



FY 2020 Financial Results and Business Update

February 24, 2021



On Today's Earnings Call



Brett Monia, Ph.D.
Chief Executive Officer



Beth Hougen
Chief Financial Officer



Richard Geary, Ph.D.
Executive Vice President, Development



Eric Swayze, Ph.D.
Executive Vice President, Research



Onaiza Cadoret-Manier
Chief Corp. Development & Commercial Officer



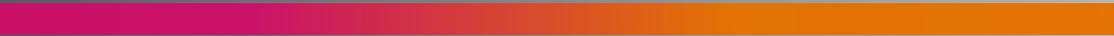
Forward Looking Language Statement

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

Introduction



Brett Monia, Ph.D.
Chief Executive Officer

2020: A New Beginning

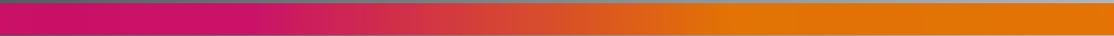
New leadership, new vision

Accelerated plans to commercialize Ionis medicines

Advanced late- and mid-stage pipeline towards market

Expanded therapeutic scope through technology advancements

FY 2020 Financial Performance



Beth Hougen
Chief Financial Officer

Achieved 2020 Guidance and Strengthened the Business

2021 Focused on Investments to Drive Future Revenue Growth

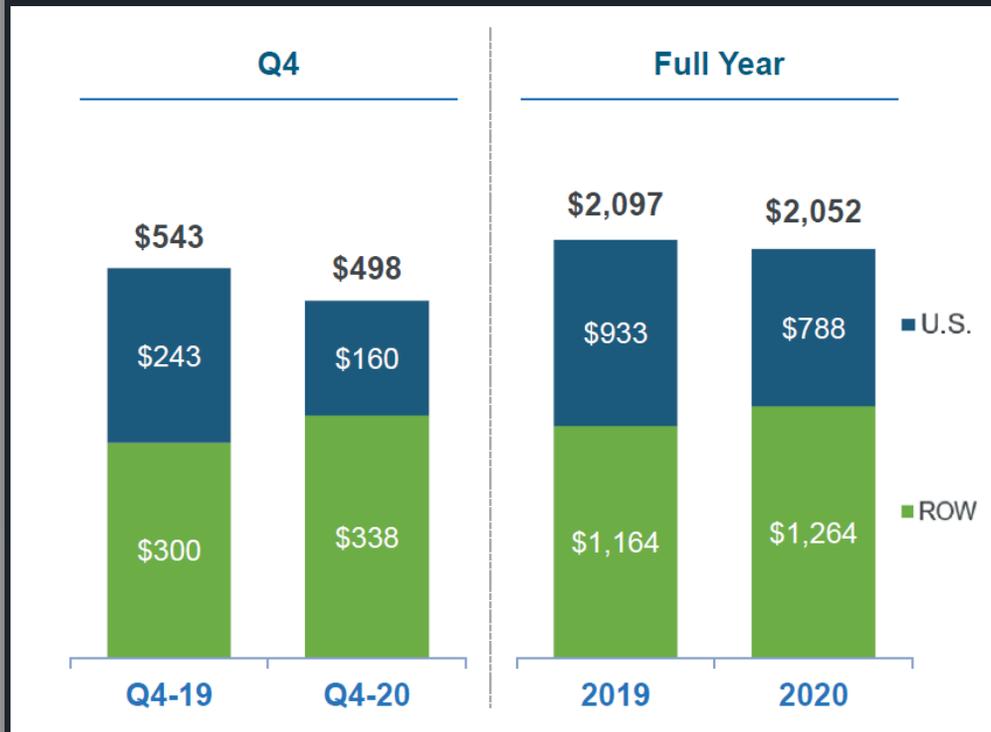
Achieved 2020 financial guidance*

**Further strengthened and streamlined the business
through Akcea and Sobi transactions**

**Well capitalized with the financial strength
to achieve our strategic goals**

Continued Blockbuster Performance with \$2B in 2020 Sales

\$287M in Royalties to Ionis

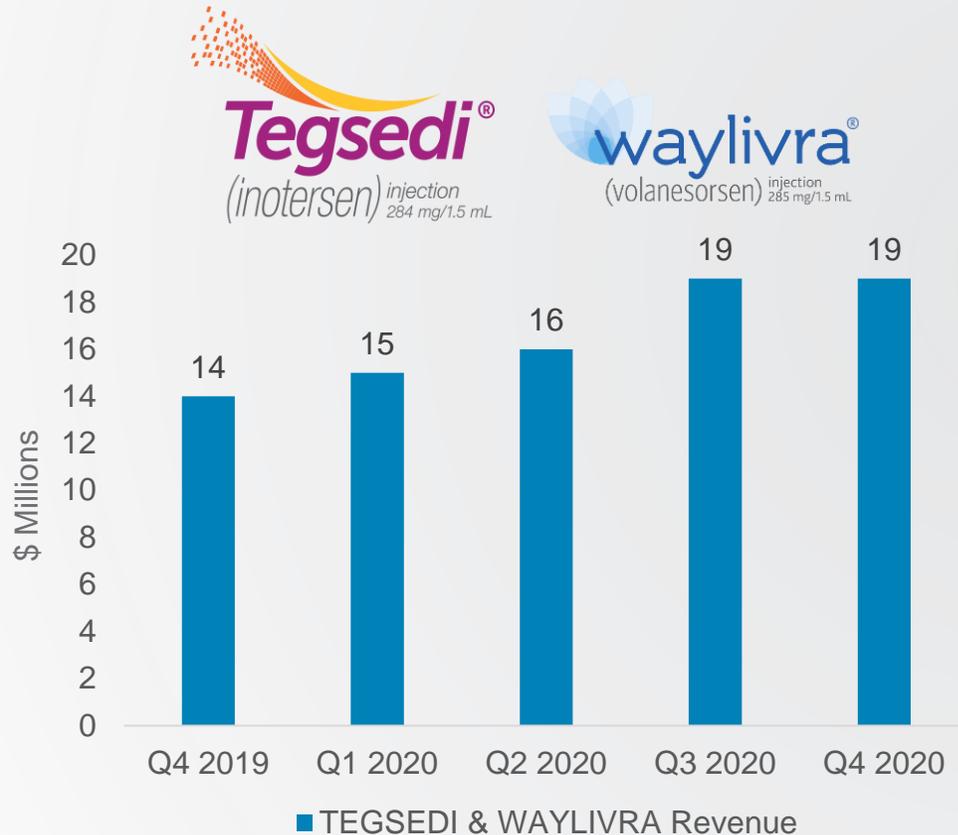


Source: Biogen YE 2020 Financial Results and Business Update; 1. Includes patients from post-marketing, EAP and clinical settings; 2. As of December 31, 2020; 3. Biogen estimate, data on file; 4. RESPOND study: clinicaltrials.org/NCT04488133; 5. DEVOTE study: clinicaltrials.org/NCT04089566

- >11,000 patients on SPINRAZA worldwide^{1,2}
- >60,000 SMA patients in markets where Biogen has a commercial presence³
- Approved in over 50 countries
- Ongoing commitment to improving outcomes for SMA patients of all ages
 - RESPOND study in SMA patients with suboptimal response to gene therapy now underway⁴
 - DEVOTE study of higher SPINRAZA doses, pivotal, blinded cohort now underway⁵

TEGSEDI and WAYLIVRA

Continued Meaningful Revenue Contributions from Two Rare Disease Products



