



Unlocking Better Futures, Delivering Next-Level Value

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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 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. 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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Executing on a Clear Vision

Next-Level Value for Patients and All Stakeholders

**Delivering a
Steady Cadence of
Potentially Transformational
Medicines**

**Prioritizing and
Expanding the Ionis
Wholly Owned Pipeline**

**Delivering Ionis Medicines
Directly to Patients**

**Technology
Leadership**

Financial Strength and Responsibility

Key 2023 Achievements

2

FDA Approvals¹

QALSODY™
(tofersen)
100 mg/15 mL
injection

WAINUA
(eplontersen)
45 mg
injection for subcutaneous use

2

Positive Phase 3 Readouts²

**neuro
TTRansform**

Balance
a familial chylomicronemia syndrome study

3

Phase 3 Study Starts

Bepirovirsen (HBV)

IONIS-FB-L_{Rx} (IgAN)

Zilganersen (Alexander disease)

4

Key Studies Fully Enrolled³

OASIS

**cardio
TTRansform**



GOLDEN



HALOS

5

Additional Positive Clinical Data Readouts

1. WAINUA: www.wainua.com; QALSODY: www.qalsody.com; Biogen is responsible for commercializing QALSODY. 2. NEURO-TTRansform (eplontersen for ATTRv-PN); Balance (olezarsen for FCS). 3. OASIS (donidalorsen for HAE); CARDIO-TTRansform (eplontersen for ATTR-CM); GOLDEN (IONIS-FB-L_{Rx} for GA); HALOS (ION582 for Angelman syndrome)

Well Positioned to Achieve Even Greater Success in 2024¹

2

**New Commercial
Launches²**

Including

1st Independent Launch

2

Phase 3 Readouts



2

NDA Filings

FCS | HAE

5

**Mid-Stage
Data Readouts**

Additional

**Regulatory Filings
and
Approvals²**

1. Timing expectations based on current assumptions and subject to change. 2. Assuming approval.

WAINUA Approved for ATTRv-PN: Delivering the First Ionis Co-Commercialized Medicine to Patients This Month^{1,2}



**FDA Approved on
December 21**

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

1. WAINUA: www.wainua.com; co-developing and commercializing in the US with AstraZeneca. 2. Timing based on current estimates and subject to change.

WAINUA: Potential to be the Preferred Treatment Option for Patients with ATTR^{1,2}

Strong Clinical Profile³

Targeted Knockdown



Targeted TTR knockdown at the source with **consistent** and **sustained suppression**

Halted Disease Progression



Demonstrated **halting of neuropathy disease progression**

Sustained Benefit



Significant improvements in measures of **neuropathy** and **quality of life** in a substantial number of patients through **85 weeks**

1. WAINUA: www.wainua.com 2. Assuming approval for ATTR-CM. 3. Based on data generated to date and published in *JAMA*.

WAINUA: Potential to be the Preferred Treatment Option for Patients with ATTR^{1,2}

Strong Clinical Profile³

Significant Commercial Reach

Targeted Knockdown



Targeted TTR knockdown at the source with **consistent** and **sustained suppression**

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Global Partnership



Alliance with a global footprint & industry leader in CVD medicines

Patient Support



Seamless **patient support** leveraging **Ionis' deep understanding** of these patients and the physicians who treat them

