Q1:24 Business Update and Financial Results

May 7, 2024

Nasdaq: IONS

On Today's Earnings Call

Brett Monia, Ph.D.
Chief Executive Officer

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Chief Commercial Officer

Forward-Looking Statements

This presentation includes forward-looking statements regarding our business, financial guidance and the therapeutic and commercial potential of our commercial medicines, additional medicines in development and technologies. 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. Except as required by law, we undertake no obligation to update any forward-looking statements for any reason. 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, 2023, 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.

Introduction

Brett Monia, Ph.D.
Chief Executive Officer

2024 Off To Strong Start with Several Important Achievements

WAINUA (eplontersen) 45 mg injection for subcutaneous use

WAINUA Launched in U.S. for ATTRv-PN[1]

2

Positive Phase 3 Readouts[2]

Balance – a familial chylomicronemia syndrome study

OASIS

2

Phase 3 Studies Fully Enrolled[3]

CORE – a hypertriglyceridemia study

Essence – TIMI-73b

2

Additional Pipeline Achievements[4]

ION224 Positive Phase 2 Data (MASH)

Orbit – ION356 Study Start (PMD)

1. WAINUA: www.wainua.com. 2. Balance (olezarsen for FCS), OASIS (donidalorsen for HAE). 3. CORE and Essence (olezarsen for sHTG). 4. Phase 2 readout of ION224 for MASH; Started Orbit study in 2024 (ION356 for PMD).

WAINUA for ATTR-CM: Global Phase 3 Development Program Designed to Deliver Robust Results

Robust Development Program

cardio TTRansform

Most comprehensive study to date in ATTR-CM, a fatal disease

Positioned to deliver most robust data in broad patient population

Largest study conducted in ATTR-CM now fully enrolled with >1,400 patients

MRI and scintigraphy sub-studies underway to assess the effects on cardiac structure and function

Next Steps

Data as early as 2025[1]

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

Olezarsen is Delivering Robust Data Supporting its Potential as a Breakthrough Treatment for FCS and sHTG[1]

Familial Chylomicronemia Syndrome (FCS)

Balance
a familial chylomicronemia syndrome study

- Demonstrated substantial reductions in apoC-III, TGs, marked acute pancreatitis reductions, substantial reduction in hospitalizations and favorable safety and tolerability[2]
- Positive data presented at ACC, published in *NEJM*[3]
- **NDA submitted**; EU filing on track this year
- EAP in U.S. for FCS now open, OLE progressing well
- U.S. Breakthrough Therapy and Orphan Drug designations
- Prepared to launch in advance of anticipated approval[4]

Bridge
TIMI 73a

- Phase 2b study in patients with TG ≥150 mg/dL (HTG) and TG ≥500 mg/dL (sHTG)
- Supportive exposure study
- Statistically significant reductions in apoC-III and TGs (including nearly all HTG patients achieving normal TGs)
- Meaningful reductions in apoB, non-HDL-C, markers of CV risk
- Favorable safety and tolerability
- Positive data presented in late-breaker presentation at ACC, published in *NEJM*[5]

1. Timing expectations are based on current assumptions and are subject to change. 2. Due to statistical hierarchy, reductions in apoC-III and acute pancreatitis are considered exploratory. 3. Stroes E, et al. *N Engl J Med*. 2024.
4. Assuming priority review and approval. 5. Bergmark, B, et al. *N Engl J Med*. 2024.

Olezarsen is Delivering Robust Data Supporting its Potential as a Breakthrough Treatment for FCS and sHTG[1]

Severe Hypertriglyceridemia (sHTG)

CORE a hypertriglyceridemia study

- Pivotal study in patients w/ TG ≥500 mg/dL (sHTG)
- Registrational study
- >600 patients
- **Enrollment complete**

CORE2 a hypertriglyceridemia study

- Pivotal study in patients w/ TG ≥500 mg/dL (sHTG)
- Confirmatory registrational study
- 390 patients
- Full enrollment expected mid-year

Essence TIMI-73b

- Supportive Ph3 study in patients w/ TG ≥200-500 mg/dL (HTG)
- Supportive exposure study
- >1,400 patients
- **Enrollment complete**

On Track for Data From All Three Studies by Mid-2025

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

Donidalorsen is Delivering Robust Data Supporting its Potential to Advance Prophylactic HAE Treatment[1,2]