- Product sales **increased >65 percent** year-over-year to **\$70 million** in 2020
- Generated **growing revenues** as **major markets** launched in 2020
- Restructured **European** operations with Sobi **distribution** agreement

2020 Financial Results

Achieved Financial Guidance While Managing COVID-19 Challenges

\$729 million in revenue

Half from commercial revenues

\$111 million of net income*

Continued financial strength



\$2 billion

Continued blockbuster performance

\$1.9 billion of cash

Enabling increasing investment in three key value-driving areas

Substantial Financial Benefits of Akcea and Sobi Transactions

Retained full value of Akcea's portfolio

Realizing significant cost savings through efficiencies

Gained full access to Akcea's cash of ~\$400 million*

Gained access to nearly \$300 million of deferred tax assets

2021 Financial Guidance Reflects Focus on Wholly Owned Medicines

Revenue

>\$600 million

Operating Expenses

\$675-\$725 million*

Net Loss

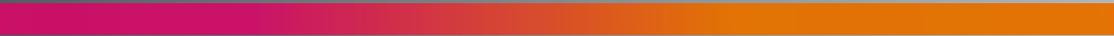
<\$75 million*

Investing in our Strategic Priorities to Drive Future Revenue and Earnings Growth



*Non-GAAP – please see Financial Impacts of Akcea Acquisition and Restructured European Operations and reconciliation to GAAP in Q4'20 press release

Pipeline Performance



Richard Geary, Ph.D.
Executive Vice President, Development

Pioneering New Markets & Changing Standards of Care

Advancing Phase 3 Pipeline

	Tofersen	SOD1-ALS Biogen	Prevalence¹ ~ 1.4K patients in G7 countries	Phase 3 Data² 2021
	Tominersen	Huntington's disease Roche	~ 80K patients in major markets	2022
	IONIS-TTR-L_{Rx}	hATTR polyneuropathy ATTR cardiomyopathy Wholly owned	> 250K patients worldwide	2022 (PN) 2024 (CM)
	IONIS-APOCIII-L_{Rx}	FCS Wholly owned	~ 3-5K patients worldwide	2023
	Pelacarsen	Lp(a) CVDRR Novartis	> 8M patients worldwide	2024



1. Market data on file. 2. Timing of partnered program catalysts based on partners' most recent publicly available disclosures
 ALS, amyotrophic lateral sclerosis. FCS, familial chylomicronemia syndrome. hATTR, hereditary transthyretin amyloidosis. CVDRR, cardiovascular disease risk reduction. TG, triglyceride.

