2024 Annual Shareholders Meeting

Corporate Update

June 6, 2024

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.ionis.com.

In this presentation, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries.

Executing on a Clear Vision

Extending Leadership in RNA-Targeted Therapeutics

Delivering a Steady Cadence of Potentially Transformational Medicines

- **Leading Technology**
- **Prioritizing and Expanding the Ionis Wholly Owned Pipeline**
- **Delivering Ionis Medicines Directly to Patients**
  while Supporting our Partnered Pipeline

Financial Strength and Responsibility

2024 Off To Strong Start with Several Important Achievements

2

New Product Launches

WAINUA (eplontersen) 45 mg injection for subcutaneous use

U.S launch (ATTRv-PN[1])

QALSODY™ (tofersen) 100 mg/15 mL injection

EU launch SOD1-ALS[2]

3

Positive Phase 3 Readouts[3]

Balance — a familial chylomicronemia syndrome study

OASIS — Hereditary Angioedema

OASIS plus — Hereditary Angioedema

4

Phase 3 Studies Fully Enrolled[4]

CORE — Severe hypertriglyceridemia (sHTG)

Essence — sHTG-supporting study

B-Well 1 & B-Well 2 in Chronic HBV

2

Positive Phase 2 Readouts[5]

ION224 in MASH

ION582 in Angelman's Syndrome

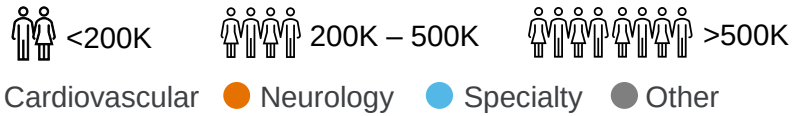
1. WAINUA: www.wainua.com. 2. QALSODY: www.ema.Europa.eu; Biogen is responsible for commercializing QALSODY. 3. Balance (olezarsen for FCS), OASIS (donidalorsen for HAE). 4. CORE and Essence (olezarsen for sHTG). B-Well 1 & B-Well 2 (chronic HBV). 5. Phase 2 readout of ION224 for MASH; Phase 2 readout of ION582 for Angelman syndrome.

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		**OUS approvals (2024)**
	ATTR-CM		**Ph3 data (2026)[4]**
Olezarsen (IONIS)	FCS		**FDA approval (2024)[5]**
	sHTG		**Ph3 data (2025)**
Donidalorsen (IONIS)	HAE		**NDA & MAA 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]		**Ph3 data IgAN (TBD)** **Ph2 data in GA (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.



Realizing the Promise of our Innovative Medicines[1]

First Ionis-Branded Medicine[2]

WAINUA (eplontersen) 45 mg injection for subcutaneous use

Launched in ATTRv-Polyneuropathy January 2024

Ongoing fully enrolled Phase 3 study for ATTR Cardiomyopathy[3]

Co-developing and commercializing in the U.S. with AstraZeneca

First Ionis Independent Launches[1,4]

Olezarsen

Launch in FCS expected by YE:2024[4]

Pivotal sHTG program on track

Blockbuster opportunity[5]

Donidalorsen

Launch in HAE expected in 2025[4]

Efficient commercial organization

Establishing global access

Next Wave of Wholly Owned Medicines

Leading Neurology Pipeline

Proven track record of delivering first-in-class disease modifying medicines

ION582

Angelman Syndrome data planned in July[1]

7 wholly owned medicines in clinical development by YE:2024

1. Timing expectations and peak sales estimates based on current assumptions and subject to change. 2. WAINUA: www.wainua.com. 3. Data planned for ATTR-CM as early as 2025. 4. Assuming approval. 5. In aggregate.

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

For Hereditary 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 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 the richest 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

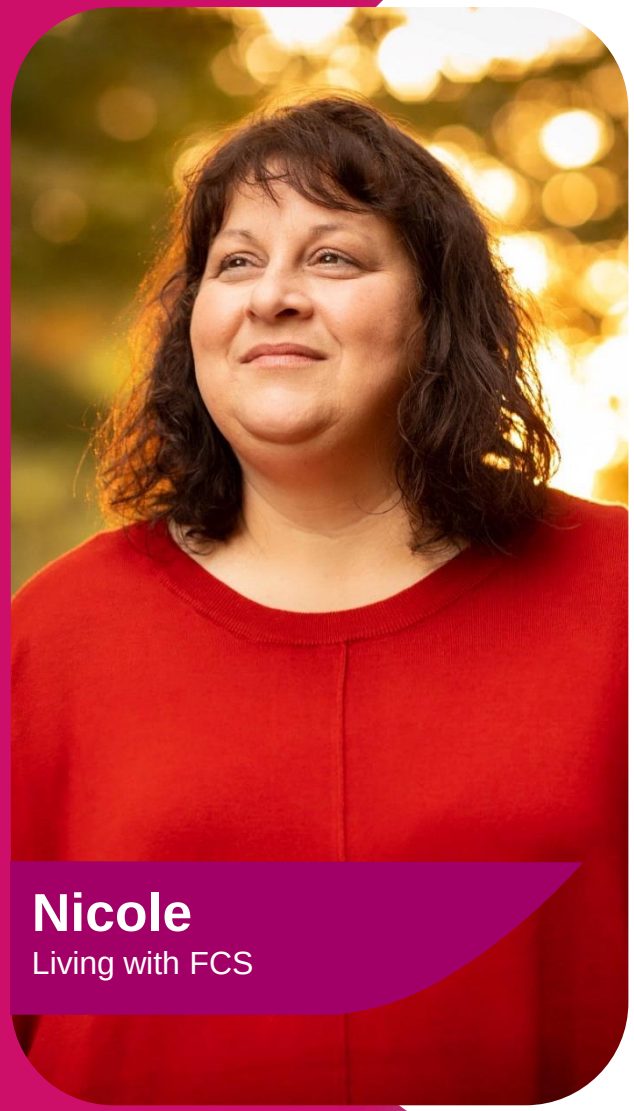
Next Steps

Data in 2026[1,2]

1. Timing expectations based on current assumptions and subject to change. 2. Potential to read out data as early as 2025.

