Corporate Presentation

December 2024

Nasdaq: IONS

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.

Ionis Today: Fully Integrated, Commercial-Stage Biotechnology Company

SPINRAZA® (nusinersen) injection 12 mg/5 mL

QALSODY® (tofersen) 100 mg/1.5 mL injection

Rich History

Discovery & development of transformational medicines

WAINUA™ (eplontersen)

First Ionis-branded Medicine

Co-commercializing with AstraZeneca[1]

Tryngolza™ (olezarsen) 80 mg injection

First Independent Ionis Launch

First FDA-approved treatment for adults with familial chylomicronemia syndrome (FCS), adjunct to diet[2]

More to Come …

- **3 additional independent launches in 3 years**[3,4,5]
- **Rare and prevalent disease opportunities**
- **Multi-billion-dollar revenue potential**[3,4]

1. AstraZeneca co-developing, commercializing WAINUA for ATTRv-PN and ATTR-CM in U.S. 2. TRYNGOLZA is approved in the U.S. for Familial Chylomicronemia Syndrome in adults; see Full Prescribing Information
3. Timing expectations based on current assumptions and subject to change. 4. Assuming approval. 5. donidalorsen, HAE; olezarsen, sHTG; zilganersen, AxD.

Important 2024 Achievements

1

Wholly Owned Medicine Approved

Tryngolza™ (olezarsen) 80 mg injection

U.S launch before year end (FCS)[1,2]

2

New Product Launches

WAINUA™ (eplontersen) 45 mg injection for subcutaneous use

U.S launch (ATTRv-PN)[3]

QALSODY® (tofersen) 100 mg/15 mL injection

EU launch (SOD1-ALS)[4]

4

Positive Phase 3 Readouts[5]

Olezarsen
Familial Chylomicronemia Syndrome (FCS)

Donidalorsen
(OASIS-HAE & OASISplus Studies)
Hereditary Angioedema (HAE)

Nusinersen
(DEVOTE)
Spinal Muscular Atrophy (SMA)

6

Phase 3 Studies Fully Enrolled[6]

Olezarsen
(CORE, CORE2 & ESSENCE Studies)
Severe hypertriglyceridemia (sHTG)

Zilganersen
Alexander disease

Bepirovirsen
(B-Well 1 & B-Well 2 Studies)
Chronic HBV

4

Positive Phase 2 Readouts[7]

Donidalorsen
(OLE study)
Hereditary Angioedema (HAE)

IONIS-FB-L$_{Rx}$
IgAN

ION582
(HALOS study)
Angelman Syndrome

ION224
MASH

1. TRYNGOLZA is approved in the U.S. for Familial Chylomicronemia Syndrome in adults; see Full Prescribing Information 2. Timing expectations based on current assumptions and subject to change. 3. WAINUA: www.wainua.com. 3. QALSODY: www.ema.Europa.eu; Biogen is responsible for commercializing QALSODY. 5. Balance (olezarsen for FCS), DEVOTE (higher dose nusinersen for SMA), OASIS-HAE and OASISplus (donidalorsen for HAE). 6. CORE, CORE2 and Essence (olezarsen for sHTG). B-Well 1 & B-Well 2 (chronic HBV). Phase 3 study for zilganersen (Alexander disease) 7. Phase 2 readouts of: donidalorsen for HAE, ION224 for MASH, IONIS-FB-L$_{Rx}$ for IgAN and ION582 for Angelman syndrome.

Upcoming Key Value-Driving Events[1]

