IONIS®

A Genetic Medicines Company

FY 2022 Financial Results and Business Update

Nasdaq: IONS

Every Moment Matters...
in the Discovery, Development & Delivery
of Life Transforming Genetic Medicines

On Today's Earnings Call

Brett Monia, Ph.D.
Chief Executive Officer

Eugene Schneider, M.D.
Executive Vice President,
Chief Clinical Development Officer

Onaiza Cadoret
Executive Vice President,
Chief Global Product Strategy and Operations Officer

Beth Hougen
Chief Financial Officer

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

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Forward-Looking Statements

This presentation includes forward-looking statements regarding our business, financial guidance and the therapeutic and commercial potential of SPINRAZA® (nusinersen), TEGSEDI® (inotersen), WAYLIVRA® (volanesorsen), eplontersen, olezarsen, donidalorsen, ION363, tofersen, pelacarsen, bepirovirsen, Ionis' technologies, and Ionis' other 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 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, 2021, 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.

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Introduction

Brett Monia, Ph.D.
Chief Executive Officer

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Building On Momentum from 2022 Successes[1]

Pipeline & Technology

- Eplontersen: positive Ph3 data[2] supported NDA filing; on track for 66-week ATTRv-PN data H1:23
- Olezarsen: granted Fast Track designation for FCS; on track for Ph3 FCS data H2:23
- Donidalorsen: New data reinforces potential best-in-class profile
- Technology: advanced muscle LICA, MsPA backbone, gene editing

Commercial Readiness

- On track to launch eplontersen, olezarsen and donidalorsen
  - Co-commercializing eplontersen with AstraZeneca
  - Independently launching olezarsen and donidalorsen
- Key functions in place: global product strategy, medical affairs, in-line commercial teams, etc.

Financial Foundation

- Completed 2 strategic transactions worth up to $1.5 billion
  - >$700 million already received[3]
  - Supports investments in pipeline and commercial readiness for multiple late-stage programs

Positioned for Substantial Growth

1. Timing expectations based on current assumptions and subject to change 2. 35-week interim analysis of NEURO-TTRansform study 3. $500M in January 2023 from royalty monetization transaction

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Pipeline Performance

Eugene Schneider, M.D.
Executive Vice President, Chief Clinical Development Officer

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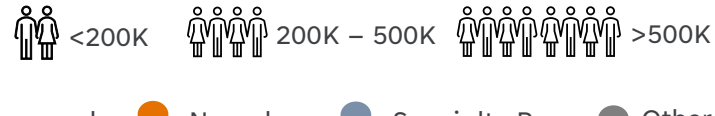
Expanding Rich Late-Stage Pipeline

Positioned to Deliver Steady Cadence of New Drugs to the Market



		Indication	Prevalence[1]	Next Event[2]
Eplontersen	IONIS / AstraZeneca	ATTRv-PN		Full data (2023) OUS submissions (2023) US approval (2023)
		ATTR-CM		Ph3 data (2025)
Olezarsen	IONIS	FCS		Ph3 data (2023)
		SHTG		Ph3 data (2024)
Donidalorsen	IONIS	HAE		Ph3 data (2024)
ION363	IONIS	FUS-ALS		Ph3 data (2025)
Tofersen	Biogen	SOD1-ALS		US, EU approval (2023)
		Presymptomatic SOD1-ALS		Ph3 data (TBD)
Pelacarsen	NOVARTIS	Lp(a) CVD		Ph3 data (2025)
Bepirovirsen	GSK	HBV		Ph2b B-Together data (2023)

IONIS-FB-L$_{Rx}$ (Roche) expected to enter Phase 3 pipeline in H1:23[2]

1. Market data on file. 2. Timing expectations are based on current assumptions and are subject to change.

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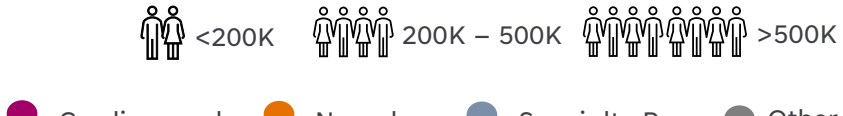
Expanding Rich Late-Stage Pipeline

