IONIS®

A Genetic Medicines Company

Annual Meeting of Stockholders

June 1, 2023

Nasdaq: IONS

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

Participating in Today's Presentation

- There will be a Q&A session at the end of today's program, following prepared remarks
- Questions may be submitted at any time during the live event
- Simply type your question into the "Submit a Question" field located on your screen and clicking "Send"
- A replay will be available on the Investors section of the Ionis website within 24 hours of the live event
- Today's slides may be downloaded from the Investors section of the Ionis website under Events

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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 QALSODY™ (tofersen), SPINRAZA® (nusinersen), TEGSEDI® (inotersen), WAYLIVRA® (volanesorsen), eplontersen, olezarsen, donidalorsen, ulefnersen, 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 our Form 10-K for the year ended December 31, 2022, 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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On Today's Call

Brett Monia, Ph.D.
Chief Executive Officer

Beth Hougen
Chief Financial Officer

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

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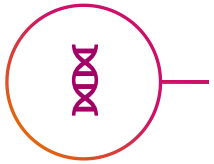
Building Momentum by Executing on Strategic Priorities

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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Ionis: Uniquely Positioned To Drive Growth[1]

Commercial Portfolio Growing

- SPINRAZA continues to lead in the SMA global market
- QALSODY approval further validates the strength of Ionis' platform in the CNS

Late-stage Pipeline Delivering

- Eplontersen US approval in ATTRv-PN anticipated in December
- Olezarsen Phase 3 data in FCS expected in H2:2023
- Donidalorsen Phase 3 study in HAE fully enrolled, with data expected in H1:2024

Leading Neuro Franchise

- IONIS-MAPT$_{Rx}$ (BIIB080) Phase 1b data in AD showed substantial tau pathology reductions
- 12 programs for a range of neurological diseases advancing in clinical development

Technology Advancing & Diversifying

- Advanced first muscle-targeting LICA using Bicycle technology into preclinical development
- Advanced new backbone chemistry, MsPA, into preclinical development

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

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

Eplontersen

Data support strong efficacy and safety with **at-home self-administration** profile for the **global ATTR market**

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

Well positioned with Ionis' **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 for first independent **launch** in FCS

Independent launch in **larger** SHTG indication **to follow**

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

Donidalorsen

Data to date support a **competitive** & **differentiated** prophylactic profile for patients with HAE[4]

On track for independent **launch** in HAE

Attractive **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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Eplontersen: Positioned to Serve the Broad and Largely Underserved Global ATTR Patient Population[1]

Mark
Living with ATTRv

Eplontersen

Data support strong efficacy and safety with **at-home self-administration** profile for the **global ATTR market**

First Potential Approval: **2023**[2]

Estimated Peak sales:
Multibillion[3]

Global Patient Segments[1]
Expanding Patient Population

	Indication	Patients
	ATTR	~500K
Cardio	wtATTR	300K-500K
Cardio	ATTRv-CM	10K
Polyneuro	ATTRv-Mixed	30K
Polyneuro	ATTRv-PN	10K

1. Market data on file 2. Eplontersen is under regulatory review for approval in the US for ATTRv-PN. 3. Peak sales estimates are based on current assumptions and are subject to change.

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Eplontersen's Development Program is Designed to Deliver Robust Dataset Supporting Treatment for ATTR[1]

ATTRv POLYNEUROPATHY

neuro TTRansform

- Met co-primary + secondary endpoints in Phase 3 with favorable safety and tolerability
- **NDA accepted, PDUFA date of December 22, 2023**
- **On track for oUS submissions 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 readout in H1:25**

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 based on current assumptions and subject to change.