Q4:2024 and 2025

Phase 2 Clinical Data Events

Sapablursen
Polycythemia vera

—

ION464
Multiple System Atrophy

Phase 3 Clinical Data Events

Olezarsen
CORE, CORE2,
ESSENCE data
sHTG

—

Zilganersen
Alexander disease

—

Pelacarsen
HORIZON data
Lp(a) CVD

Regulatory Actions

Eplontersen
OUS approvals,
ATTRv-PN

—

TRYNGOLZA
FDA approval, FCS
EU approval, FCS

—

Donidalorsen
FDA approval, HAE
EU filing, HAE
EU approval, HAE

—

Nusinersen
(higher dose)
FDA filing, SMA
OUS filings, SMA

New Product Launches

WAINUA
EU + other countries
ATTRv-PN

—

TRYNGOLZA
U.S. FCS
EU FCS

—

Donidalorsen
U.S. HAE
EU HAE

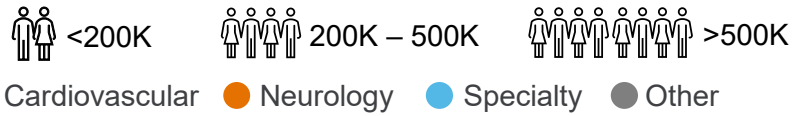
1. Timing expectations are based on current assumptions and are subject to change, timing of partnered program catalysts based on partners' most recent publicly available disclosures.

Positioned to Deliver Steady Cadence of Potentially Transformational Medicines[1]

9 investigational medicines in Phase 3 for 11 indications

		Indication	Prevalence[2]	Anticipated Next Event[3]
WAINUA (eplontersen)	IONIS / AstraZeneca	ATTRv-PN		**OUS approvals (2024)**
		ATTR-CM		**Ph3 data (2026)[4]**
TRYNGOLZA (olezarsen)	IONIS[5]	FCS		**U.S. launch (2024)[6]**
		sHTG		**Ph3 data (2025)[7]**
Donidalorsen	IONIS[5,8]	HAE		**MAA filing (2024)[9]**
Zilganersen	IONIS	Alexander disease		**Ph3 data (2025)**
Ulefnersen	Otsuka	FUS-ALS		**Ph3 data (2026)**
Pelacarsen	NOVARTIS	Lp(a) CVD		**Ph3 data (2025)**
Bepirovirsen	GSK	HBV		**Ph3 data (2026)**
IONIS-FB-L_{Rx}	Roche	IgA nephropathy		**Ph3 data (2026)**
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. Data expected in H2:2026. 5. Granted Theratechnologies exclusive rights to commercialize olezarsen and donidalorsen in Canda. 6. olezarsen sHTG data expected in H2:2025. 7. U.S. launch by YE:24. 8. Granted Otsuka exclusive rights to commercialize donidalorsen in Europe and Asia Pacific regions. 9. MAA filing planned for Q4:2024.



Delivering Medicines to People in Need

WAINUA™ (eplontersen) 45 mg injection for subcutaneous use

Co-Developing and Co-Commercializing in the U.S. with AstraZeneca

Launched in ATTRv-PN January 2024[1]

Leading patient engagement program

AstraZeneca leading other customer-facing commercial and medical affairs teams

Pre-commercialization activities and investments underway to support potential ATTR-CM opportunity

Tryngolza™ (olezarsen) 80 mg injection

First FDA-Approved Treatment for Adults with FCS[2]

On track for U.S. launch by YE:24[3]

FCS field team hired and trained

Patient and caregiver support team

Further scale capabilities to realize blockbuster potential in sHTG[3]

Donidalorsen

Independent U.S. Launch in HAE expected in 2025[2,3]

Building on WAINUA and olezarsen infrastructure

Established market with concentrated prescriber base

Otsuka to bring to people with HAE in Europe and Asia Pacific Regions[4]

1. WAINUA: www.wainua.com. 2. TRYNGOLZA is approved in the U.S. for Familial Chylomicronemia Syndrome in adults; see Full Prescribing Information . 3. Timing expectations based on current assumptions and subject to change. 4. Granted Otsuka exclusive rights to commercialize donidalorsen in Europe and Asia Pacific regions.

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

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

Substantial and sustained Q-o-Q growth of 44% driven by strong demand[2]

Encouraging patient mix and breadth of prescribers

Physicians report positive patient experience:

- Quality-of-life improvements
- Ability to access treatment
- Self-administration via an autoinjector

High unmet need remains with <20% of ATTRv-PN patients on treatment

1. WAINUA: www.wainua.com; co-developing and commercializing in the U.S. with AstraZeneca. 2.Q3:2024 compared to Q2'2024 WAINUA product sales.