Positioned to Deliver Steady Cadence of New Drugs to the Market



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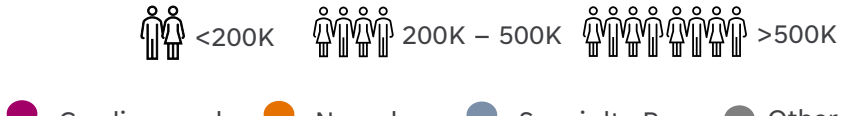
Expanding Rich Late-Stage Pipeline

Positioned to Deliver Steady Cadence of New Drugs to the Market



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Key Value Driving Events in 2023[1]

Regulatory Actions

- **Tofersen:** FDA approval decision, SOD1-ALS
- **Tofersen:** EU approval decision, SOD1-ALS
- **Eplontersen:** FDA approval decision, ATTRv-PN
- **Eplontersen:** OUS filings, ATTRv-PN

Clinical Achievements

- **Eplontersen:** Phase 3, NEURO-TTRansform 35-week & 66-week data, ATTRv-PN
- **Olezarsen:** Phase 3, BALANCE study data, FCS
- **Eplontersen:** Phase 3, CARDIO-TTRansform full enrollment, ATTR-CM
- **Donidalorsen:** Phase 3, OASIS full enrollment, HAE

Phase 3 Initiations

- **Bepirovirsen:** Phase 3 initiation, chronic HBV
- **IONIS-FB-L_{Rx}:** Phase 3 initiation, IgA nephropathy

1. Timing expectations are based on current assumptions and are subject to change, timing of partnered program catalysts based on partners' most recent publicly available disclosures.

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Commercial Readiness

Onaiza Cadoret
Executive Vice President, Chief Global Product Strategy and Operations Officer

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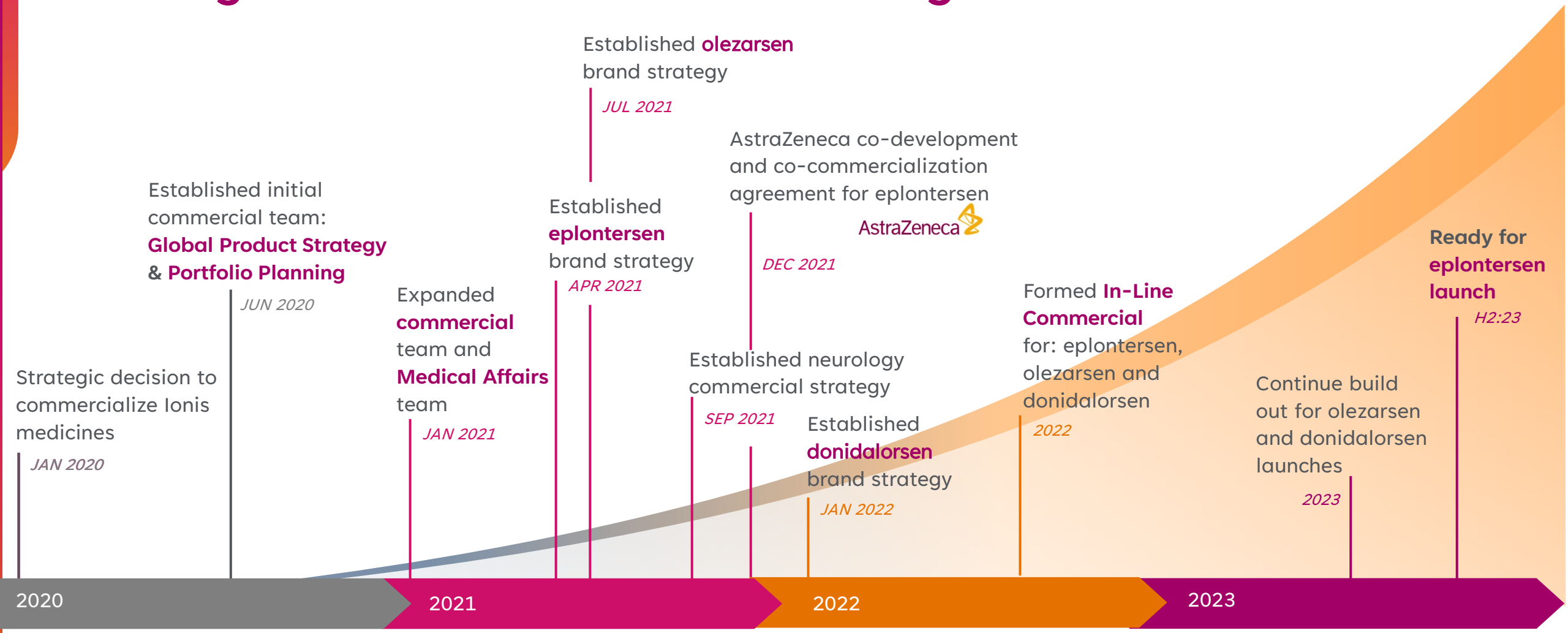
Building a World Class Commercial Organization