Olezarsen:

Blockbuster opportunity with potential to become the **Standard-of-Care** for Patients with **Severely Elevated Trigylcerides**[1,2]



Two planned indications:
- Starting with rare disease opportunity in FCS
- Expanding to broader sHTG population

Substantial unmet need

Positive Balance (FCS) 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**[4]**; EU filing planned** for this year[2]

1st independent launch[5]

Phase 3 sHTG program to **complete enrollment soon** (data in 2025)[2]

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. Assuming priority review in the U.S. 5. If approved.

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

Familial Chylomicronemia Syndrome (FCS)

Balance
a familial chylomicronemia syndrome study

- Demonstrated substantial reductions in: apoC-III, TGs, acute pancreatitis, hospitalizations and inpatient hospitalizations[2]
- Favorable safety and tolerability
- 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
- Granted U.S. Breakthrough Therapy and Orphan Drug designations
- Prepared to launch in advance of anticipated approval[4]

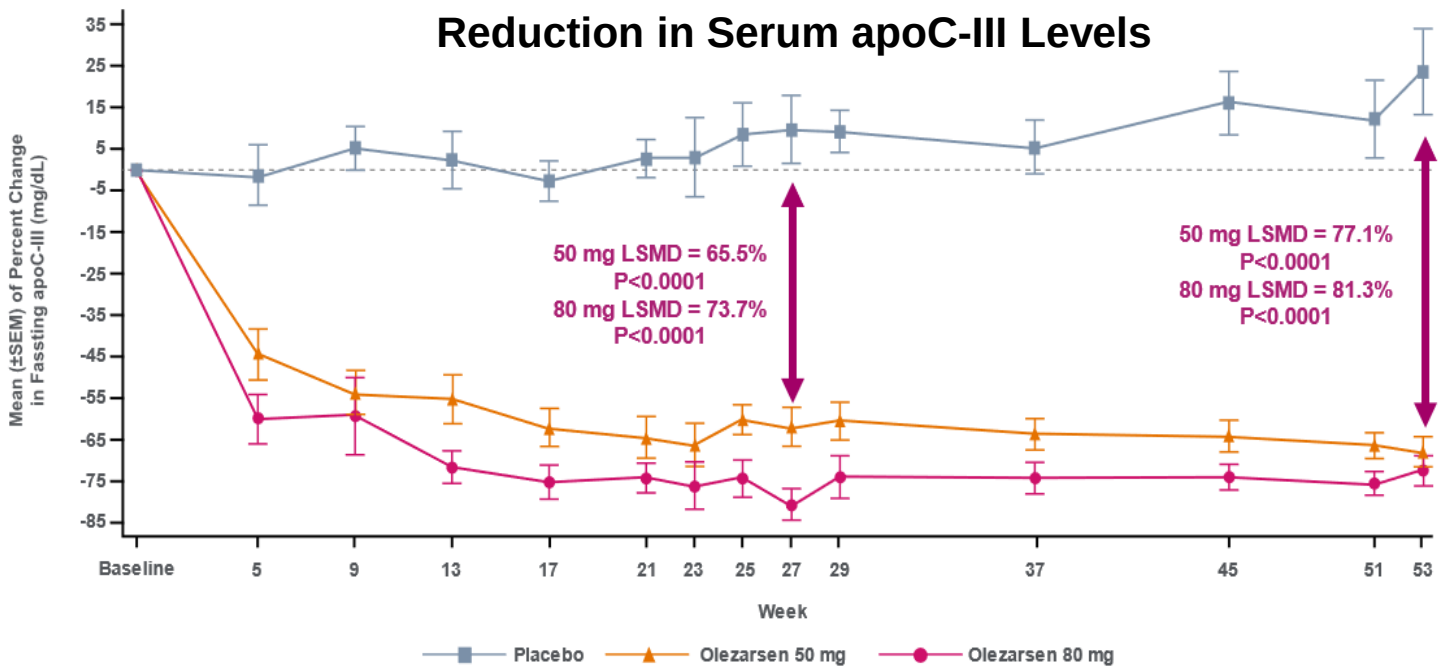
1. Timing expectations are based on current assumptions and are subject to change. 2. Due to statistical hierarchy, reductions in apoC-III and acute pancreatitis are considered exploratory. 3. Stroes E, et al. *N Engl J Med*. 2024.
4. If approved.