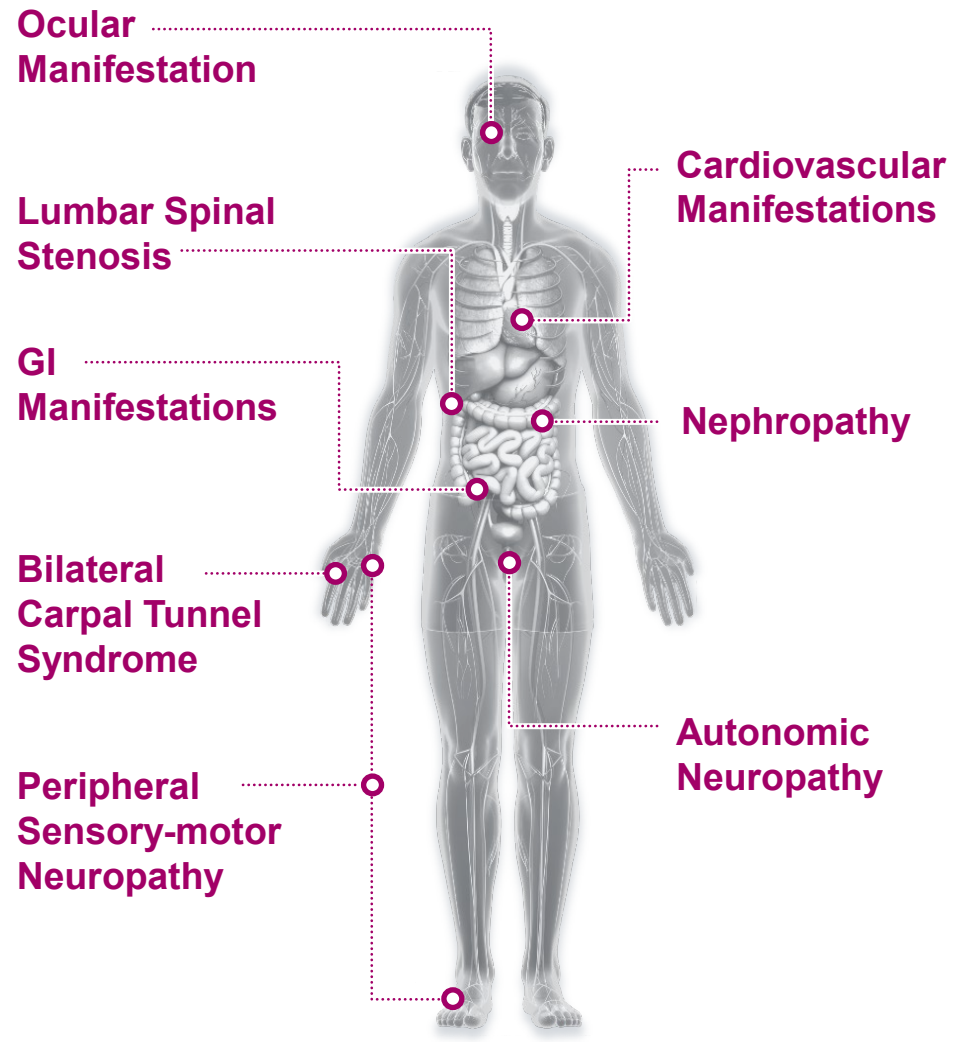
WAINUA: Positioned to Address the High Unmet Need in ATTR[1,2,3,4]

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.

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 Expected in H2:2026[1]