Administration Profile



Monthly **self-administration** with auto-injector

1. WAINUA: www.wainua.com 2. Assuming approval for ATTR-CM. 3. Based on data generated to date and published in *JAMA*.

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



Robust Development Program



Most comprehensive study to date in ATTR-CM, a fatal disease of the heart muscle

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 2025¹

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

Realizing the Promise of our Innovative Medicines¹

First Ionis-Commercialized Medicine Positioned to Reach Patients²



ATTRv-Polyneuropathy

Ongoing fully enrolled
Phase 3 study for
ATTR Cardiomyopathy^{3,4}

Co-developing and
commercializing in the
US with AstraZeneca

Accelerated commercial
infrastructure build

First Ionis Independent Launches^{1,4}

Olezarsen

FCS & SHTG

Donidalorsen

HAE

Built an agile commercial
operating model

Establishing global access
for our medicines

Next Wave of Wholly Owned Medicines

Leading Neurology
Pipeline

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

6 wholly owned medicines in
clinical development by YE:2024

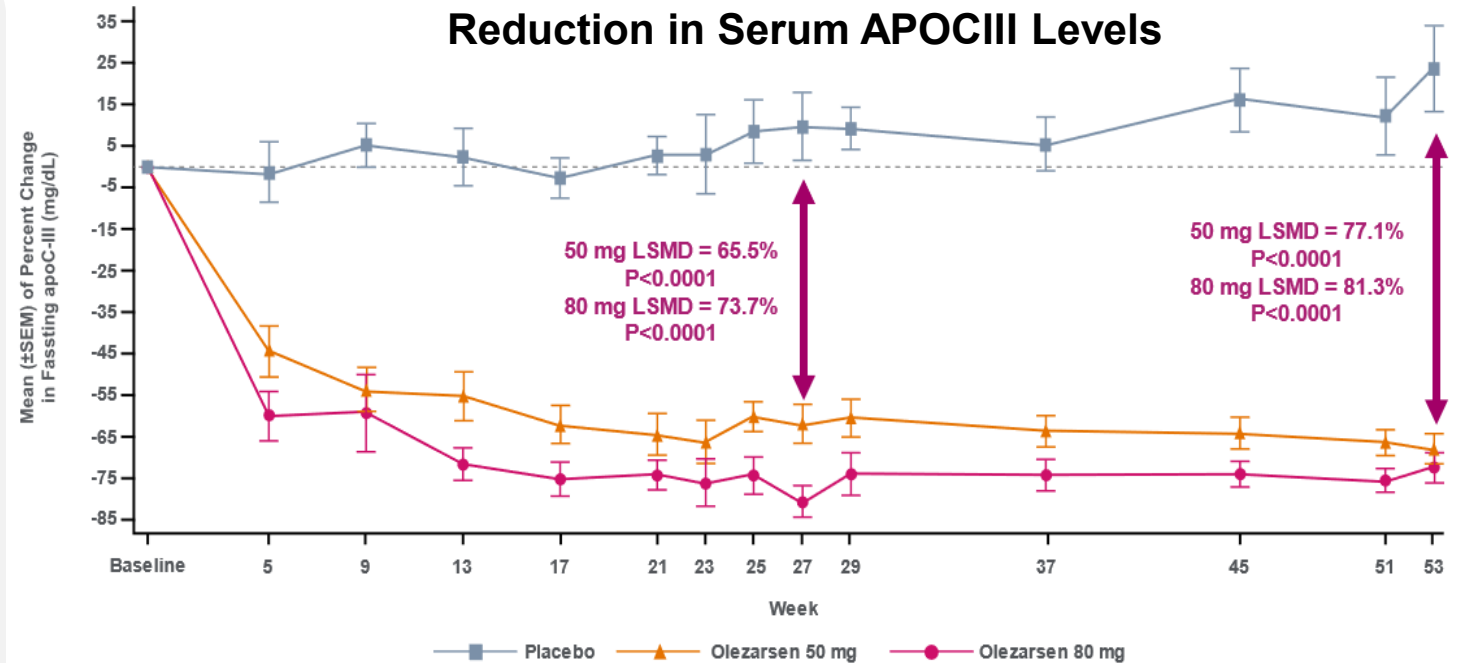
1. Timing based on current estimates and subject to change. 2. WAINUA: www.wainua.com 3. Data planned for ATTR-CM as early as 2025. 4. Assuming approval.