Pioneering New Markets

Tofersen¹

*First of four medicines
targeting ALS*

**Projected Phase 3 Data
2021**

- Phase 3 **VALOR** study **fully enrolled**
- **Next** potential **commercial medicine**
- Phase 3 **ATLAS** study in **presymptomatic** SOD1-ALS patients expected to start in 2021
- Demonstrated **robust reductions** in SOD1 with trends in **slowing disease** progression²

Value-Driving Catalysts in 2021

DATA READOUTS ¹			H1	H2
GHR-L _{Rx}	Phase 2	Acromegaly	●	
ENAC-2.5 _{Rx}	Phase 2	Cystic Fibrosis	●	
PKK-L _{Rx}	Phase 2	Hereditary Angioedema	●	
AGT-L _{Rx}	Phase 2	Hypertension	●	
Tominersen	OLE & NHS	Huntington's Disease		●
MAPT _{Rx}	Phase 1/2	Alzheimer's Disease		●
Vupanorsen	Phase 2b	Dyslipidemia		●
C9 _{Rx}	Phase 1/2	C9-ALS		●
Tofersen	VALOR Phase 3	SOD1-ALS		●
KEY STUDY INITIATIONS ¹			H1	H2
SPINRAZA	RESPOND Phase 4	SMA, Suboptimal gene therapy response	✓	
ION363	Phase 3	FUS-ALS	●	
ION373	Phase 2	Alexander disease	●	
AGT-L _{Rx}	Phase 2b	Resistant hypertension	●	
AGT-L _{Rx}	Phase 2	Heart failure with reduced ejection fraction	●	
ION224	Phase 2b	NASH	●	
Tofersen	ATLAS Phase 3	Presymptomatic SOD1-ALS		●
APOCIII-L _{Rx}	Phase 3	Second indication		●
ENAC-2.5 _{Rx}	Phase 2	Cystic Fibrosis with rare mutations		●

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

Regular cadence of Phase 3 data...

 **SPINRAZA**[®]
(nusinersen) injection
12 mg/5 mL

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

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

Wholly owned Neuro

TTR-L_{Rx} (hATTR-PN)
ION716 (Prion)
ION373 (Alexander)
ION363 (FUS-ALS)
ION283 (Lafora)

Partnered Neuro

Tofersen (SOD1-ALS)
Tominersen (HD)
C9_{Rx} (C9-ALS)
ION541 (Broad ALS)

Wholly owned Cardio

TTR-L_{Rx} (ATTR-CM)
APOCIII-L_{Rx} (FCS)
APOCIII-L_{Rx} (TG diseases)
AGT-L_{Rx} (RHTN)

Partnered Cardio

Pelacarsen (Lp(a) CVDRR)
Vupanorsen (sHTG/CVDRR)
FXI-L_{Rx} (ESRD)

Wholly owned Other

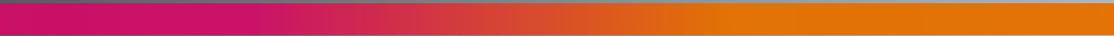
TMPRSS6-L_{Rx} (β-thal)
PKK-L_{Rx} (HAE)
GHR-L_{Rx} (Acromegaly)

Partnered Other

HBV_{Rx} (Hep B)

...Positions Ionis
for 12+ marketed
products in 2026

Conclusion: 2021 and Beyond



Brett Monia, Ph.D.
Chief Executive Officer

Accelerating our Next Stage of Growth

Advancing
pipeline
&
technology

Pioneering new
markets
&
Changing
standards of care

Financial
strength
to invest in areas
with the greatest
value-driving
potential

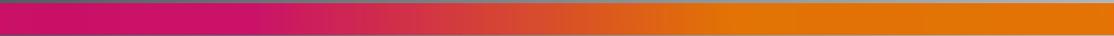
Delivering Life-changing Medicines



Celebrating Rare Disease Day 2021

IONIS[™]

Q&A



Brett Monia, Ph.D.
Chief Executive Officer



IONIS™

IONIS: A FORCE FOR LIFE