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

Tryngolza™
(olezarsen) 80 mg injection

The first FDA-approved therapy for adults with FCS

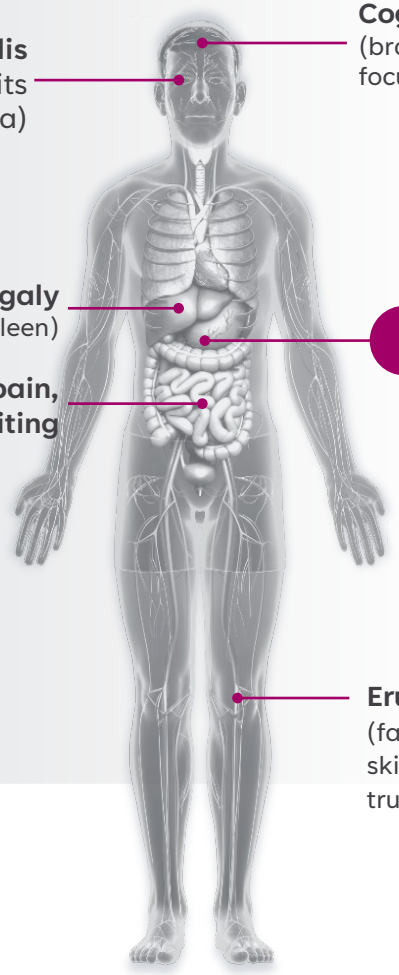
NOW APPROVED

To reduce triglycerides in adults with FCS as an adjunct to diet

FCS: Rare, Genetic, Potentially Fatal Disease

- Genetic form of sHTG caused by loss of LPL activity[1,2]
- Triglyceride levels 10-100x greater than normal[1,2]
- Increased potentially fatal acute pancreatitis risk, debilitating daily symptoms, frequent hospitalizations[3,4]
- High disease burden also results in psychological stress and reduced quality of life[5]

Clinical Manifestations of FCS[3,6]



1. Moulin P, et al. *Atherosclerosis* 2018;275:265-72. 2. Brown EE, et al. *J Clin Lipidol* 2020;14(4):398-413. 3. Davidson M, et al. *J Clin Lipidol*. 2018;12(4):898–907. 4. Nawaz H, et al. *Am J Gastroenterol* 2015; 110;1497-1503. 5. Gaudet D, et al. *Lipids Health Dis*. 2020;19(1):120. 6. Brunzell JD, Bierman EL. *Med Clin North Am*. 1982;66(2):455–68.

IONIS

TRYNGOLZA:
First FDA-Approved Treatment for Familial Chylomicronemia Syndrome[1]

Compelling Clinical Results:

- Significant and sustained triglyceride reductions
- Consistent reductions in apoC-III
- Substantial reduction in acute pancreatitis events
- Favorable safety and tolerability profile

