code on Neurological Diseases

Big pharma has either exited or been forced to acquire

BIOPHARMA DIVE Deep Dive Opinion Library Events Topics

COLUMN

Pharmacquired: Neuroscience M&A is top of mind but a hard pill to swallow

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BiopharmaDive 7/19

Ionis is Delivering



Validated platform

- Proof of mechanism
- Proof of efficacy
- Proof of safety
- Commercial success



A rapidly expanding premier pipeline tackling the most severe diseases



Continued technology advancement

- Greater efficacy
- Less frequent dosing
- Systemic applications (e.g. neuromuscular)

Ionis is Cracking the Code in Neurological Diseases

SPINRAZA

(Spinal muscular atrophy)

ATTR amyloidosis

*TEGSEDI for hATTR polyneuropathy
AKCEA-TTR-L_{Rx} for all forms*

Huntington's disease

IONIS-HTT_{Rx} (RG6042)

Dementia (Alzheimer's and FTD)

IONIS-MAPT_{Rx} (BIIB080)

Amyotrophic lateral sclerosis

*Tofersen (IONIS-SOD1_{Rx})
IONIS-C9_{Rx} (BIIB078)*

Centronuclear myopathy

IONIS-DNM2-2.5_{Rx}

Severe epilepsies

Multiple Programs

Leukodystrophies

Prion disease

Lafora disease

Spinal and Bulbar muscle atrophy

Charcot-Marie-Tooth

Parkinson's disease

Myotonic dystrophy

Spinocerebellar ataxias

Angelman syndrome

Multiple sclerosis

Severe pain

***And many more in
research stage***

Ionis is Cracking the Code in Neurological Diseases

Ionis-owned neurological assets

SPINRAZA

(Spinal muscular atrophy)

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Charcot-Marie-Tooth

Parkinson's disease

Myotonic dystrophy

Spinocerebellar ataxias

Angelman syndrome


Multiple sclerosis

Severe pain

**Substantial growth
expected with many
more in research stage**

Broader Ionis-owned Pipeline

	Medicines	Indication	Preclinical	Phase 1	Phase 2	Phase 3
Rare	AKCEA-APOCIII-L _{Rx}	FCS				
	IONIS-GHR-L _{Rx}	Acromegaly				
	IONIS-PKK-L _{Rx}	Hereditary angioedema				
	IONIS-TMPRSS6-L _{Rx}	β-thalassemia				
	IONIS-ENAC-2.5 _{Rx}	Cystic fibrosis				
	ION663	Pulmonary disease				
Cardiometabolic & Renal	AKCEA-APOCIII-L _{Rx}	Cardiometabolic disease				
	IONIS-AGT-L _{Rx}	Resistant hypertension				
	ION547	Cardiometabolic disease				
	ION904	Cardiometabolic disease				
	ION224	NASH				
Cancer	IONIS-AR-2.5 _{Rx}	Prostate cancer				
	ION929	Cancer				
	ION251	Multiple myeloma				
	ION674	Lymphomas				



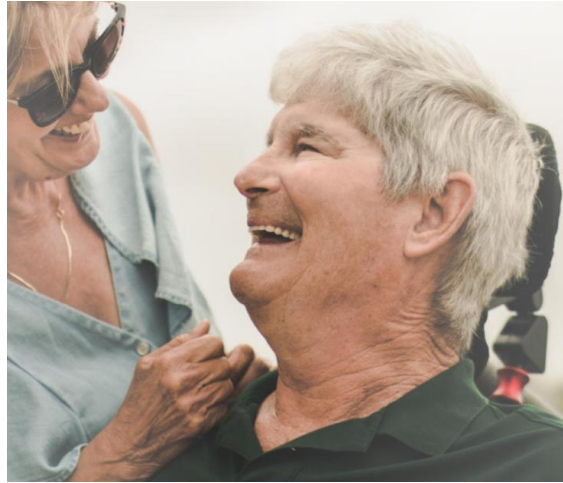
Near and Mid-term Commercial Opportunities Continue on Track

Four Potentially Transformative Medicines Advancing in Phase 3 Studies



IONIS-HTT_{Rx}
Huntington's disease
(Roche - RG6042)

- Potentially **the first** disease-modifying medicine for the **treatment of HD**
- ~ 60K patients in US and EU