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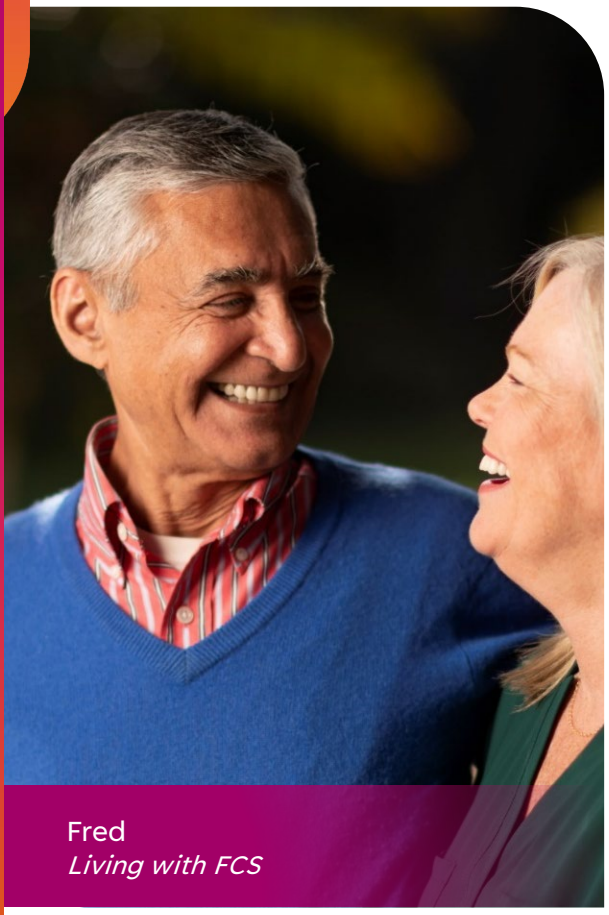
Olezarsen: Positioned to Address Diseases Associated with Severely Elevated Triglycerides[1]



Fred
Living with FCS

Severely elevated triglycerides (TGs)

- Associated with acute, potentially fatal pancreatitis and atherosclerotic cardiovascular disease
- Endocrinology and cardiology guidelines recognize the risks of SHTG and recommend pharmacologic therapy
- Patients unable to achieve guideline recommended TG levels with current standard-of-care (High Unmet Need)

Indication	Peak Sales[2]
FCS SHTG	**>$1 Billion**

Familial chylomicronemia syndrome (FCS)

- Rare, genetically defined
- Significant risk for acute, potentially fatal pancreatitis
- ~1-2 per million patients worldwide

Severe hypertriglyceridemia (SHTG): TG >500 mg/dL

- Significant risk for acute, potentially fatal pancreatitis
- Elevated risk for CVD
- >3 million total US patients

1. Market data on file. 2. Peak sales estimates are based on current assumptions and are subject to change.

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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
- 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: Clinical Results to Date Demonstrate a Competitive HAE Prophylactic Profile

Sydney
Living with HAE

Hereditary Angioedema (HAE)

- Rare genetic disease
- Severe and potentially fatal swelling of the arms, legs, face and throat

Donidalorsen

- Targets the prekallikrein pathway, the root cause of HAE

>20K

Patients in the United States and Europe suffering from HAE[1]

Indication	Peak Sales[2]
HAE	**>$500 Million**

1. Market data on file. 2. Peak sales estimates are based on current assumptions and are subject to change.

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

Hereditary Angioedema

OASIS

- Fully enrolled with data expected in H1:2024
- Positive Phase 2 and 1-year OLE data, including QoL data reported
- New 2-year Phase 2 OLE data reinforce donidalorsen's competitive profile