Positive Olezarsen Phase 3 Results in FCS Patients[1,2]

Balance
a familial chylomicronemia syndrome study

Olezarsen treatment resulted in:

- **Robust and significant reduction in serum apoC-III levels** at 6 and 12 months
- **Statistically significant reductions in triglycerides** at 80mg dose
- **Substantial reductions in acute pancreatitis attacks**
- **Significant reductions in hospitalizations and in hospital days**
- **Favorable safety and tolerability profile**



81% LSMD in apoC-III Levels at 12 months with 80mg dose

P<0.0001 At 6 months and 12 months

1. Data reported on at ACC on April 7, 2024. 2. LSMD = Least squares mean difference

Olezarsen is Delivering Positive 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

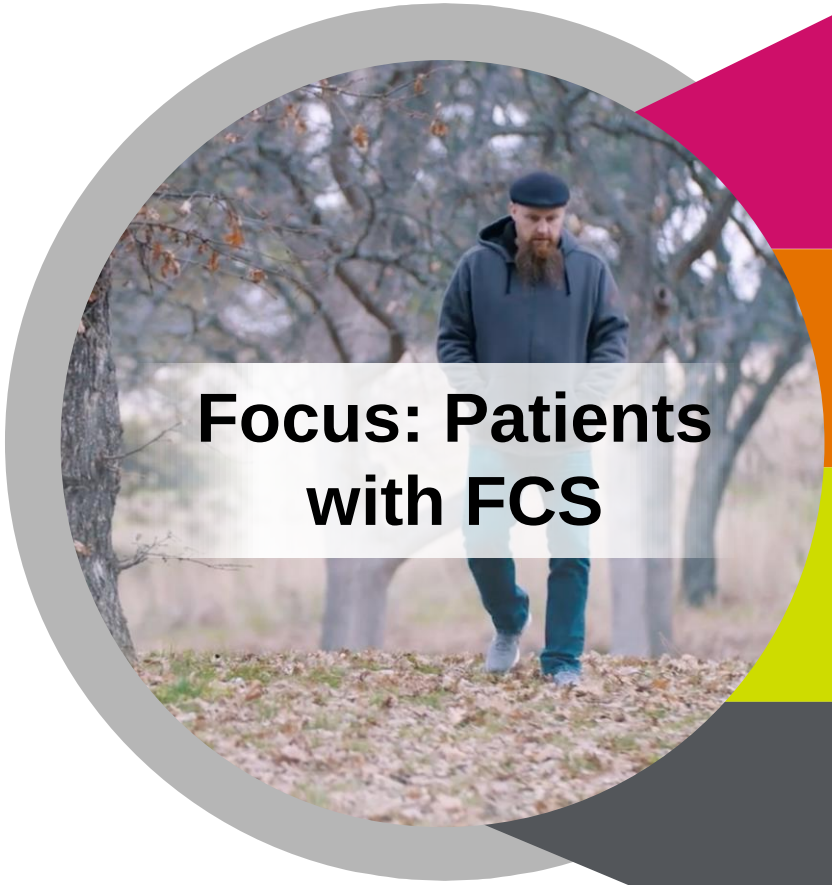
- Supportive Ph3 study in patients w/ TG ≥200-500 mg/dL (HTG)
- Supportive exposure study
- >1,400 patients
- **Enrollment complete**

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

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

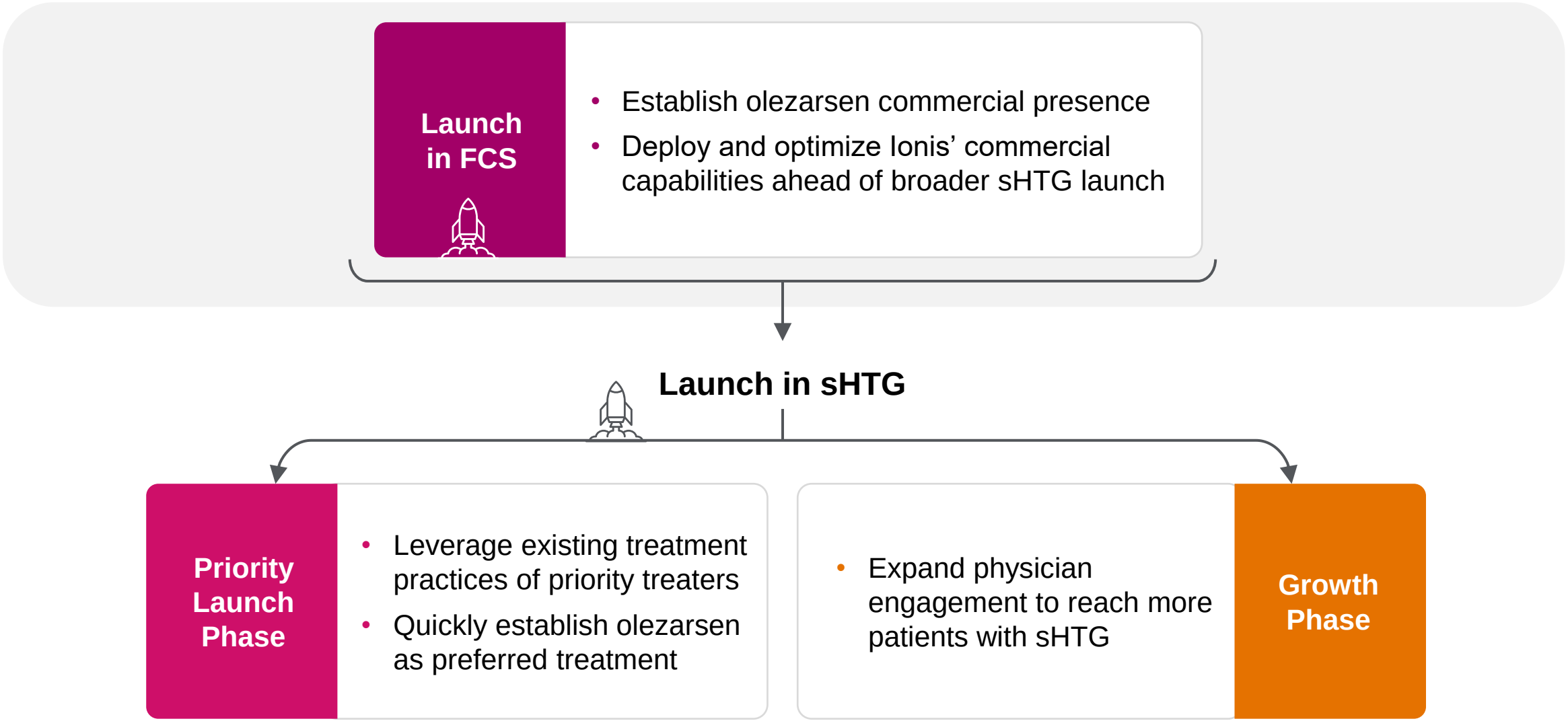
Poised to Deliver Olezarsen to the Market…