Tofersen
Familial ALS-SOD1
(Biogen)

- **First medicine** demonstrating SOD1 reductions and trends in **slowing disease progression**
- >1,000 patients worldwide



AKCEA-APO(a)-L_{Rx}
Lp(a)-driven CVD
(Novartis - TQJ230)

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



AKCEA-TTR-L_{Rx}
TTR amyloidosis

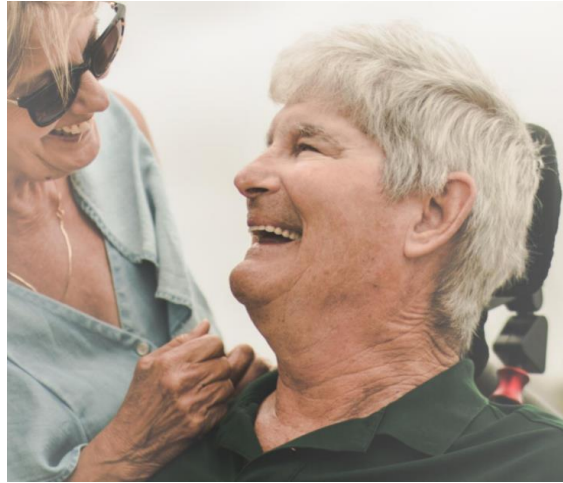
- **Robust TTR reductions** with positive safety and tolerability profile demonstrated
- >200K patients worldwide

Four Potentially Transformative Medicines Advancing in Phase 3 Studies



IONIS-HTT_{Rx}
Huntington's disease
(Roche - RG6042)

- Potentially **the first** disease-modifying medicine for the **treatment of HD**
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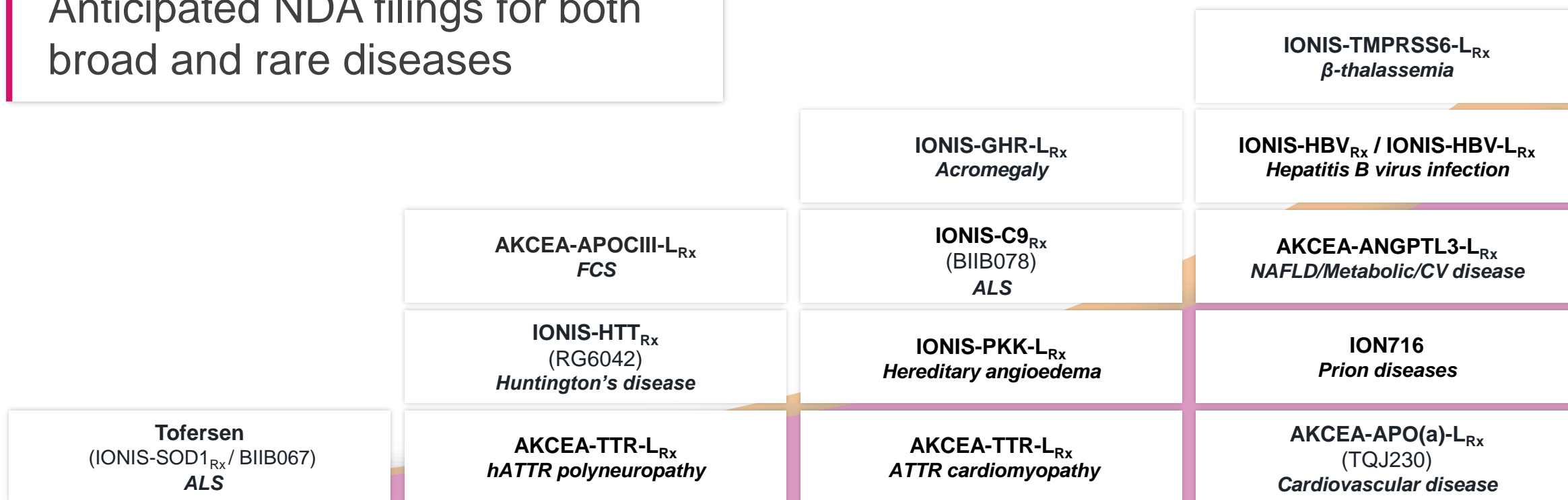