Hereditary Angioedema

Phase 2

- Positive Phase 2 data published in *New England Journal of Medicine*
- Positive Phase 2 1-year and 2-year OLE data, including positive QoL data reported
- Presenting Phase 2 3-year OLE data in H2:24

OASIS

- Positive Phase 3 topline data, including achieving:
  - Statistically significant reduction in HAE attack rates in patients treated every 4 weeks or 8 weeks
- EAP in U.S. now open
- Presenting data at EAACI, May 31st

OASIS plus

- Phase 3 OLE study in patients who have completed OASIS-HAE
  - Expanded enrollment
- Switch cohort in patients previously treated with other prophylactic therapies
- Presenting data at EAACI, May 31st

Preparing to Submit NDA with US FDA; Otsuka Preparing to Submit MAA in EU[3]

1. Based on Phase 3 data, double blind Phase 2 study data published in *NEJM* in 2022 and Phase 2 OLE data. 2. Timing expectations based on current assumptions and subject to change. 3. Licensed European commercialization rights to Otsuka in 2023.

Leading and Validated Neurology Franchise

3

Approved Medicines[1]

12

Medicines in Clinical Development

6

Wholly Owned Medicines in Clinical Development by YE:2024[2]

SPINRAZA
SMA (SMN2)

QALSODY
SOD1-ALS (SOD1)

WAINUA
ATTRv-PN (TTR)

Zilganersen
Alexander disease
(GFAP)

ION717
Prion disease
(PRNP)

Ulefnersen
FUS-ALS
(FUS)

ION541
ALS (ATXN2)

ION356
Pelizaeus-Merzbacher
Disease (PLP1)

ION582
Angelman syndrome
(UBE3A-ATS)

ION306
SMA (SMN2)

Tofersen
Presymptomatic SOD1-ALS
(SOD1)

IONIS-MAPT$_{Rx}$/BIIB080
Alzheimer's disease
(Tau)

ION859
Parkinson's disease
(LRRK2)

Tominersen
Huntington's disease
(HTT)

ION464
Parkinson's disease and
Multiple System Atrophy
(alpha-synuclein)

1. SPINRAZA: www.spinraza.com; QALSODY: www.qalsody.com; Biogen is responsible for commercializing SPINRAZA and QALSODY; WAINUA: www.wainua.com. 2. Timing based on current estimates and subject to change.

Key Value-Driving Events Planned For 2024[1]

Phase 3 Clinical Data Events

Donidalorsen
✓ OASIS-HAE topline data

OASIS-HAE full data

OASIS-PLUS OLE + Switch data

Olezarsen
✓ Balance study full data, FCS

Phase 2 Clinical Data Events

Donidalorsen
3-year OLE, HAE

IONIS-FB-L$_{Rx}$
Geographic Atrophy

IgA nephropathy

ION224
✓ NASH

ION582
Angelman syndrome

ION541
ALS

Regulatory Actions

Eplontersen
OUS approval decisions, ATTRv-PN

✓ OUS filings, ATTRv-PN

Olezarsen
NDA filing, FCS[2]

FDA approval decision, FCS[3]

EU filing, FCS

Donidalorsen
NDA filing, HAE

QALSODY
EMA approval decision, SOD1-ALS

New Product Launches

WAINUA
✓ ATTRv-PN[4]

Olezarsen
FCS[3]

QALSODY
EU, SOD1-ALS[5]

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. NDA submission completed. 3. Assuming priority review. 4. WAINUA: www.wainua.com 5. Assuming approval in 2024.

Preparing to Bring Important Ionis Medicines to Patients

Kyle Jenne
Chief Global Product Strategy and Operations Officer

WAINUA Approved for ATTRv-PN: Launch Underway for the First Ionis Co-Commercialized Medicine[1]