OASIS plus

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

Positioned to demonstrate competitive HAE prophylactic profile

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

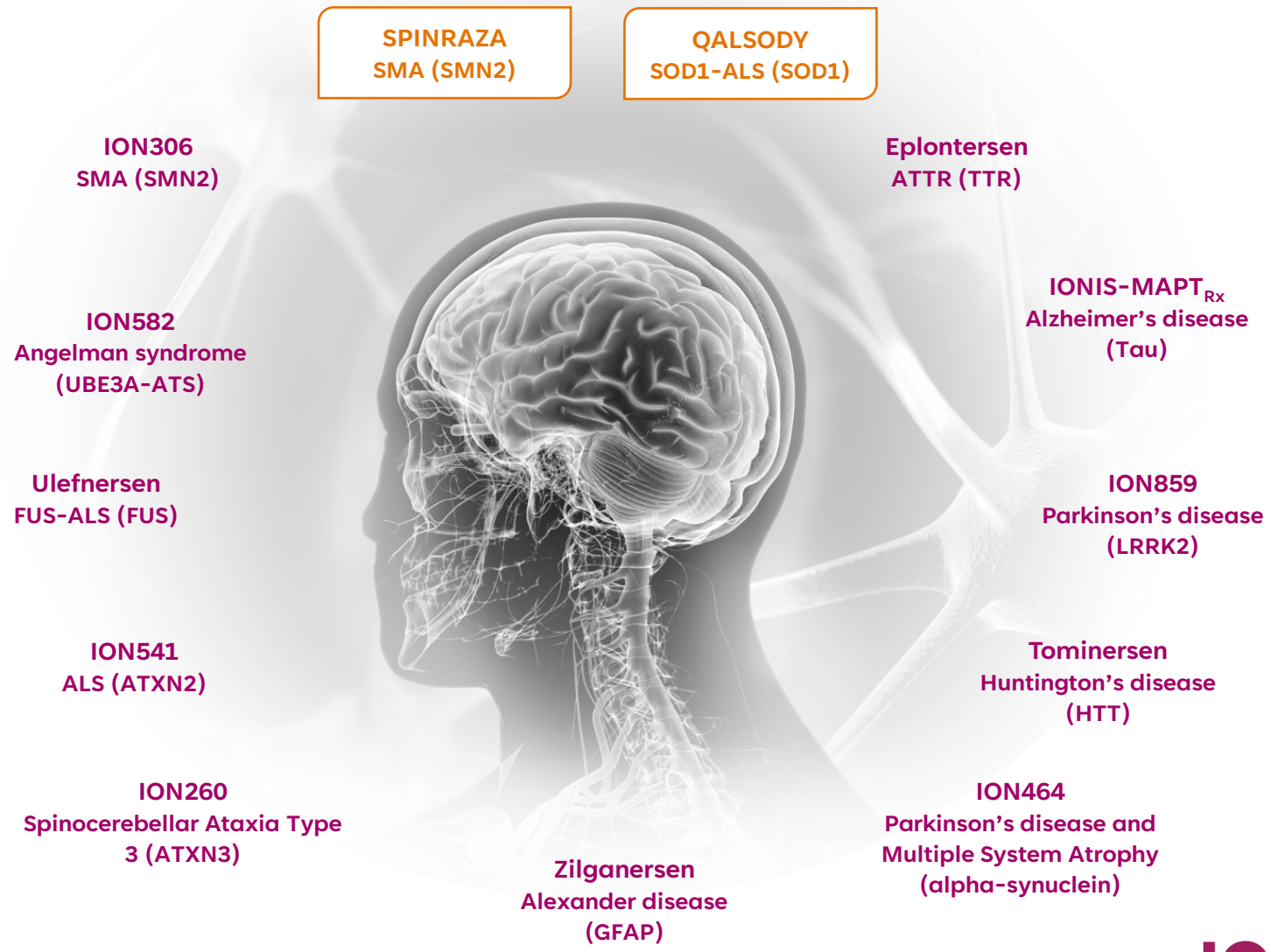
Leading Neurology Franchise: Addressing Major Neurological Diseases

2

Approved Medicines

12

Medicines in Development



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QALSODY: The First Treatment Approved To Target A Genetic Cause of ALS[1,2]

QALSODY to Treat SOD1-ALS

Received Accelerated Approval From FDA

MAA Accepted by EMA

Phase 3 ATLAS Presymptomatic Study Ongoing

FDA approval based on a reduction in neurofilament, a marker of neurodegeneration[1]

Approval supported by 12-month VALOR[3] and OLE integrated data

Data published in the *New England Journal of Medicine*

1. For important prescribing and safety information, please refer to: www.qalsody.com 2. Biogen is responsible for commercializing QALSODY. 3. 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.