AKCEA-TTR-L_{Rx}
TTR amyloidosis

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

Potential Next Wave of Commercial Products

Anticipated NDA filings for both broad and rare diseases



2021

2025 and beyond

Growing Opportunities Driven by Advances in Technology



Increasing our Leadership Position Through Continued Technology Advancements

INVESTMENTS

Improved Drug Candidate
Selection Processes

IMPACT

- Improved drug discovery efficiency
- Improved overall drug performance

Increasing our Leadership Position Through Continued Technology Advancements

INVESTMENTS

**Improved Drug Candidate
Selection Processes**

Human Genomics Investments

IMPACT

- Improved drug discovery efficiency
 - Improved overall drug performance
-
- Novel target identification
 - Improved drug discovery efficiency (e.g. patient selection, biomarkers, disease natural history)
 - Increased probability for clinical success

Increasing our Leadership Position Through Continued Technology Advancements

INVESTMENTS

Improved Drug Candidate Selection Processes

Human Genomics Investments

New Routes of Delivery

IMPACT

- Improved drug discovery efficiency
 - Improved overall drug performance
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- Even more patient convenience (e.g. oral)
 - Opens up new target organs/cell types (e.g. pulmonary, ocular)
-

Increasing our Leadership Position Through Continued Technology Advancements

INVESTMENTS

Improved Drug Candidate Selection Processes

Human Genomics Investments

New Routes of Delivery

Medicinal Chemistry
(e.g. LICA)

IMPACT

- Improved drug discovery efficiency
 - Improved overall drug performance
-
- Novel target identification
 - Improved drug discovery efficiency (e.g. patient selection, biomarkers, disease natural history)
 - Increased probability for clinical success
-
- Even more patient convenience (e.g. oral)
 - Opens up new target organs/cell types (e.g. pulmonary, ocular)
-
- 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

LICA Chemistry is Another Breakthrough for Antisense Medicines

Selective delivery to the desired target cell type

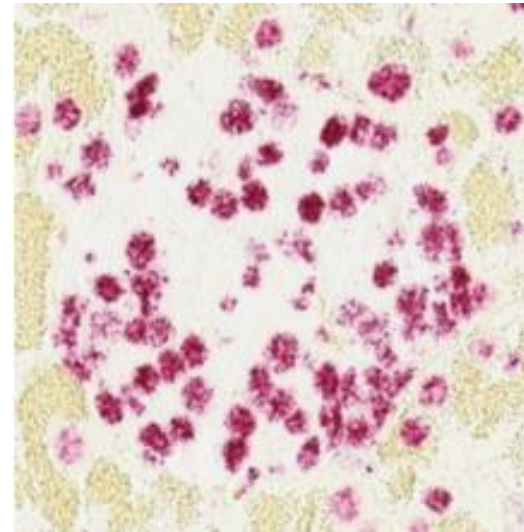
Greatly enhanced drug performance expanding therapeutic scope

- Substantial potency increase
- Less frequent dosing

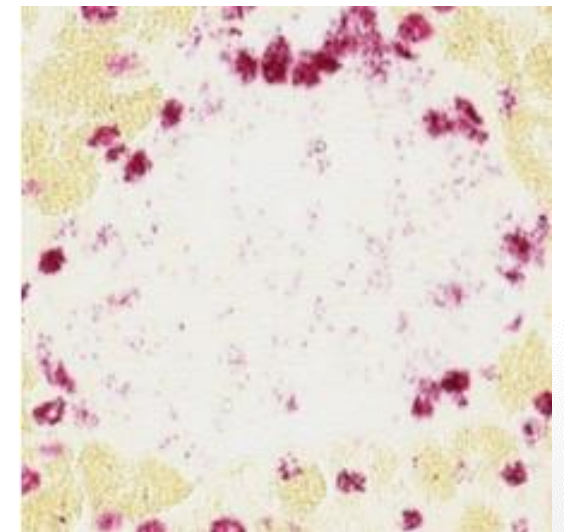
Opening up new organ systems and new routes of delivery