For ATTR Polyneuropathy, a systemic, progressive and fatal neurological disease

1. WAINUA: www.wainua.com; co-developing and commercializing in the U.S. with AstraZeneca.

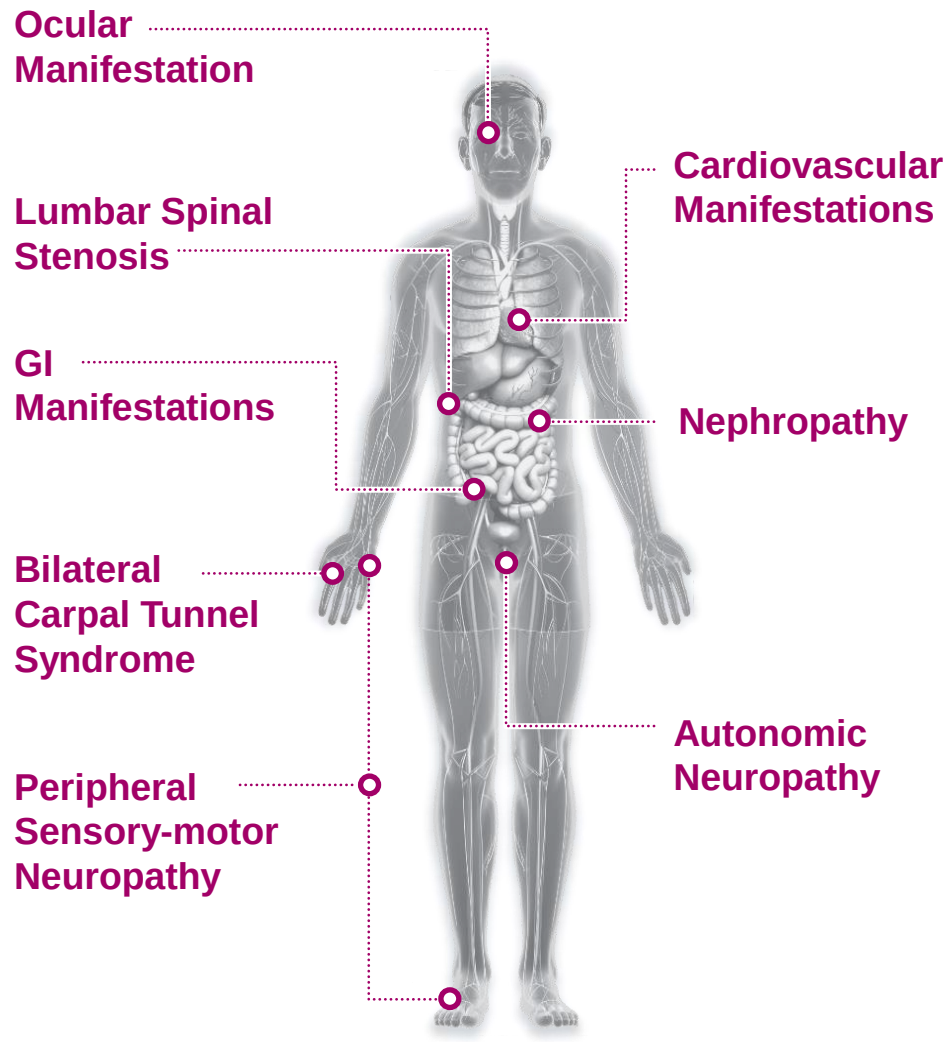
WAINUA: Positioned to Address the High Unmet Need in ATTR[1,2,3,4]

Potential to be the **treatment of choice** for the **global ATTR population** with **strong clinical profile** and **monthly self-administered** auto-injector dosing

Expanding Patient Population

	Indication	Patients[3,4]
	ATTR	~500K
CM	wtATTR & ATTRv	300K-500K
PN	ATTRv-PN + Mixed	40K