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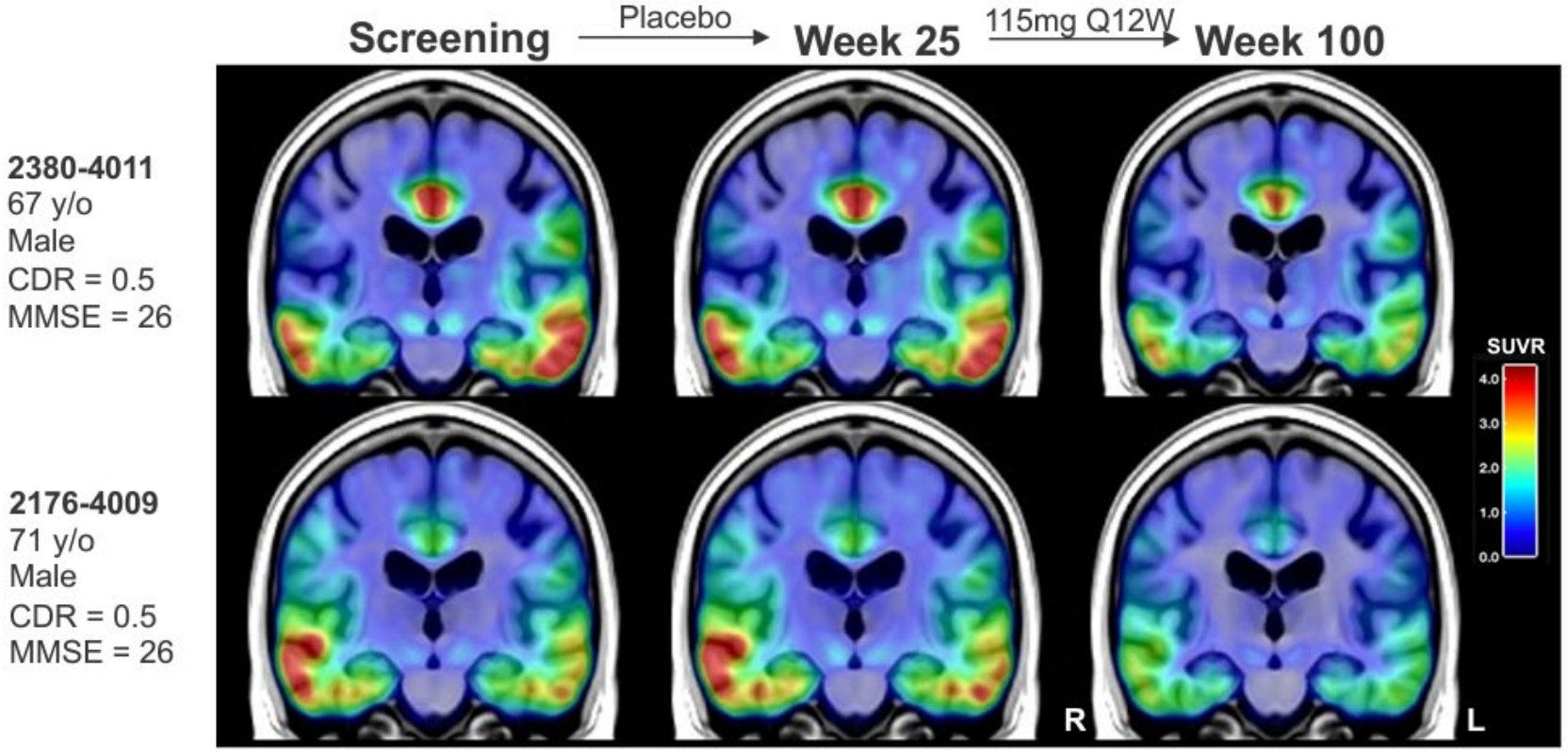
IONIS-MAPT$_{Rx}$ (BIIB080) Showed Consistent Reduction in Tau Burden Across all Brain Regions