Two organ systems validated (liver and pancreas) with more expected

> 50-fold increase in potency in mouse pancreas



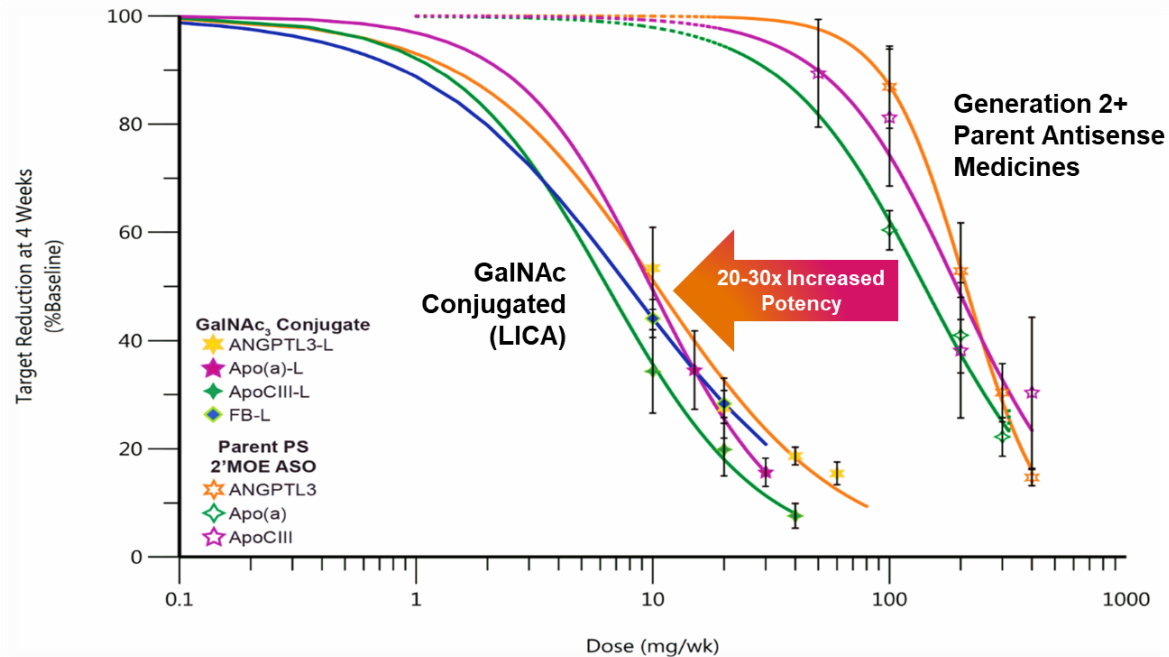
Gen 2.5 ASO



Gen 2.5 + LICA ASO

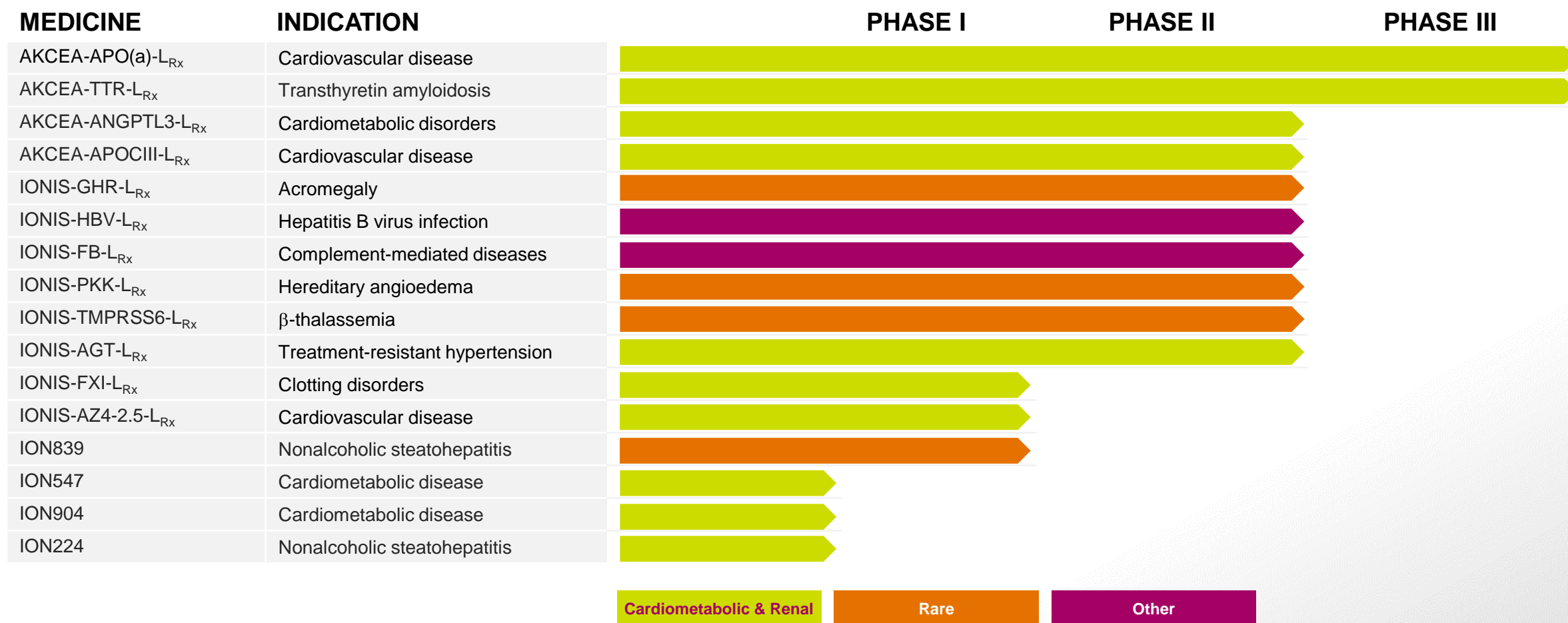
Ammala et al, Sci Adv.,v.4(10); 17 Oct 2018