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Positioned to Commercialize Our Near-Term Opportunities[1,2]

Eplontersen

Potential to **change the standard-of-care** for patients with TTR amyloidosis

On track to **launch** for ATTRv-PN

Well positioned with **ATTR market knowledge &** AstraZeneca's **global scale**

Estimated peak sales: **Multibillion**[3]

Olezarsen

Expected to be a **first-in-class** treatment for patients with severely elevated triglycerides

On track to **launch** for FCS

1st independent launch in FCS; **Larger** SHTG indication **to follow**

Estimated peak sales: **>$1 Billion**

Donidalorsen

Potential to be a **best-in-class** prophylactic treatment for patients with HAE[4]

On track to launch

Attractive growing market with **concentrated prescriber** base

Estimated peak sales: **>$500 Million**

1. Market data on file 2. Timing expectations and global peak sales estimates are based on current assumptions and are subject to change.
3. Estimated global peak sales includes ATTRv-PN and ATTR-CM. 4. Profile based on Phase 2 and OLE data

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FY 2022 Financial Performance & FY 2023 Financial Guidance

Beth Hougen
Chief Financial Officer

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FY 2022 Financial Results

$587 million in revenue
Generated from numerous diverse sources

$898 million in operating expenses[1]
Investments in advancing our medicines, go-to-market activities and technology

$311 million net loss[1]

$2.0 billion of cash
Added $500 million in January 2023[2]

Substantial financial resources to bring transformational medicines to the market

1. Non-GAAP – please see reconciliation to GAAP in FY 2022 press release 2. $500M from royalty monetization transaction in January 2023

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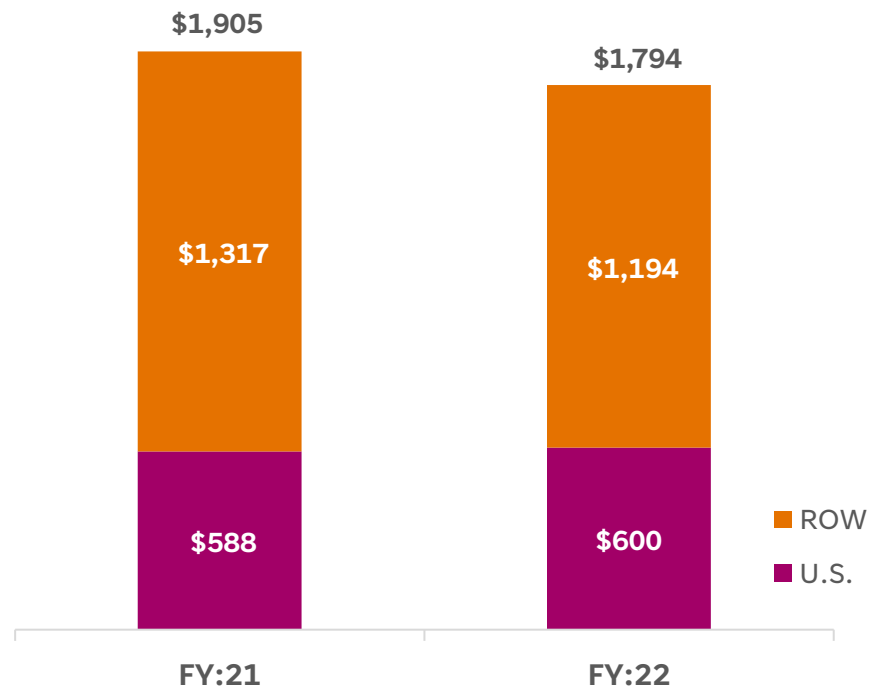
SPINRAZA® (nusinersen) injection 12 mg/5 mL