Tau PET Results:

- Patients initially on placebo then MAPT$_{Rx}$ (BIIB080) showed reduced tau burden following treatment
- Impacted tau burden as early as 25 weeks of treatment
- Reduced tau burden at all doses and dose frequencies in LTE
- Generally well-tolerated at all doses and dose frequencies
- CELIA Phase 2 Study underway in patients with mild AD

Source: Collins et al., AD/PD 2023 *CDR* Clinical Dementia Rating scale; *MMSE* Mini Mental State Examination; *SUVR* standard uptake value ratio; CELIA Study: Clinialtrials.gov/NCT05399888

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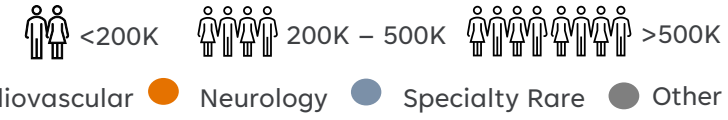
Late-Stage Pipeline is Advancing and Expanding



		Indication	Prevalence[1]	Next Event[2]
Eplontersen	IONIS / AstraZeneca	ATTRv-PN		US approval (2023) oUS submissions (2023)
		ATTR-CM		Complete enrollment (2023) Ph3 data (2025)
Olezarsen	IONIS	FCS		Ph3 data (2023)
		SHTG		Ph3 data (2024)
Donidalorsen	IONIS	HAE		Ph3 data (2024)
Ulefnersen	IONIS	FUS-ALS		Ph3 data (2025)
Tofersen	Biogen	Presymptomatic SOD1-ALS		Ph3 data (2027)
Pelacarsen	Novartis	Lp(a) CVD		Ph3 data (2025)
Bepirovirsen	GSK	HBV		Ph2b B-Together data (2023)
IONIS-FB-L_{Rx}	Roche	IgA nephropathy		Ph3 data (TBD)

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

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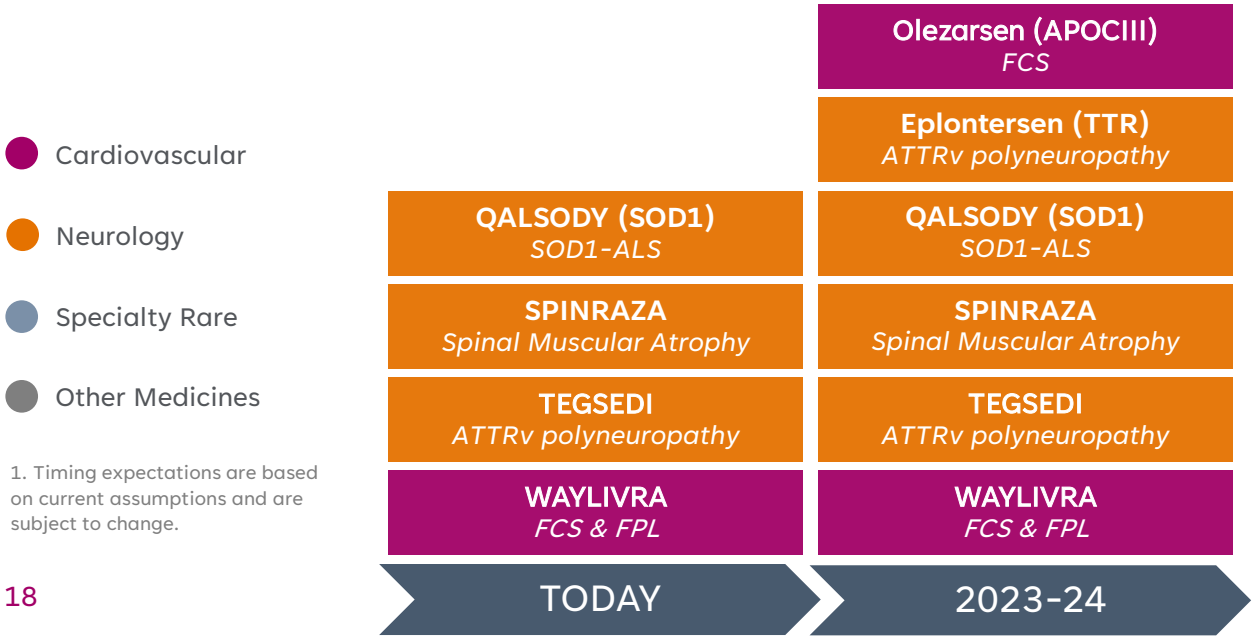
Positioned to Deliver a Steady Cadence of New Approved Products[1]