Outstanding and Consistent Performance for Liver (GaINAC) LICA Antisense Medicines



- Marked increase in potency (20-30x)
- Enhanced dosing flexibility (monthly-quarterly SC)
- Potential for oral delivery
- Attractive safety and tolerability
- Broad experience
 - 16 LICA medicines in clinic
 - > 1,100 patients treated
 - ~ 400 patients dosed up to a year

16 Liver-targeted LICA Medicines Advancing



Numerous Potential Catalysts in 2020

3 Phase 3 Initiations



AKCEA-TTR-L_{Rx}
ATTR cardiomyopathy

Plus, **2** additional programs

≥10 Phase 2 Initiations

- Neurological diseases
- Rare diseases
- Cardiometabolic diseases
- Cancer

≥6 Clinical POC Results

- Cardiometabolic diseases
- Rare diseases
- Cancer
- Oral delivery
- Pulmonary delivery

Ionis Continues to Lead the Way in RNA-targeted Therapeutics



Growing leadership position

Ionis Continues to Lead the Way in RNA-targeted Therapeutics



Growing leadership position



Strong financial position

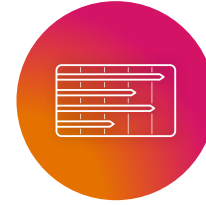
Ionis Continues to Lead the Way in RNA-targeted Therapeutics



Growing leadership position



Strong financial position



Rapidly advancing pipeline

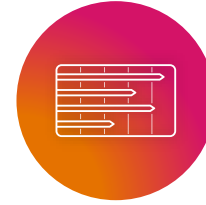
Ionis Continues to Lead the Way in RNA-targeted Therapeutics



Growing leadership position



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**Rapidly advancing
technology**

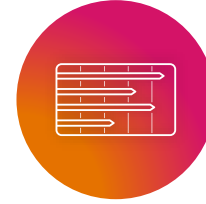
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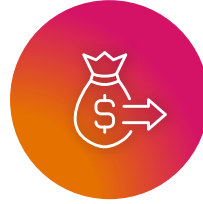


Commitment to expand the Ionis-owned pipeline & our commercial capabilities

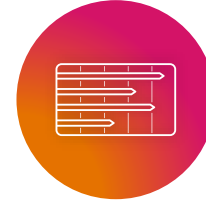
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Growing leadership position



Strong financial position



Rapidly advancing pipeline



Rapidly advancing technology



Commitment to expand the Ionis-owned pipeline & our commercial capabilities



Incredible momentum supporting even greater productivity

A black and white photograph of a young boy with glasses, laughing heartily. He is holding a round object, likely an apple, in his hands. The background is a blurred outdoor setting. The image is overlaid with a semi-transparent magenta banner at the bottom.

IONIS™

A Force for Life