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



- **Building launch momentum through disease awareness and patient identification campaign**
- **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**

Olezarsen Launch is Designed for Commercial Success



Donidalorsen:

A Potential **Preferred Treatment** for People with **Hereditary Angioedema**[1,2]

New prophylactic treatments needed[3]

Donidalorsen profile[1]:

- Substantial and sustained reductions in HAE attacks
- >80% preference for donidalorsen over other prophylactic treatments
- Favorable safety and tolerability
- Patient-friendly monthly or every two-month self-administration with an autoinjector

Plan to reach underserved HAE patients globally[4]

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

Launch planned for 2025[2,4]

1. Based on data generated to date including Phase 2, Phase 2 OLE, Phase 3 and Phase 3 OLE + Switch data. 2. Assuming approval. 3. Sandra C. Christiansen MD , Joyce Wilmot MS , Anthony J. Castaldo MPA , Bruce L. Zuraw MD , For the US HAEA Medical Advisory Board members, The US HAEA Scientific Registry: Hereditary Angioedema Demographics, Disease Severity, and Comorbidities, Annals of Allergy, Asthma Immunology (2023) 2. HAEI (https://haei.org/hae/faq/ accessed May 2024). 4. Timing based on current estimates and subject to change.

Donidalorsen: Robust Data Supports Potential Preferred Treatment for HAE Prophylaxis[1]

OASIS

- Substantial reductions in HAE attack rates + favorable safety and tolerability
- Improved QoL measures
- High levels of disease control
- U.S. and EU Orphan drug designations
- Positive data presented at EAACI; published in *NEJM*[2]