Positive Olezarsen Phase 3 Results in FCS Patients^{1,2}



Olezarsen treatment resulted in:

- Robust and significant reduction in serum APOCIII levels at 6 and 12 months
- Statistically significant reductions in triglycerides at 80mg dose
- Substantial reductions in acute pancreatitis attacks
- Favorable safety and tolerability profile



81% LSMD in APOCIII Levels at 12 months with 80mg dose

P<0.0001 At 6 months and 12 months

1. Topline data reported on September 26, 2023. 2. LSMD = Least squares mean difference

Olezarsen:

A Potential New
Standard-of-Care
Treatment for Patients
with **Severely Elevated
Triglycerides**^{1,2}



Nicole

Living with FCS

Familial Chylomicronemia Syndrome



Regulatory filings planned and potential
FDA approval in **2024** based on **positive
Phase 3 results**³



1st independent launch³

Severe Hypertriglyceridemia



Significant opportunity with **large SHTG
patient population with >3 million
patients in the US**⁴



SHTG Phase 3 study data expected in **2025**

1. Based on data generated to date. 2. Timing based on current estimates and subject to change. 3. Assumes priority review and approval. 4. Market data on file.

Donidalorsen:

A Potential
First-in-Class
Silencer for
Hereditary Angioedema



Sydney
Living with HAE



Phase 3 data planned for Q1:2024¹



Substantial unmet need remains

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



Donidalorsen anticipated profile²:

- Significant, rapid and sustained reductions in HAE attacks (near elimination)
- Simplicity of a monthly or bi-monthly self-administration with an autoinjector



Ionis to commercialize in the US

- EU access through Otsuka (tiered royalties ranging from 20-30%)³

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

Donidalorsen: Potential Preferred Treatment for HAE Prophylaxis¹



- Phase 3 OASIS-HAE global study in 91 patients
- Monthly and bi-monthly dosing
- Fully enrolled
- Topline data expected Q1:2024



- Phase 3 OLE study underway in patients who have completed OASIS-HAE
- Switch study underway in patients previously treated with other prophylactic therapies
 - Expanding enrollment
- Data expected mid-2024

**Efficient and Targeted Approach to Bring
Donidalorsen to Patients**

Field Team Focused on Concentrated Prescriber Base of Top Allergists and Immunologists

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

Realizing the Promise of our Innovative Medicines¹

First Ionis-Commercialized Medicine Positioned to Reach Patients²



ATTRv-Polyneuropathy

—
Ongoing fully enrolled
Phase 3 study for
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Co-developing and
commercializing in the
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Accelerated commercial
infrastructure build