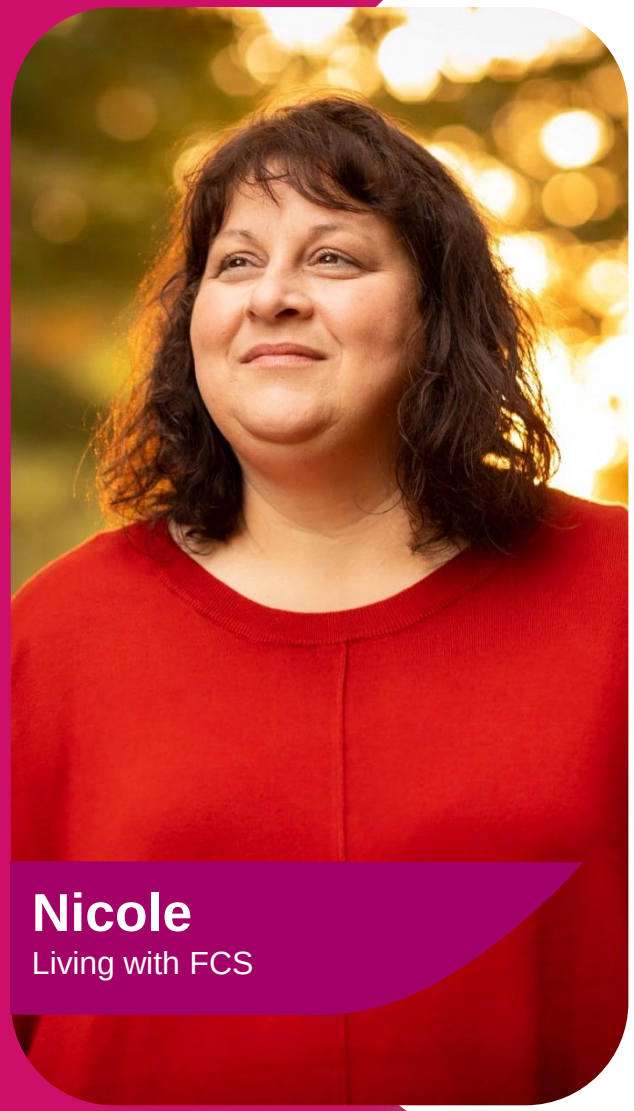
Currently <20% of ATTR patients are treated[2]



amyloidosis.org (https://amyloidosis.org/facts/familial/; https://amyloidosis.org/facts/wild-type/
NOTE: For illustrative purposes only. 1. ATTRv-PN potential approval this year. 2. Market data on file. 3. Conceição I et al. *J Peripher Nerv Syst*. 2016;21:5-9. 4. Ando Y et al. *Orphanet J Rare Dis*. 2013;8:31.

Olezarsen:

Potential to become the **Standard-of-Care** for Patients with **Severely Elevated Triglycerides**[1,2]



Substantial unmet need

Positive Balance study results[3]**:**

- Robust reductions in apoC-III, TGs & favorable safety and tolerability
- Markedly lower rate of acute pancreatitis vs. placebo

NDA submitted for **FCS,** potential FDA approval in **2024; EU filing planned** for this year[2]

1st independent launch[4]

Two planned indications:

- Starting with exciting rare disease opportunity in FCS
- Expanding to broader sHTG population

1. Based on data generated to date. 2. Timing based on current estimates and subject to change. 3. Due to statistical hierarchy, reductions in apoC-III and acute pancreatitis are considered exploratory. 4. Assumes priority review and approval.

Poised to Deliver Olezarsen to the Market…

Focused on the unique needs of patients, caregivers, physicians and payers

- **Building launch momentum through disease awareness and patient identification**
- **Market research to identify physicians most likely to prescribe olezarsen**
- **Patient & caregiver support to assist patients through their treatment journey**
- **Efficient and targeted commercial team built to address HCP and patient needs**

Donidalorsen:

A Potential
First-in-Class
RNA-Targeted Medicine for
Hereditary Angioedema[1]

Substantial unmet need remains

- Potentially fatal breakthrough attacks
- Desire for greater treatment simplicity and tolerability

Donidalorsen profile[1,2]:

- Significant and sustained reductions in HAE attacks (near elimination)
- Attractive tolerability and safety
- Simplicity of monthly or bi-monthly self-administration with an autoinjector