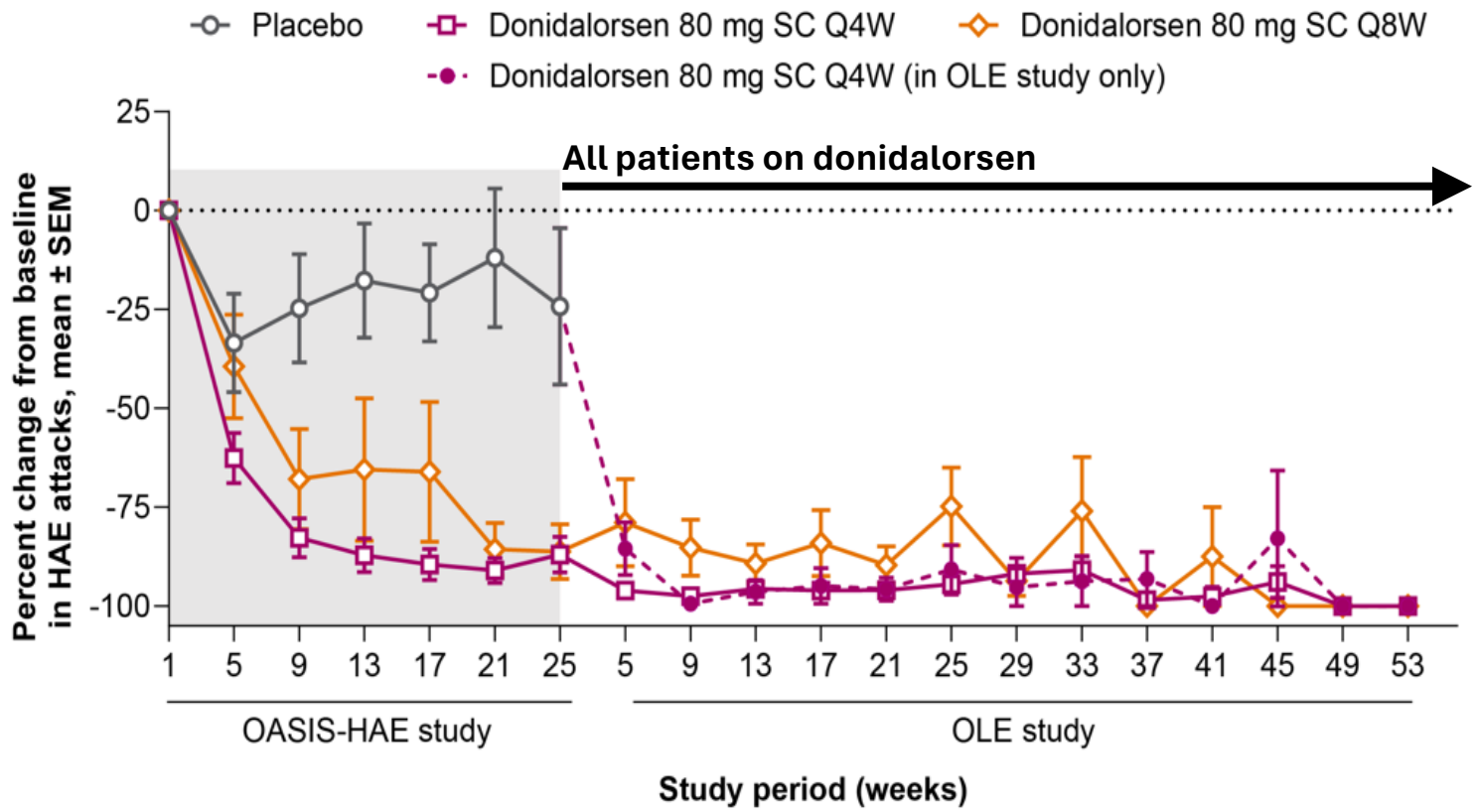
OASIS plus

- OLE cohort demonstrated that long-term treatment continued to improve HAE attack rates and QoL measures
- Positive results from Switch cohort in patients previously treated with other prophylactic therapies showed:
  - Improved HAE attack rates, QoL measures and disease control
  - Strong preference for donidalorsen
  - Useful data to inform potential switching
- Positive data presented at EAACI

U.S. and EU filings on track this year; Prepared to launch in 2025

1. Timing expectations based on current assumptions and subject to change. 2. Riedl, M et al. *N Engl J Med.* 2024.

OLE: Further Reduction in HAE Attacks with Extended Donidalorsen Treatment[1,2]



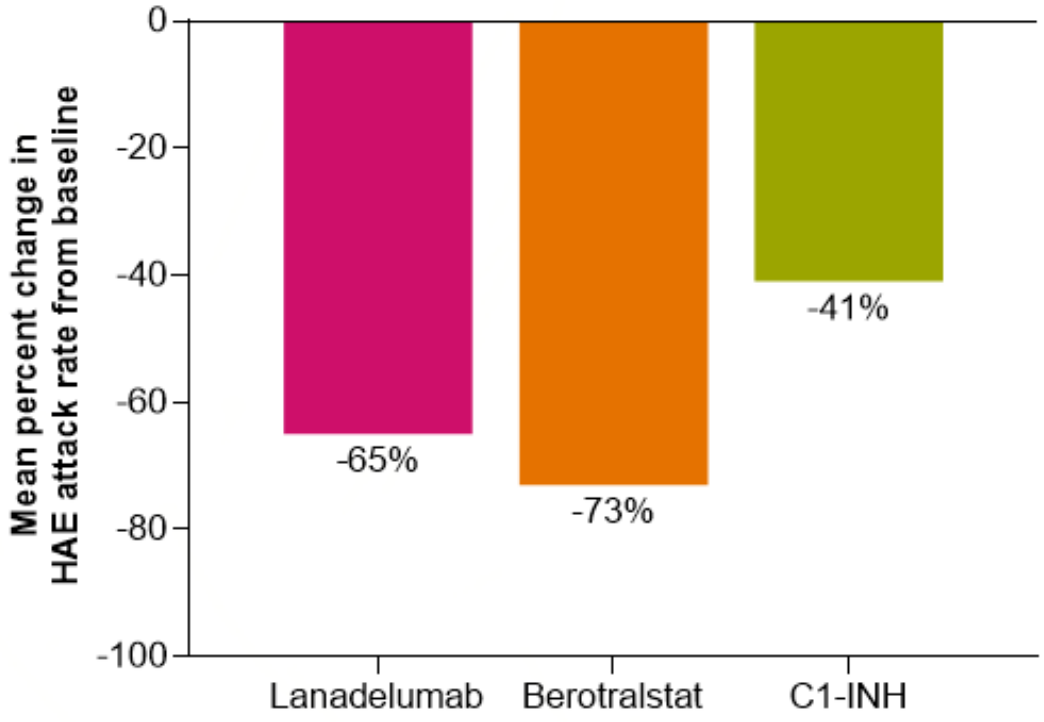
Placebo, n =	19	19	19	19	18	17	16	19	19	19	19	16	15	13	10	6	5	5	4	2
Donidalorsen 80 mg Q4W, n =	44	44	44	44	44	43	43	44	44	43	43	36	30	26	24	18	11	8	4	3
Donidalorsen 80 mg Q8W, n =	20	20	20	20	20	20	19	20	20	20	20	16	14	13	12	8	4	3	2	2

- **Q4W substantially reduced** mean **HAE attack rates:**
  - **93% improvement** from baseline at the start of OASIS-HAE[3]
- **Q8W** had a **similar effect** as **Q4W** dosing
  - **92% improvement** from baseline at the start of OASIS-HAE in HAE attack rates[3]

1. OASIS-HAE primary endpoint evaluation at 25 weeks, after which patients rolled over into the OASISplus OLE study. 2. Patients previously on placebo in OASIS-HAE transitioned to Q4W dosing. 3. Change in time-normalized mean HAE attacks per month.