First Ionis Independent Launches^{1,4}

Olezarsen

FCS & SHTG

Donidalorsen

HAE

—
Built an agile commercial
operating model

—
Establishing global access
for our medicines

Next Wave of Wholly Owned Medicines

Leading Neurology Pipeline

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

—
6 wholly owned medicines in
clinical development by YE:2024

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

Leading and Validated Neurology Franchise

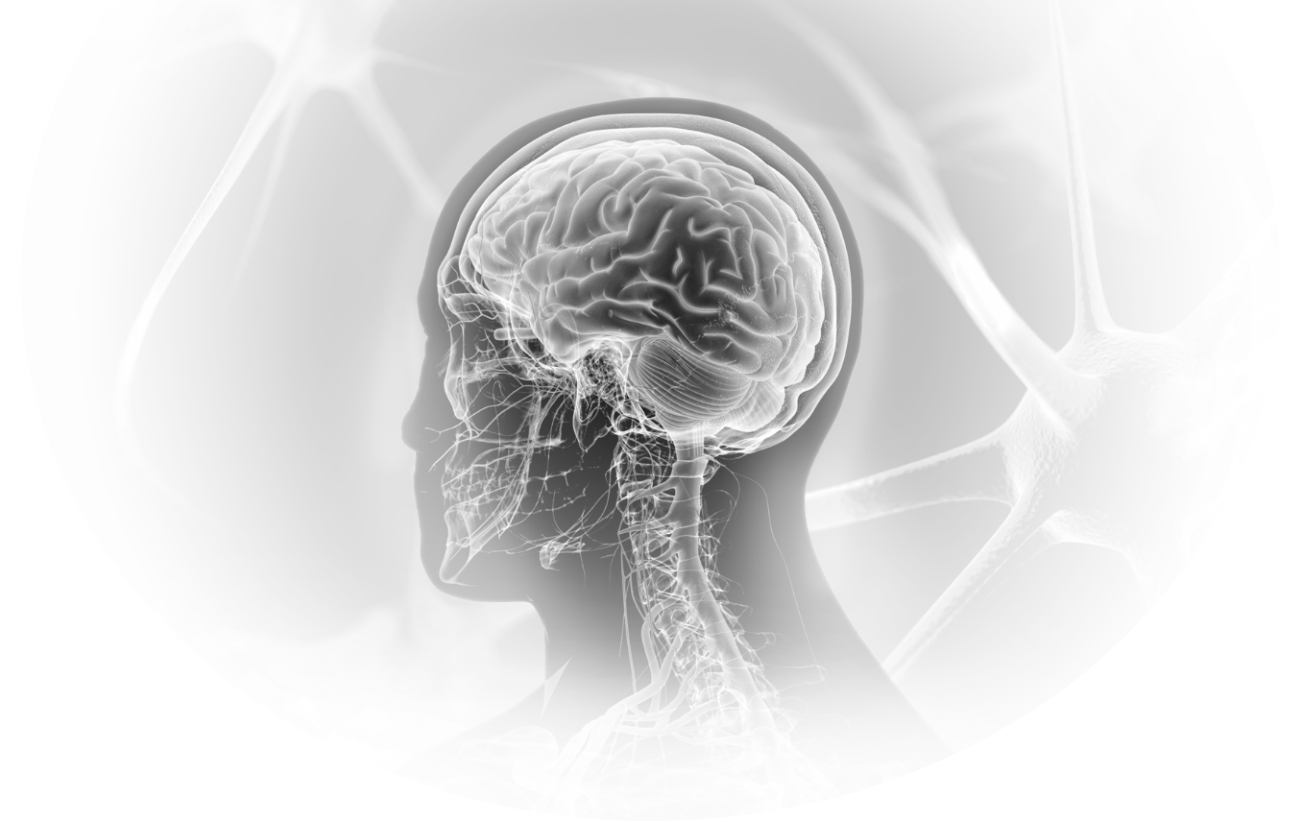
3

Approved
Medicines¹

SPINRAZA
SMA (SMN2)

QALSODY
SOD1-ALS (SOD1)

WAINUA
ATTRv-PN (TTR)



1. SPINRAZA: www.spinraza.com; QALSODY: www.qalsody.com; Biogen is responsible for commercializing SPINRAZA and QALSODY; WAINUA: www.wainua.com

Leading and Validated Neurology Franchise

3

Approved
Medicines¹

11

Medicines
in Clinical
Development

6

Wholly Owned
Medicines
in Clinical
Development by
YE:2024²

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)

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.

Our Next Wave: 6 Wholly Owned Neurology Medicines in Clinical Development by YE:2024 with More to Follow¹



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

Our Next Wave: 6 Wholly Owned Neurology Medicines in Clinical Development by YE:2024 with More to Follow¹



Rare Pediatric Neurology

Zilganersen

Alexander Disease
Pivotal study underway

ION356

Pelizaeus-Merzbacher Disease (PMD)
(PLP1)
First in patient study to start in 2024

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.