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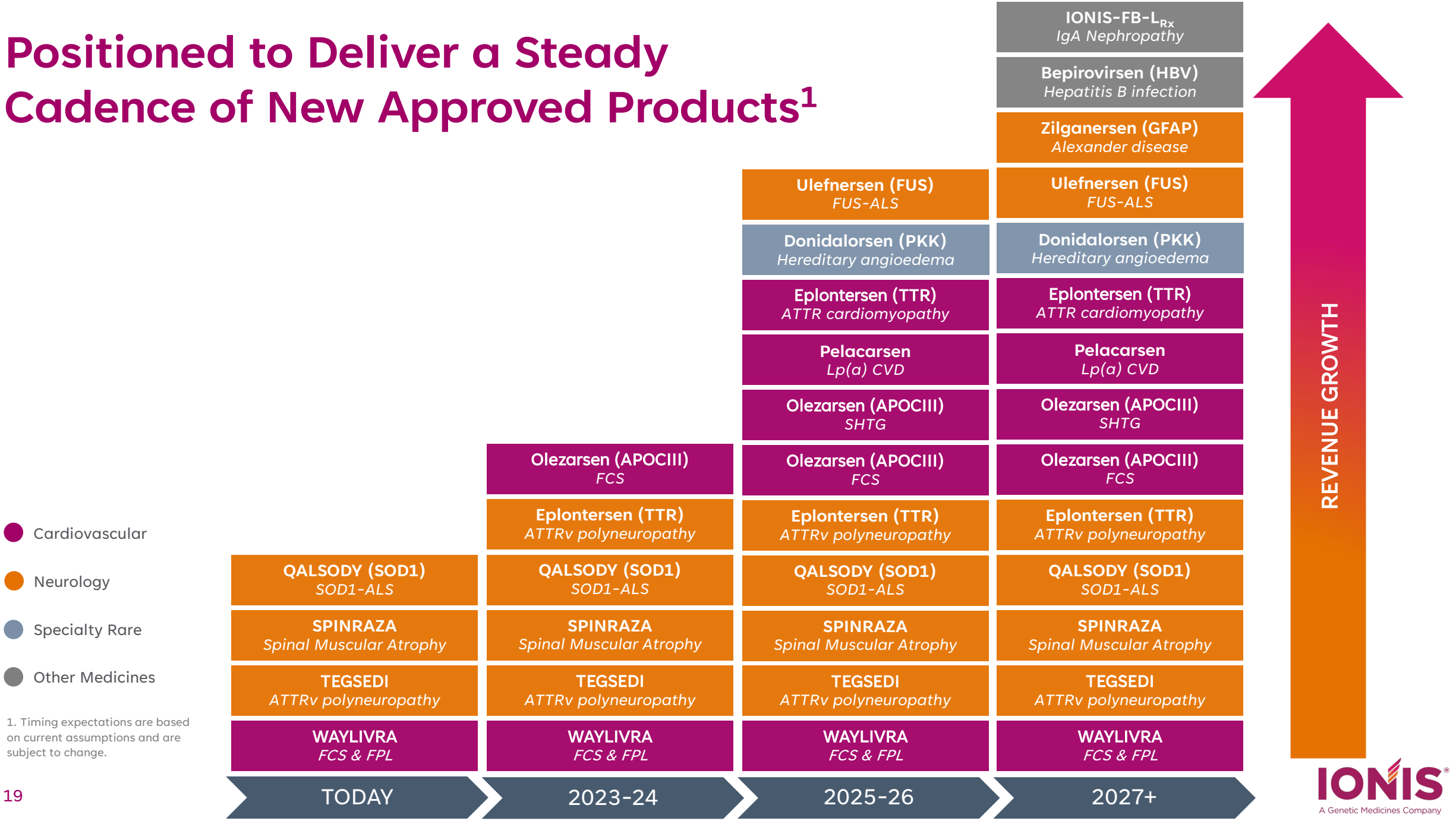
Positioned to Deliver a Steady Cadence of New Approved Products[1]