First Mover Advantage

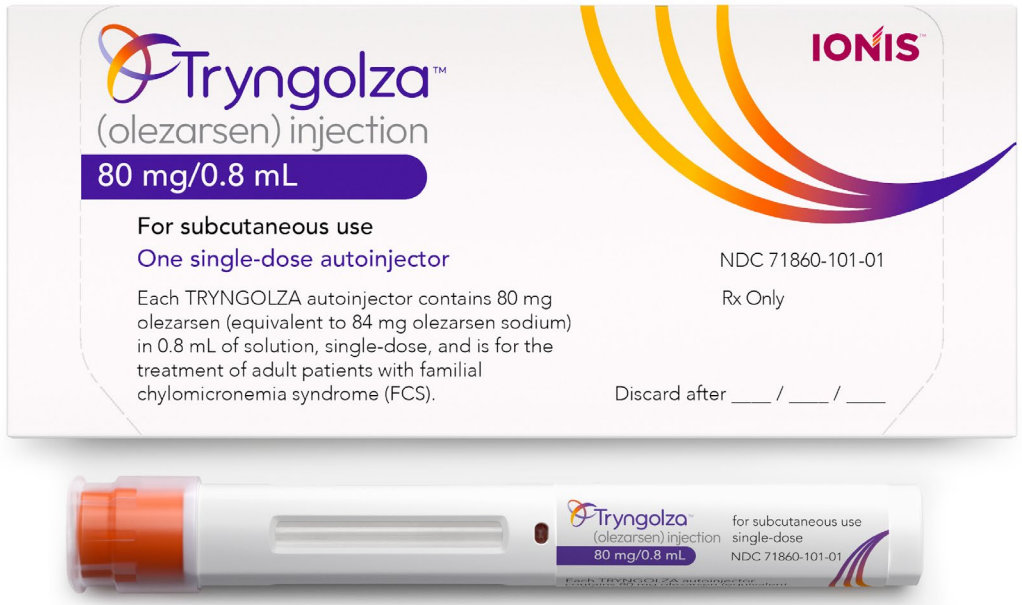
U.S. Launch Before Year End

Prepared for Commercial Success

IONIS

1. TRYNGOLZA is approved in the U.S. for Familial Chylomicronemia Syndrome in adults; see Full Prescribing Information.

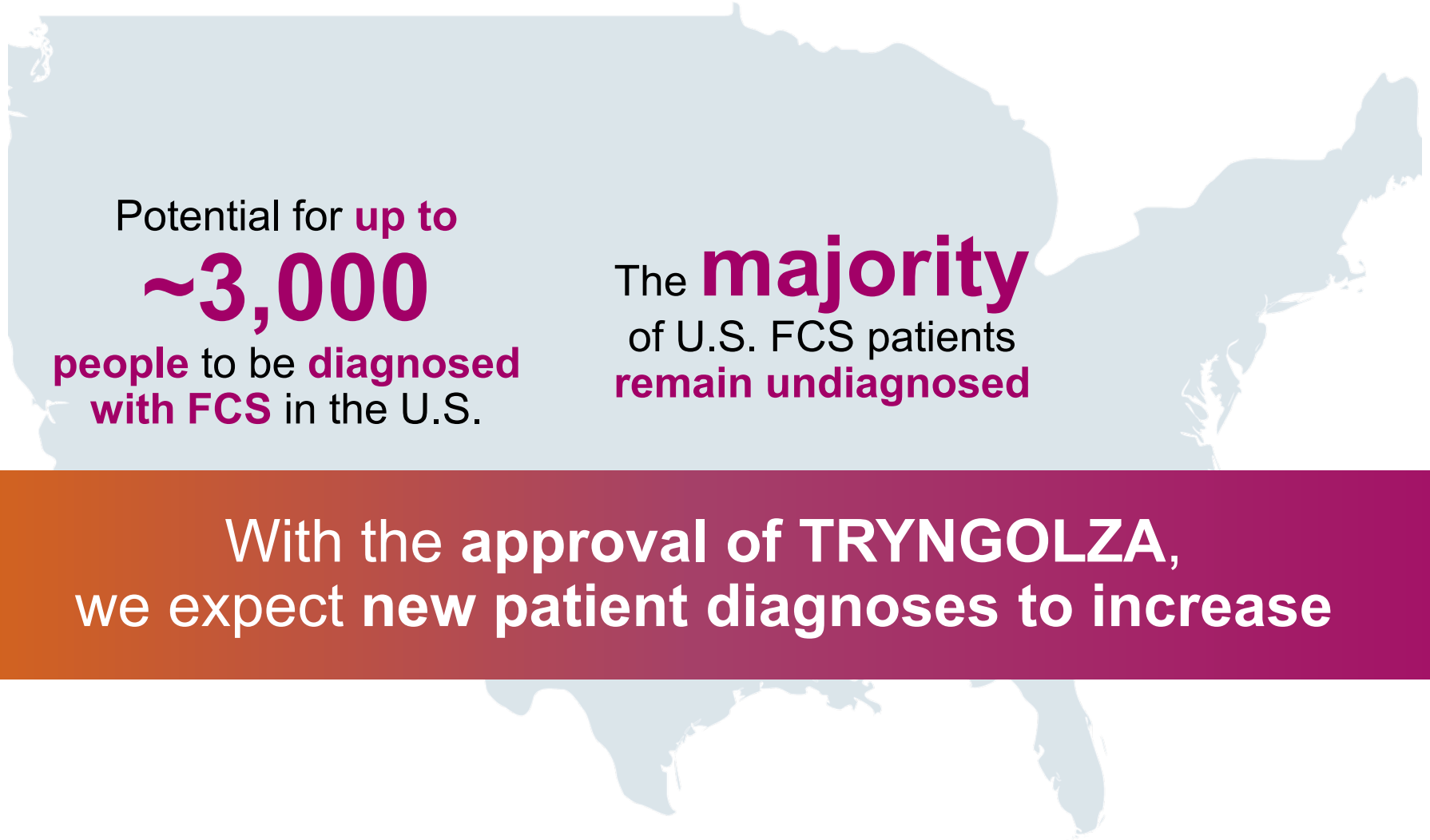
TRYNGOLZA Label Enables Treatment of Adults with Genetically or Clinically Confirmed FCS[1]