Donidalorsen Substantially Reduced HAE Attack Rates After Switching[1-3]

% Reduction in HAE Attack Rate[4]

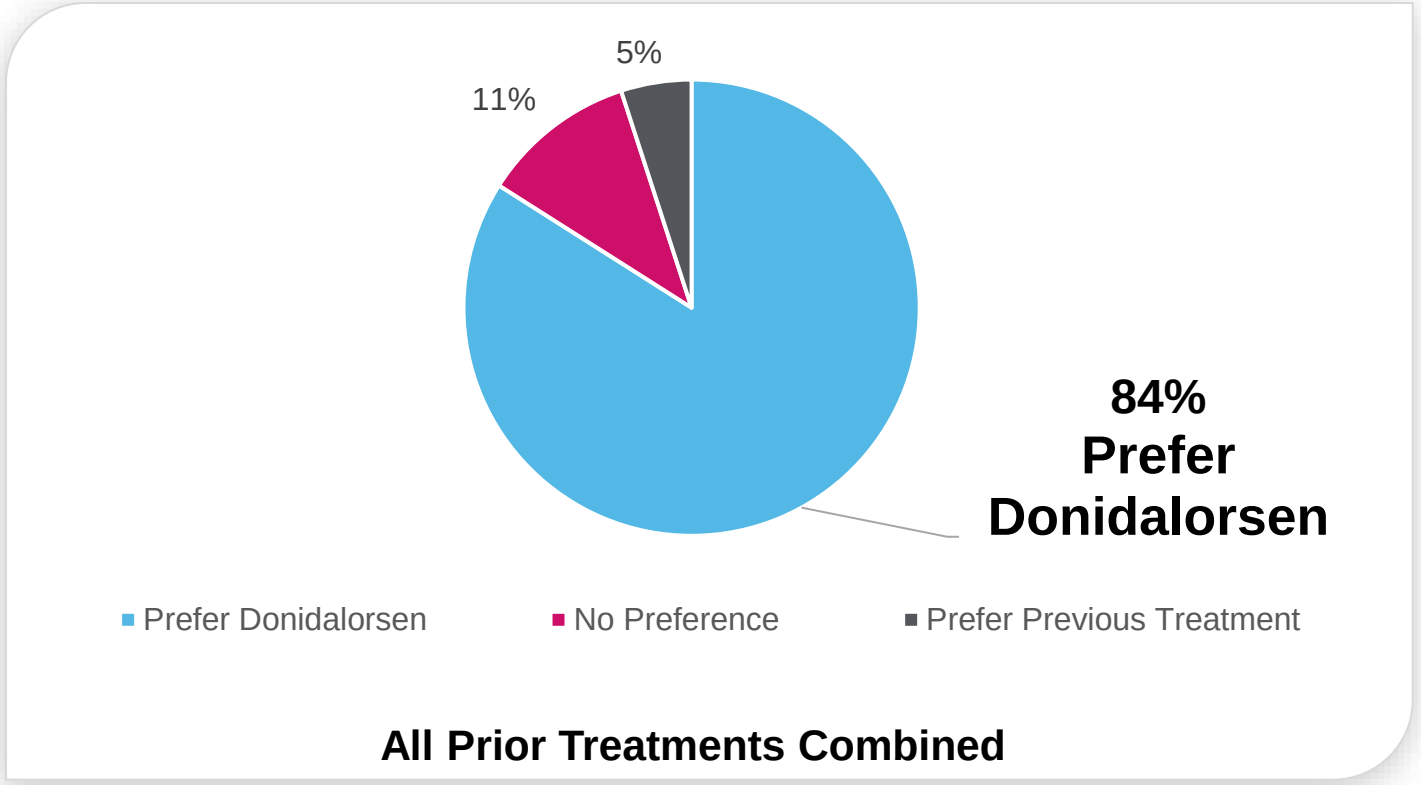


n =	31	11	22
Baseline, mean ± SD =	0.69 ± 1.09	1.80 ± 1.92	0.61 ± 0.96
Donidalorsen Q4W, mean ± SD =	0.24 ± 0.33	0.48 ± 0.53	0.36 ± 0.69

1. As of February 28, 2024 for Weeks 1-17. 2. Mean (SD). 3. Baseline HAE attack rate during the screening period for the Switch study. 4. Time-normalized number of HAE attacks per month (Weeks 1–17).

>80% of Switch Patients Preferred Donidalorsen[1,2]

Data generated from independently administered survey



	Lanadelumab (n=25)	Berotralstat (n=10)	C1-INH (n=20)	Total (n=55)
% of Patients who Preferred Donidalorsen	72%	90%	95%	84%

1. As of February 28, 2024. 2. Assessed at Week 17.

Donidalorsen: A Potential Preferred Choice for People with HAE[1,2]

HAE is a severe, rare, genetic disease

New prophylactic treatments are needed

Donidalorsen robust data demonstrated**:**

- **Substantial** and **sustained** reduction in HAE attacks
- **Improvement** in **QoL** measures and **≥90% were well-controlled**[3]
- **Extended dosing** to monthly and every two-months with simple self-administered **autoinjector**
- **All patients had a reduction in HAE attack rates after switching to donidalorsen**[4] and **>80% preference** over **other prophylactic treatments**
- **Favorable safety and tolerability profile**

1. Based on data generated to date including Phase 2, Phase 2 OLE, Phase 3 and Phase 3 OLE + Switch data as of February 28, 2024. 2. Assuming approval. 3. In Q4W dose in OASIS-HAE, Q4W and Q8W in OLE and in switch. Weller K, et al. *J Allergy Clin Immunol Pract*. 2020;8(6):2050-7.e4; well controlled is defined as an AECT score ≥10. 4. Compared to baseline.