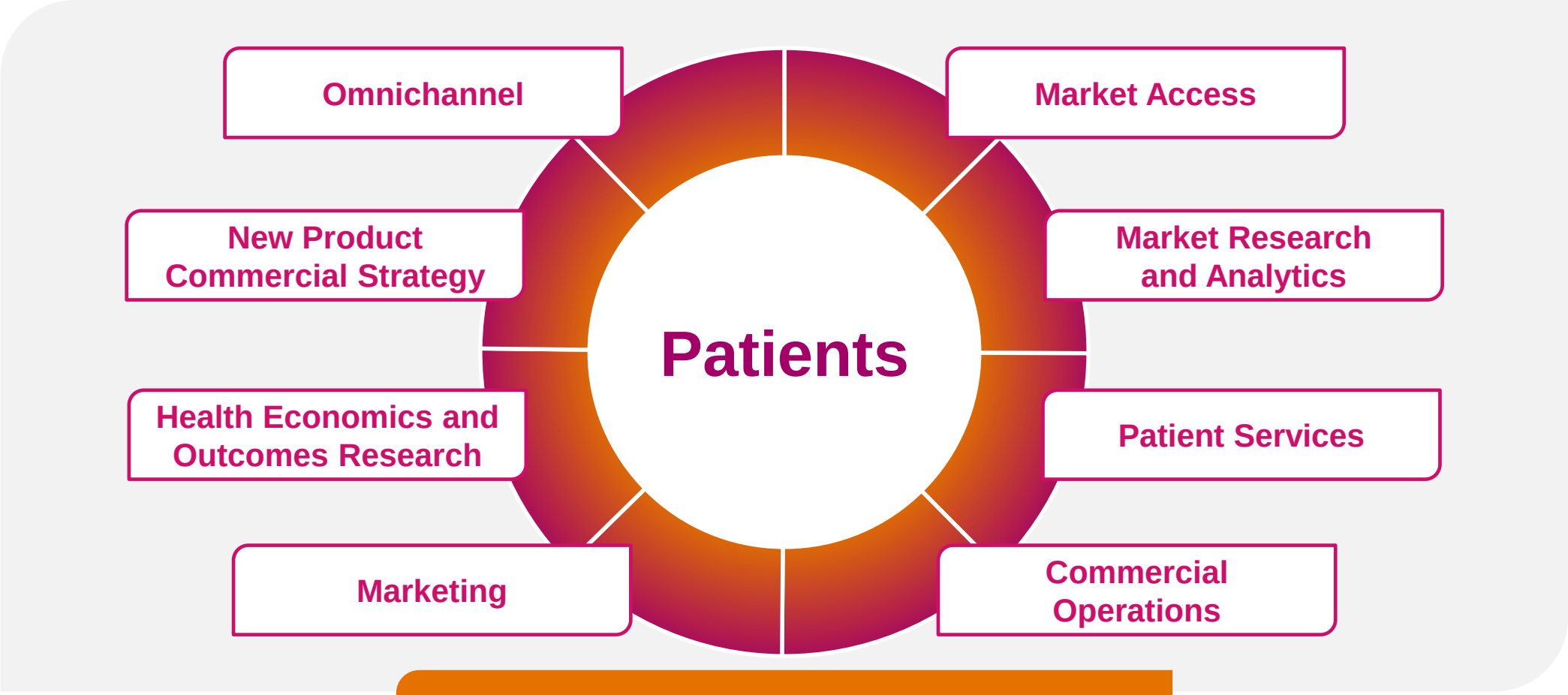
Plan to reach underserved HAE patients globally[2]

- Ionis to commercialize in the US
- EU access through Otsuka (tiered royalties ranging from 20-30%)

Launch planned for 2025[3]

1. Based on data generated to date including Phase 2, Phase 2 OLE and Phase 3. 2. Assuming approval. 3. Timing based on current estimates and subject to change.

Commercial Infrastructure in Place: Ready to Deliver Medicines to People in Need



Ionis' Q1 2024 Financial Performance & Clear Path to Positive Cash Flow

Beth Hougen
Chief Financial Officer

Q1:2024 Financial Highlights[1]

On Track to Achieve 2024 Guidance

$119M **Revenue**

Commercial Revenue: $59M

- SPINRAZA comprised largest component
- New stream of royalty revenue with WAINUA launch

R&D Revenue: $60M

- Reflects the value Ionis' pipeline and technology create as programs advance

$238M **Operating Expenses[2]**

R&D Expenses[2]: $192M

- Increased YoY primarily from advancing late-stage programs

SG&A Expenses[2]: $44M

- Increased YoY from launch of WAINUA and advancing go-to-market activities for multiple near-term launches

$2.2B **Cash & short-term investments**

Enables continued investments to drive increasing value

1. For the three months ended March 31, 2024. 2. Non-GAAP – please see reconciliation to GAAP in Q1 2024 press release.

On Track to Achieve 2024 Financial Guidance

Revenue	Operating Loss	Cash
>$575 million	**<$475** million[1]	**~$1.7** billion

Expectations for 2024:

Revenue: Substantial and sustained

- **Commercial:** sustained SPINRAZA royalties; WAINUA royalties
- **R&D:** multiple sources from numerous advancing programs