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

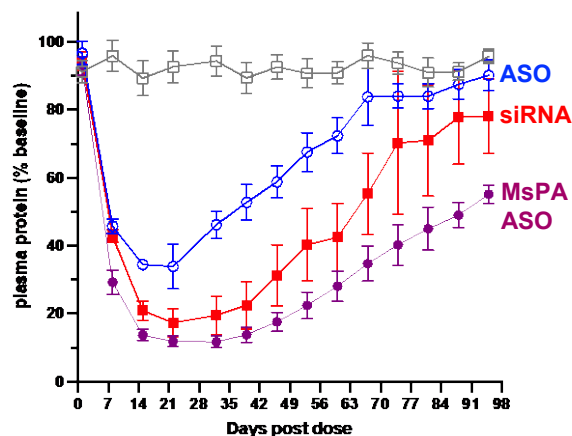
Leading Medicinal Chemistry Platform

Technology Advancements Powering Future Medicines

Expanding Technology Platform

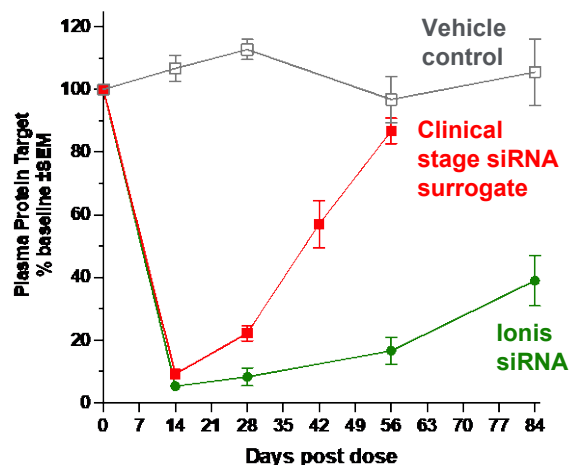
MsPA Backbone

Enables
Less Frequent Dosing^{1,2}



Ionis siRNA

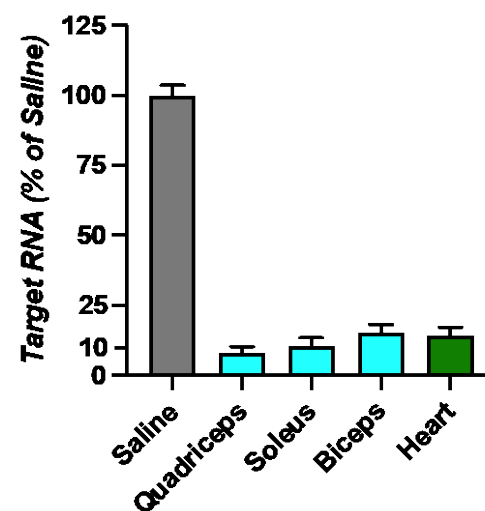
Demonstrates
Competitive Profile^{2,3}



Optimizing Delivery for New Therapeutic Opportunities

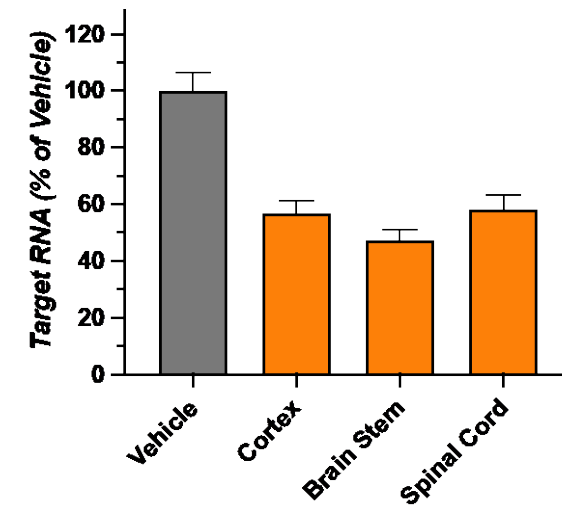
Bicycle-siRNA

Target Reduction
in Muscle¹



Bicycle ASO

Target Reduction
in CNS (Systemic Dosing)³



1. Data from nonhuman primate. 2. Single dose. 3. Data from transgenic mouse.

Key 2023 Achievements

Positive Clinical Data Events

- ✓ **Eplontersen:** Phase 3, NEURO-TTRansform 35, 66 & 85-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
- ✓ **SPINRAZA:** Phase 4, interim RESPOND data, SMA
- ✓ **Bepirovirsen:** Phase 2, B-Together data, HBV
- ✓ **IONIS-FB-L_{Rx}:** Phase 2, IgAN interim data, IgAN