Efficient and Targeted Approach to Reach People with HAE and HCPs

Lauren & Lindsey
Sisters Living with HAE

Concentrated Prescriber Base

Majority of People with HAE in the US are Treated by Allergists

~1,000 Allergist/Immunologists Manage >70% of HAE Patients[1]

Efficient Field Team

Planning for <100 Person Customer-Facing Team

Field Sales Reps Focused on Top Allergist & Immunologist Prescribers

Patient Education Managers Supporting Donidalorsen Patients

Direct-to-Patient Engagement

Dedicated High-Touch Patient Services

Continued Engagement and Adherence Through Integrated Omnichannel Solutions

1. Ionis secondary market research (2021).

Leading and Validated Neurology Franchise

3

Approved Medicines[1]

11

Medicines in Clinical Development

7

Wholly Owned Medicines in Clinical Development by YE:2024[2,3]

SPINRAZA® (nusinersen) injection 12 mg/5 mL

QALSODY™ (tofersen) 100 mg/15 mL injection

WAINUA® (eplontersen) 45 mg injection for subcutaneous use

Zilganersen
Alexander disease
(GFAP)

Ulefnersen
FUS-ALS
(FUS)

ION582
Angelman syndrome
(UBE3A-ATS)

ION717
Prion disease
(PRNP)

ION356
Pelizaeus-Merzbacher Disease (PLP1)

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. Wholly owned programs include: zilganersen (Alexander disease), Ulefnersen (FUS-ALS), ION582 (Angelman syndrome), ION717 (Prion disease) and ION356 (PMD). ION440 (MECP2 Duplication syndrome) and an undisclosed genetic dementia target are expected to enter clinical development by YE:2024. 3. Timing based on current estimates and subject to change.

Our Next Wave: 7 Wholly Owned Neurology Medicines in Clinical Development by YE:2024 with More to Follow[1]

Rare Pediatric Neurology

Zilganersen
Alexander Disease
Pivotal study underway

ION582
Angelman Syndrome
Data planned in July[1]