Operating Loss & Cash: reflects investments toward growth opportunities

1. Non-GAAP – please see reconciliation to GAAP in Q1 2024 press release.

Investing Efficiently to Drive Positive Cash Flow

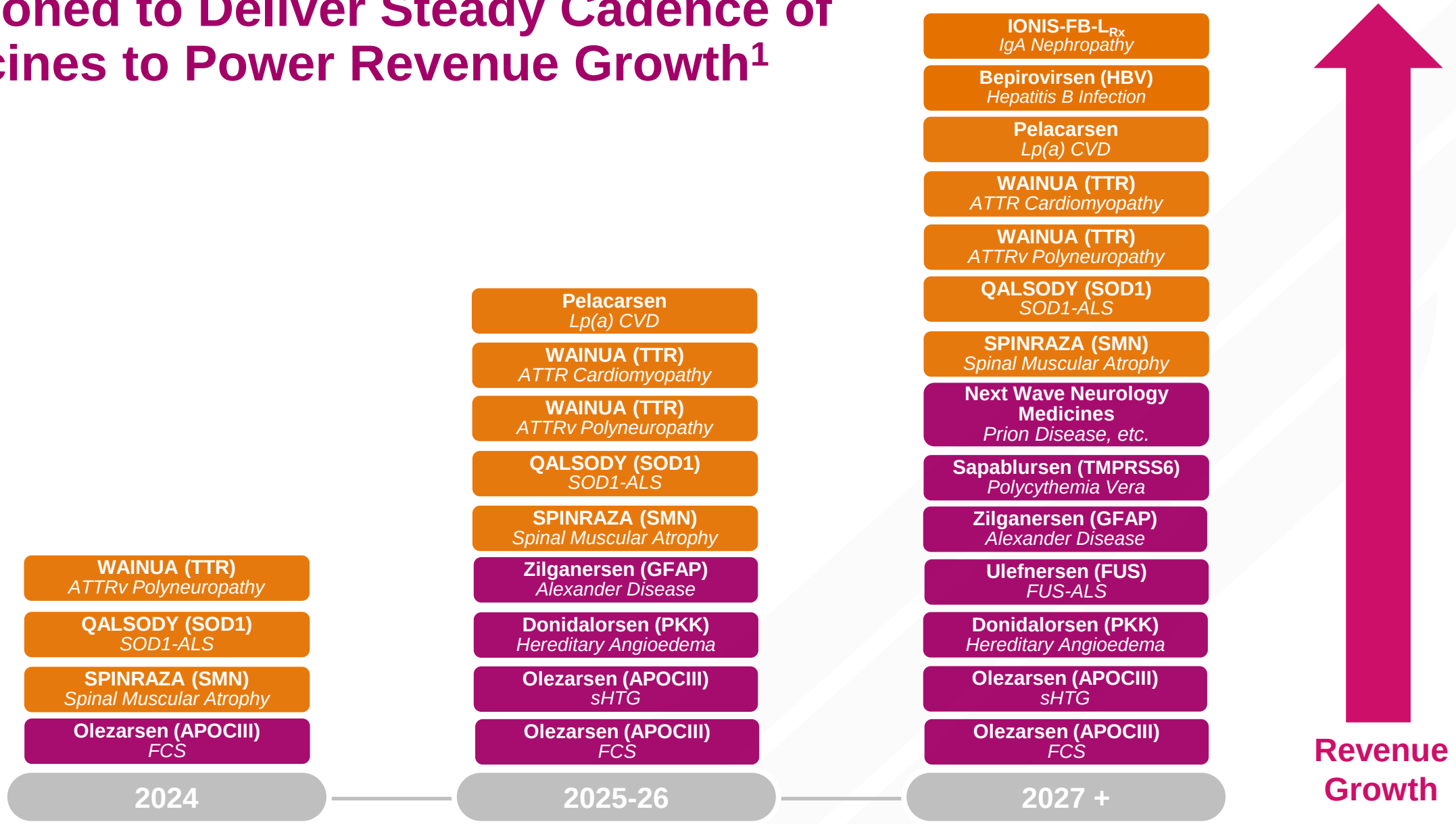
Go-to-Market Activities	Integrated commercial capabilities in place; right-sizing and scaling for successful launches
Late-Stage Medicines	Ionis' large Phase 3 studies are at or near full enrollment
Next Wave of Medicines	Investing in advancing our growing wholly owned pipeline
Cutting-Edge Technologies	Continued innovation for future medicines

Modest Expense Growth over the Short- and Mid-Term

SG&A Expenses Ramp In-line with Planned Launches

R&D Expenses Approaching Steady State

Positioned to Deliver Steady Cadence of Medicines to Power Revenue Growth[1]



1. Estimated timing of potential US approval based on current assumptions and are subject to change. 2. Donidalorsen European rights licensed to Otsuka.