Global Leader for the Treatment of SMA

$242M FY 2022 Royalties to Ionis[1]



- **$1.8B sales in FY 2022; >$240M in royalties to Ionis**
  - Ionis' royalties increased each quarter in 2022
- **$459M sales in Q4 QTD; $67M in royalties to Ionis**
  - 6% increase vs Q3'22 and 4% increase vs Q4'21
- **SPINRAZA's potential growth drivers:**
  - Market Expansion: Continued geographical expansion & existing market expansion driven by growing adult SMA population
  - Robust Life Cycle Management Program: Ongoing ASCEND[2], RESPOND[3] and DEVOTE[4] studies aim to address remaining unmet need and inform therapy decisions for the SMA community
  - Future of SMA franchise includes SPINRAZA follow-on, ION306

Source: Biogen Q4 2022 Financial Results and Business Update; 1.$ amounts in millions;
2. ASCEND: clinicaltrials.gov/NCT05067790; 3. RESPOND: clinicaltrials.gov/NCT04488133;
4. DEVOTE: clinicaltrials.gov/NCT04089566

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FY 2022 & Recent Financial Highlights

Added substantial capital to advance pipeline and commercial activities

$587M — **Revenue**

Commercial Revenue: $303M

- SPINRAZA comprised largest component

R&D Revenue: $284M

- Generated from several partners for advancing numerous programs

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$898M — **Operating Expenses***

R&D Expenses*: $759M

- Increased YoY primarily from advancing late-stage programs & Metagenomi upfront payment

SG&A Expenses*: $124M

- Increased spend on go-to-market activities in Q3 & Q4
- Decrease YoY reflected Akcea integration & Sobi savings

$2.5B — **Cash & short-term investments[1]**

2 Strategic Transactions: Royalty Monetization[2] & Sale and Leaseback

- >$700M added to cash resources[1]

*Non-GAAP – please see reconciliation to GAAP in FY 2022 press release

1. YE cash of $2.0B, plus $500M from royalty monetization transaction in January 2023 2. Royalty monetization transaction closed in January 2023

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2023 Financial Guidance

Revenue	Operating Expenses	Net Operating Loss	Cash
>$575 million	~$970-$995 million*	<$425 million*	~$2 billion

Reflects investments in our strategic priorities:

- **Deliver** an abundance of genetic medicines to the market
- **Establish** an integrated commercial organization
- **Expand** and **diversify** our technology platform

*Non-GAAP – please see reconciliation to GAAP in FY 2022 press release

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Foundation of Financial Strength for Sustainable Growth

Financial Strength + **Accelerating Investments** + **Steady Cadence of New Marketed Products**

- Significant financial resources with **~$2.5 billion in cash**[1]
- **Multiple revenue sources** with diverse margin profiles
- **Strategic transactions**[2] provided even greater financial strength

- **Advancing** new medicines to the market
- **Building** our commercial organization
- **Expanding** and diversifying our technology
- **Scaling** our infrastructure

1. YE cash of $2.0B, plus $500M from royalty monetization transaction in January 2023 2. Includes royalty monetization transaction in January 2023 and sale and leaseback transaction in October 2022

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Conclusion

Brett Monia, Ph.D.
Chief Executive Officer

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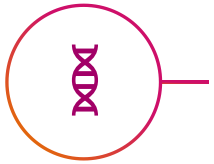
Well Positioned to Build on Momentum by Executing on Strategic Priorities

Deliver an abundance of genetic medicines to the market

Establish an integrated commercial organization



Expand and **diversify** our technology platform

Strengthen our financial foundation to support our strategic priorities

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Q&A

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Appendix

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Eplontersen: A Multibillion-Dollar Opportunity Positioned for US Approval This Year[1,2]