ION356
Pelizaeus-Merzbacher Disease (PMD)
First in patient study underway

ION440
MECP2 Duplication Syndrome
First in patient study to start in 2024

Dementia

ION717
Prion Disease
(PRNP)
First in patient study underway

Genetic Dementia Target
First in patient study to start in 2024

Future Wave

Neuromuscular and Peripheral Neuropathies

Motor Diseases

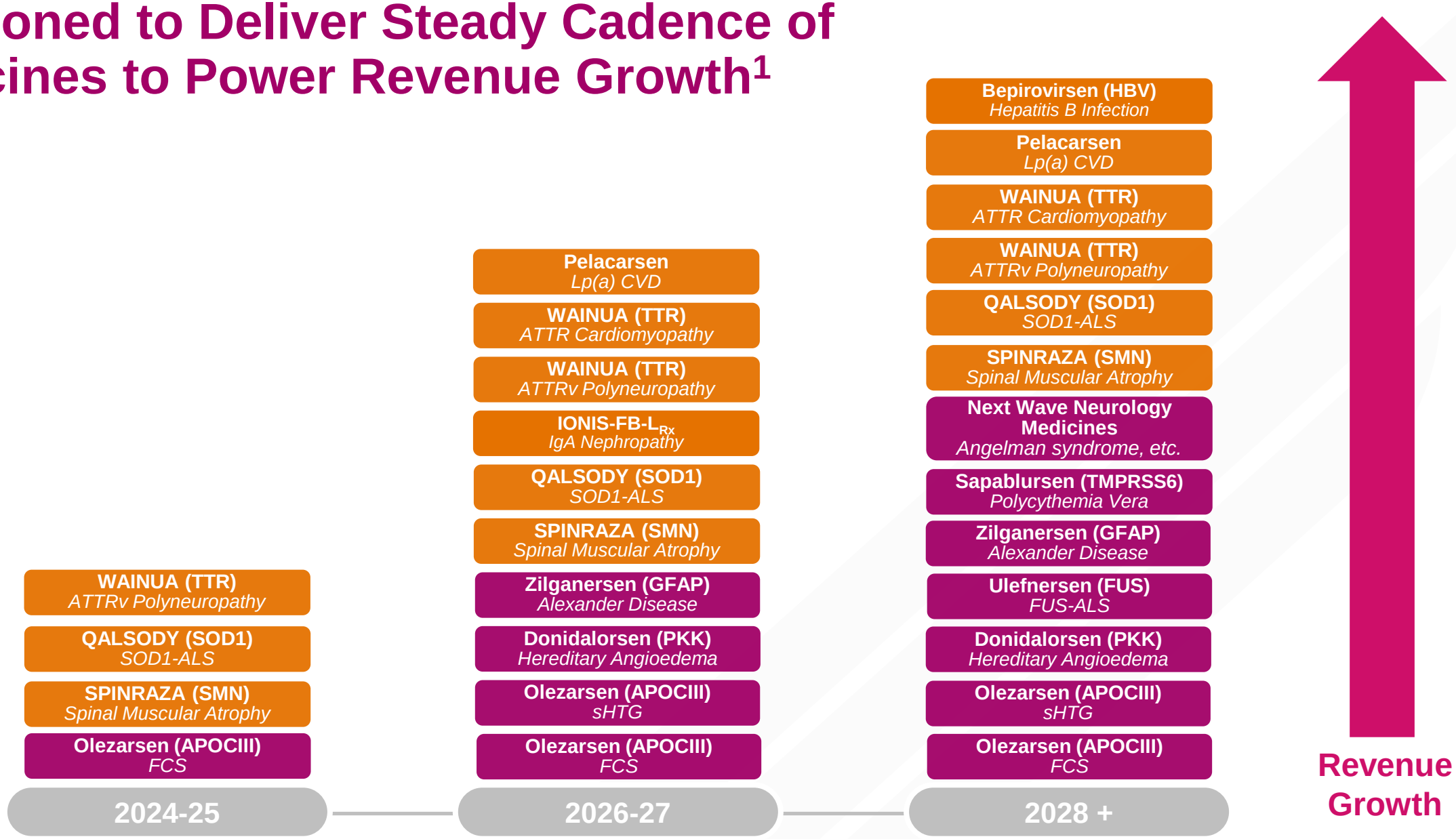
Expand into Next Key Areas of Neurology

Expand into Dementia

Rare Pediatric Neurology is the Foundation

1. Timing based on current estimates, subject to change.

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

Advancing RNA and DNA Technologies for Future Medicines

Expanding Technology Platform

Broad Range of Technologies

ASO | siRNA | DNA Editing

Optimizing Potency and Durability

Systemic and Local Applications

Optimizing Delivery

Targeted Delivery (e.g., LICA)

Cardiac Muscle

Skeletal Muscle

Blood Brain Barrier

Expanding Therapeutic Opportunities

Established Franchises

Cardiovascular | Neurology

New Potential Focus Areas

Pulmonary | Renal

Leading Medicinal Chemistry Platform

Key Value-Driving Events Planned For 2024[1]

Phase 3 Clinical Data Events

Donidalorsen
- OASIS-HAE topline data
- OASIS-HAE full data
- OASISplus OLE + Switch data

Olezarsen
- Balance study full data, FCS
- CORE & CORE2 studies fully enrolled, sHTG

Phase 2 Clinical Data Events

Donidalorsen
3-year OLE, HAE

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

IgA nephropathy (>1yr OLE)

ION224
- MASH (NASH)

ION582
- Angelman syndrome

ION541
ALS

Regulatory Actions

Eplontersen
OUS approvals, ATTRv-PN
- OUS filings, ATTRv-PN

Olezarsen
NDA filing, FCS[2]

FDA approval, FCS[3]

EU filing, FCS

Donidalorsen
NDA filing, HAE
MAA submission, HAE

QALSODY
- EMA approval, 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. Green checkmarks indicate positive outcome. Red checkmarks indicate program is not moving forward. 2. NDA submission completed. 3. Assuming priority review. 4. WAINUA: www.wainua.com 5. QALSODY: www.ema.Europa.eu; Biogen is responsible for commercializing QALSODY.

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 Session

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

IONIS®

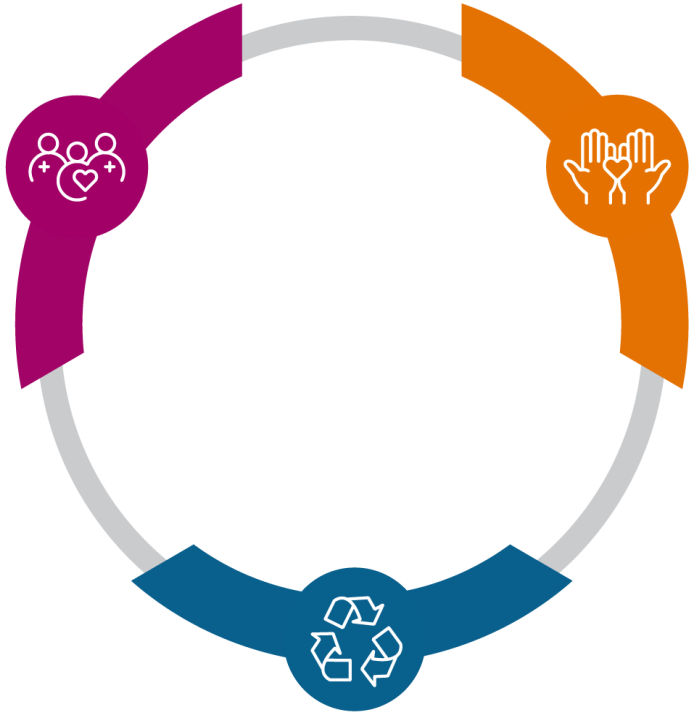
Appendix

Responsibility Program Supports Impact & Value

Ionis Corporate Responsibility Strategic Pillars

Innovate to improve the lives of people with serious diseases

We innovate across the business and work tirelessly to discover, develop and deliver important new medicines for people with serious diseases.



Empower our employees and communities

We are committed to fostering an inclusive culture that drives excellence, embraces diversity and supports our communities.

Operate responsibly and sustainably

We operate with integrity to help create a better, more sustainable future for all through environmental stewardship and responsible business practices and stakeholder interactions.