Wholly Owned[2] Partnered

Clear Path to Drive Value Creation

Foundation

Solid
Financial Foundation
and
Robust Innovative
Pipeline Position Ionis
to Drive Value

Invest

Invest to Bring Important Medicines to Patients

—

Advancing Pipeline
and Technology
to Drive Steady Cadence
of New Medicines

Growth

Positive Cash Flow
Powered by
Substantial Revenue
Growth

Conclusion

Brett Monia, Ph.D.
Chief Executive Officer

Well-Positioned to Build on Momentum by Executing on Strategic Priorities

01

Wholly Owned Pipeline

Advancing and growing our wholly owned pipeline in focused therapeutic areas (neurology and cardiology)

02

Integrated Commercial Capabilities in Place

Steady cadence of new potentially **transformational medicines** to the **market**

03

Leading Technology

Advancing technology to **expand existing franchises and address new therapeutic areas**

04

Effective Financial Strategy Poised for Growth

Multi-billion-dollar revenue opportunity to enable future **positive cash flow**

Jackson,
Angelman Syndrome Patient

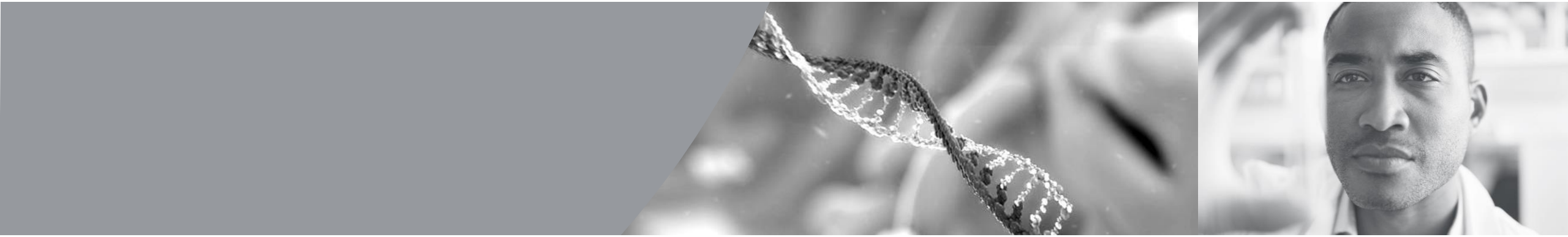
Driving Next-Level Value for Patients and All Ionis Stakeholders

Q&A

Donidalorsen Phase 3 Results

OASIS-HAE and OASIS-Plus: OLE + Switch

Webcast May 31st



Appendix

Delivering Steady Cadence of Potentially Transformational Medicines[1]

9 Medicines in Phase 3 for 11 indications

		Indication	Prevalence[2]	Next Event[3]
WAINUA (eplontersen)	IONIS / AstraZeneca	ATTRv-PN		**Additional OUS submissions (2024)**
		ATTR-CM		**Ph3 data (2025)[4]**
Olezarsen	IONIS	FCS		**OUS submissions (2024)[5]**
		sHTG		**Ph3 data (2025)**
Donidalorsen	IONIS	HAE		**NDA filing (2024)**
Zilganersen	IONIS	Alexander disease		**Ph3 data (2025)**
Ulefnersen	IONIS	FUS-ALS		**Ph3 data (2026)**
Pelacarsen	NOVARTIS	Lp(a) CVD		**Ph3 data & filing (2025)**
Bepirovirsen	GSK	HBV		**Ph3 data (2026)**
IONIS-FB-L_{Rx}	Roche	IgA nephropathy[6]		**Ph2 data (2024)**
Tofersen	Biogen	Presymptomatic SOD1-ALS		**Ph3 data (2028)**

1. Assuming approval 2. Market data on file. 3. Timing expectations are based on current assumptions and are subject to change. 4. Results as early as 2025. 5. EU submission planned. 6. IONIS-FB-L_{Rx} is also in the Phase 2 GOLDEN study in patients with Geographic Atrophy, with topline data expected in 2024.