- Indicated as an adjunct to diet to reduce triglycerides in adults with FCS
- Statistically significant and sustained triglyceride reductions
- Substantial reductions in AP events
- Favorable safety and tolerability profile
- Once-monthly self-administration with an autoinjector

1. TRYNGOLZA is approved in the U.S. for Familial Chylomicronemia Syndrome in adults; see Full Prescribing Information.

TRYNGOLZA Uptake to be Driven by Increasing FCS Awareness[1-5]



Potential for **up to**

~3,000

people to be **diagnosed with FCS** in the U.S.

The **majority** of U.S. FCS patients **remain undiagnosed**

With the **approval of TRYNGOLZA**, we expect **new patient diagnoses to increase**

1. Dron JS, et al. *BMC Med Genomics* 2020;13(1):23. 2. Hegele RA. *Nat Rev Genet* 2009;10(2):109-21. 3. Pallazola VA, et al. *Eur J Prev Cardiol* 2020;27(19):2276-8. 4. Tripathi M, et al. *Endocr Pract* 2021;27(1):71-6. 5. Warden BA, et al. *J Clin Lipidol* 2020;14(2):201-6.

TRYNGOLZA Launch Strategy Designed for Success

Education & Awareness

Education to support patient identification

HCP engagement, evidence generation, patient advocacy

Commercial Execution

Efficient and targeted U.S. commercial team

Now deployed in preparation for U.S. launch before year-end

Comprehensive Support Program

Services designed for patients and HCPs

Patient assistance, authorization support, financial support for eligible patients

Coverage & Reimbursement

Market access team engaging with payers

To ensure access for people who may benefit from TRYNGOLZA

Omnichannel Engagement

Targeted HCP and patient engagement

Innovative capabilities to identify patients, extend commercial team reach

Ionis Every Step™ Designed to Meet the Unique Needs of the FCS Community

IONIS EVERY STEP™ SUPPORT SERVICES

- Suite of services offering personal support for patients and HCPs
- Disease & nutrition education, injection training & other resources through dedicated patient education managers
- Authorization and reauthorization assistance, delivery coordination and refill reminders to support adherence
- Financial support programs to help appropriate patients afford TRYNGOLZA; commercially insured patients may pay as little as $0 out of pocket

Olezarsen sHTG Development Program Designed to Support Blockbuster Market Opportunity[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
- >400 patients
- **Enrollment complete**

Essence
TIMI-73b

- Supportive Ph3 study in patients w/ TG ≥150-500 mg/dL (HTG) or TG ≥500 mg/dL (sHTG)
- Supportive exposure study
- >1,400 patients
- **Enrollment complete**

On Track for Data From All Three Studies in H2:2025

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

Donidalorsen:

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

New prophylactic treatments needed[3]

Donidalorsen's clinical results include[1]:

- Substantial and sustained reductions in HAE attacks
  - New positive Phase 2 OLE data in patients treated up to three years
- Improved QoL measures
- High levels of disease control
- >80% preference for donidalorsen over other prophylactic treatments[4]
- Favorable safety and tolerability
- Patient-friendly monthly or every two-month self-administration with an autoinjector

August 21, 2025 PDUFA; EU submission planned for this year[5]

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); HAEI (https://haei.org/hae/faq/ accessed May 2024). 4. Switch preference data represents percentage of switch patients surveyed with total n=55 assessed at week 17 and as of February 28, 2024 who indicated donidalorsen preference over their prior prophylactic treatment. 5. Timing based on current estimates and subject to change.