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

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Technology Advancements Build on our Leadership Position in Genetic Medicine

Recent Advancements to Enhance Drug Profiles

WHERE WE ARE

- Advanced cardiac muscle LICA program using Bicycle conjugates into preclinical development
- Advanced new MsPA program into preclinical development
- Further optimized medicinal chemistry for CNS applications

Adding Value for Tomorrow's Medicines

WHERE WE ARE GOING

- Solve delivery across blood-brain-barrier
- Advance programs targeting new tissues
- Advance new routes of delivery
- Advance new targets utilizing gene editing technology (Metagenomi partnership)

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Foundation of Financial Strength for Sustainable Growth

Financial Strength + **Accelerating Investments** + **Sustained Delivery of New Marketed Products**

- Significant financial resources with **$2.3 billion in cash**[1]
- **Multiple revenue sources** with diverse margin profiles

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

1. As of March 31, 2023

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Key Value Driving Events in 2023[1]

Regulatory Actions

- **QALSODY:** FDA approval decision, SOD1-ALS
- **QALSODY:** EU approval decision, SOD1-ALS[2]
- **Eplontersen:** FDA approval decision, ATTRv-PN
- **Eplontersen:** oUS filings, ATTRv-PN

Clinical Data Events

- **Eplontersen:** Phase 3, NEURO-TTRansform 35-week & 66-week data, ATTRv-PN
- **Olezarsen:** Phase 3, BALANCE study data, FCS
- **Donidalorsen:** Phase 2, OLE 1-year data, HAE
- **Donidalorsen:** Phase 2, OLE 2-year data, HAE

Enrollment Achievements

- **Donidalorsen:** Phase 3, OASIS-HAE full enrollment, HAE
- **IONIS-FB-L_{Rx}:** Phase 2, GOLDEN Study full enrollment, GA
- **Eplontersen:** Phase 3, CARDIO-TTRansform full enrollment, ATTR-CM

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. 2. CHMP opinion anticipated in Q4:2023.

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Thoughtful Corporate Responsibility in Everything We Do

Second Annual Corporate Responsibility Report Published in December 2022

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Well-positioned to **accelerate growth** through success across our business

Numerous attractive near-term product opportunities **rapidly approaching market**

Growing & advancing **Phase 3 pipeline**

Sustained delivery of **numerous new product opportunities** for rare and broad indications

Research, development & commercial **fully integrated**

Expanded and **diversified technology** with new capabilities extending our **leadership** in **genetic medicine**

REALIZING OUR VISION TO BE THE

Leader in Genetic Medicine

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Q&A session

To ask a question,
simply type your question in the
“Submit a Question” box below and click “Send”

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