Enrollment Achievements

- ✓ **Donidalorsen:** Phase 3, OASIS-HAE full enrollment, HAE
- ✓ **Eplontersen:** Phase 3, CARDIO-TTRansform full enrollment, ATTR-CM
- ✓ **IONIS-FB-L_{Rx}:** Phase 2, GOLDEN study full enrollment, GA
- ✓ **ION541:** Phase 1/2, HALOS study full enrollment, Angelman syndrome

Phase 3 Initiations

- ✓ **Bepirovirsen:** chronic HBV
- ✓ **IONIS-FB-L_{Rx}:** IgA nephropathy
- ✓ **Zilganersen:** Alexander disease

Regulatory Actions

- ✓ **WAINUA:** FDA approval, ATTRv-PN¹
- ✓ **QALSODY:** FDA approval SOD1-ALS
- ✓ **Eplontersen:** EU MAA filing acceptance + others, ATTRv-PN
- ✓ **Eplontersen:** Health Canada filing acceptance, ATTRv-PN
- ✓ **Orphan Drug Designations:** Eplontersen (EU), Donidalorsen (US), Ulefnersen (US), ION356 (US & EU)
- ✓ **Fast Track Designation:** ION356

Business Development

- ✓ **Donidalorsen:** European license to Otsuka
- ✓ Next generation Lp(a) collaboration with Novartis
- ✓ Novel programs for AD & HD with Roche




















Key Value-Driving Events Planned For 2024¹

Phase 3 Clinical Data Events	Phase 2 Clinical Data Events	Regulatory Actions	New Product Launches
Donidalorsen OASIS-HAE data	Donidalorsen 3-year OLE, HAE	Eplontersen OUS approval decisions, ATTRv-PN	WAINUA ATTRv-PN ³
OASIS-PLUS OLE + Switch data	IONIS-FB-L_{Rx} Geographic Atrophy IgA nephropathy	OUS filings, ATTRv-PN	
	ION224 NASH	Olezarsen NDA filing, FCS	Olezarsen FCS ⁴
Olezarsen Balance study full data, FCS	ION582 Angelman syndrome	FDA approval decision, FCS ²	
	ION541 ALS	EU filing, FCS	QALSODY EU, SOD1-ALS ⁴
		Donidalorsen NDA filing, HAE	
		QALSODY EMA approval decision, SOD1-ALS	




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. Assuming priority review. 3. WAINUA: www.wainua.com
4. Assuming approval in 2024.