ATTRv POLYNEUROPATHY

neuro TTRansform

- Met co-primary + key secondary endpoints in Phase 3 (IA) with attractive safety and tolerability
- **NDA submission complete, FDA approval decision expected in 2023**
- **Plan to report Week 35 and Week 66 data in H1:2023**
- **On track for OUS filings in 2023**

ATTR CARDIOMYOPATHY

cardio TTRansform

- Most comprehensive ATTR-CM study to date
- Positioned to deliver most robust data in broad patient population
- **Full enrollment expected in 2023**
- **On track for data in H1:2025**

ATTR

TTRansform beyond

- Open-label extension studies in patients with ATTRv-PN and ATTR-CM enrolling
- Imaging sub-studies in ATTR-CM to assess the effects on cardiac structure and function underway
- Additional profile-enhancing studies planned

1. Timing expectations and peak sales estimates are based on current assumptions and are subject to change. 2. Estimated peak sales includes ATTRv-PN and ATTR-CM.

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Olezarsen Development Program Designed to Support a >$1 Billion Market Opportunity[1,2]

FAMILIAL CHYLOMICRONEMIA SYNDROME (FCS)

Balance
a familial chylomicronemia syndrome study

- FCS Phase 3 BALANCE study fully enrolled
- Phase 3 data expected H2:2023
- OLE progressing well
- Achieved fast track designation
- Launch preparations underway

SEVERE HYPERTRIGLYCERIDEMIA (SHTG)

CORE
a hypertriglyceridemia study

- SHTG Phase 3 study enrolling well
- First pivotal study in large SHTG population

CORE2
a hypertriglyceridemia study

- Confirmatory pivotal study enrolling
- Supportive of registration

ESSENCE Plus

- ESSENCE study in patients with mild TGs and CVD risk
- Strengthens safety database necessary for approval
- Additional profile enhancing studies underway

1. Timing expectations and peak sales estimates are based on current assumptions and are subject to change 2. Estimated peak sales FCS and SHTG.

Donidalorsen Phase 3 Development Program Designed to Replicate Robust Phase 2 and OLE Results[1]

Hereditary Angioedema

OASIS

- Positive Phase 2 and OLE data, including QoL data reported
- Phase 3 study on track for full enrollment this year
- Phase 3 data expected 2024

OASIS plus

- SWITCH study underway in patients previously treated with other prophylactic therapies
- Phase 3 OLE study underway in patients who have completed OASIS

Potential to demonstrate best-in-class HAE prophylactic profile

1. Timing expectations based on current assumptions and subject to change

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Tofersen: Potential to Become First Ever Disease Modifying Therapy for a Genetic Cause of ALS

Tofersen to Treat SOD-1 ALS

12-Month VALOR[1] and OLE Integrated Data Included in NDA Showed Tofersen:

- Significantly slowed decline across multiple measures of ALS disease progression
- Led to robust and sustained reductions in neurofilament light chain
- Demonstrated a safety profile supportive of continued treatment

Data published in the
New England Journal of Medicine

NDA under Priority Review

Ad Com Date: March 22, 2023
PDUFA Date: April 25, 2023

MAA Accepted by EMA

Next Potential Product to Enter the Market[2]

1. While statistical significance was not achieved on the primary endpoint of ALSFRS-R at week 28 in the Phase 3 VALOR study, signs of reduced disease progression across multiple secondary and exploratory endpoints were observed 2.Timing expectations based on current assumptions and subject to change

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Royalty Pharma Agreement Further Strengthens Ionis' Financial Foundation[1,2]

Royalty monetization transaction valued up to >$1.1B Underscores substantial upside potential for SPINRAZA & pelacarsen

$500M
Upfront

Up to **$625M**
in additional pelacarsen milestone payments

- Enables Ionis to:
  - Achieve commercial readiness for multiple late-stage programs
  - Deliver new genetic medicines to the market by further advancing a deep and innovative pipeline
- Royalty Pharma receives minority interest in SPINRAZA and pelacarsen royalties
- Ionis maintains the ability to participate in significant upside with majority royalty interest in both products and retains all development, regulatory and commercial milestones for pelacarsen

1. See SEC filing for additional details. 2. Royalty monetization transaction closed in January 2023.

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