Delivering Steady Cadence of Potentially Transformational Medicines¹

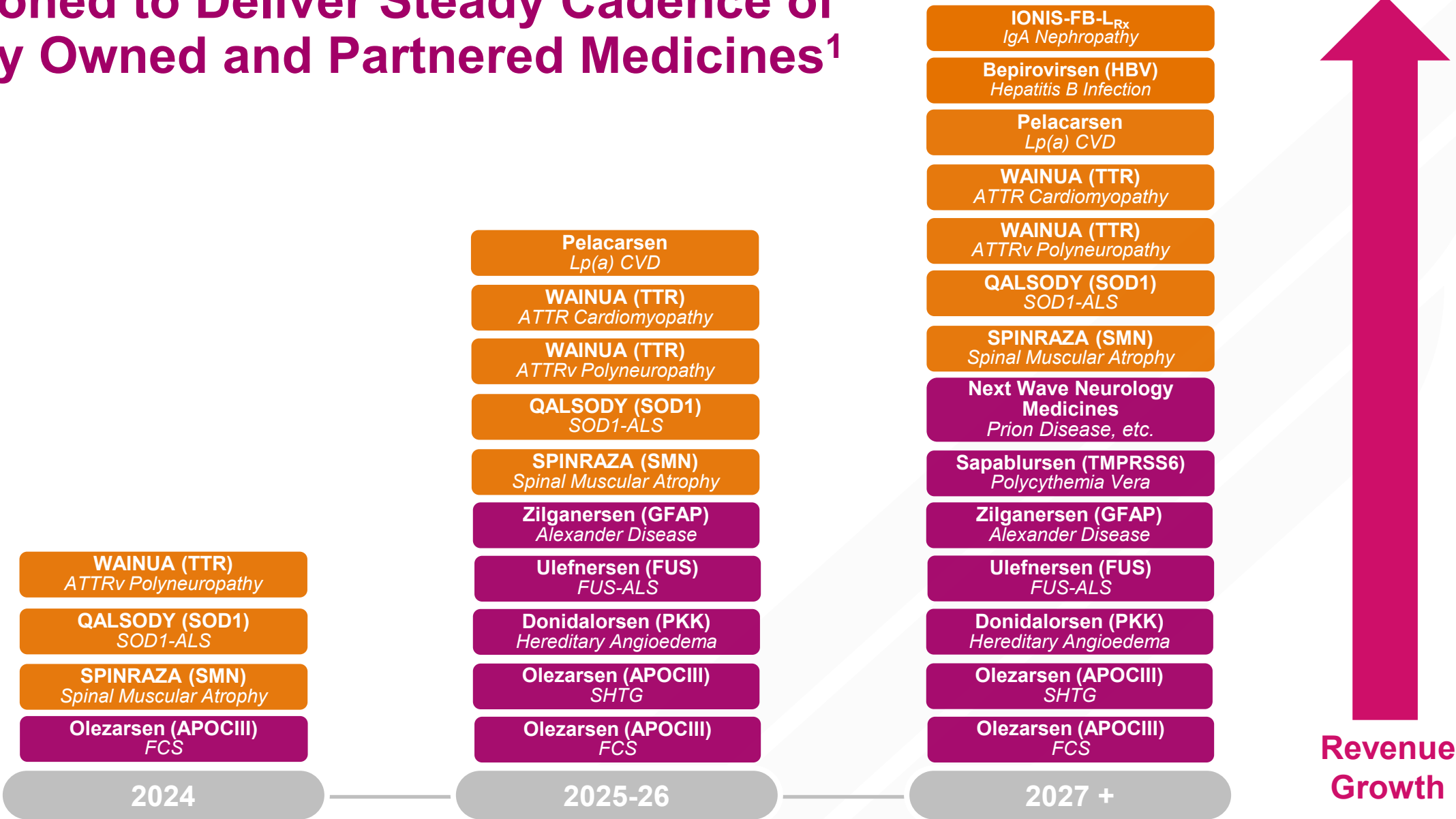
9 Medicines in Phase 3 for 11 indications

		Indication	Prevalence ²	Next Event ³
WAINUA (eplontersen)		ATTRv-PN		Additional OUS submissions (2024) Ph3 data (2025) ⁴
		ATTR-CM		
		FCS		
Olezarsen		SHTG		Ph3 data (2025)
		HAE		Ph3 data (2024)
Donidalorsen		Alexander disease		Ph3 data (2025)
Zilganersen		FUS-ALS		Ph3 data (2025)
Ulefnersen		Lp(a) CVD		Ph3 data & filing (2025)
Bepirovirsen		HBV		Ph3 data (2025)
IONIS-FB-L _{Rx}		IgA nephropathy ⁵		Ph2 data (2024)
Tofersen		Presymptomatic SOD1-ALS		Ph3 data (2027)

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. IONIS-FB-L_{Rx} is also in the Phase 2 GOLDEN study in patients with Geographic Atrophy, with topline data expected in 2024.

 <200K
  200K – 500K
  >500K
 ● Cardiovascular ● Neurology ● Specialty ● Other

Positioned to Deliver Steady Cadence of Wholly Owned and Partnered Medicines¹



1. Estimated timing of potential US approval based on current assumptions and are subject to change.

● Wholly Owned ● Partnered

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.

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

**Driving Next-Level Value
for Patients and All Ionis Stakeholders**



Jackson,
Angelman Syndrome Patient

IONIS[®]