Donidalorsen: Robust Data Supports Potential Preferred Treatment for HAE Prophylaxis[1,2]

Hereditary Angioedema

Phase 2

- Positive Phase 2 data published in *New England Journal of Medicine*
- Positive Phase 2 OLE data in up to 3 years of treatment + QoL data reported

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*[3]

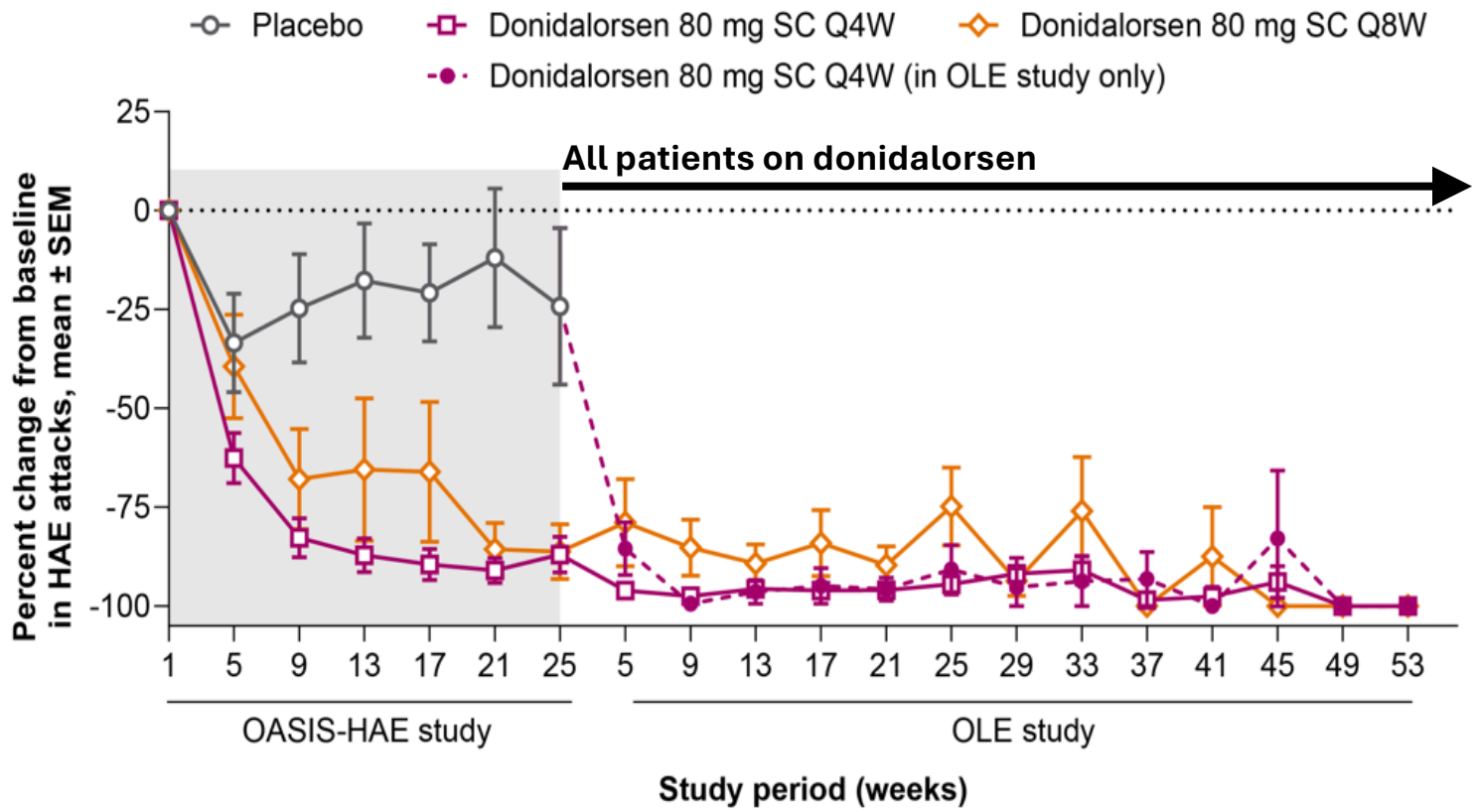
OASIS plus

- 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

August 21, 2025 PDUFA; EU filing on track this year; Prepared to launch in 2025[4]

1. Based on data generated to date including Phase 2, Phase 2 OLE, Phase 3 and Phase 3 OLE + Switch data. 2. Licensed European and Asia Pacific commercialization rights to Otsuka 3. Riedl, M et al. *N Engl J Med.* 2024. 4. Timing expectations based on current assumptions and subject to change.

OLE: Further Reduction in HAE Attacks with Extended Donidalorsen Treatment[1,2,3]



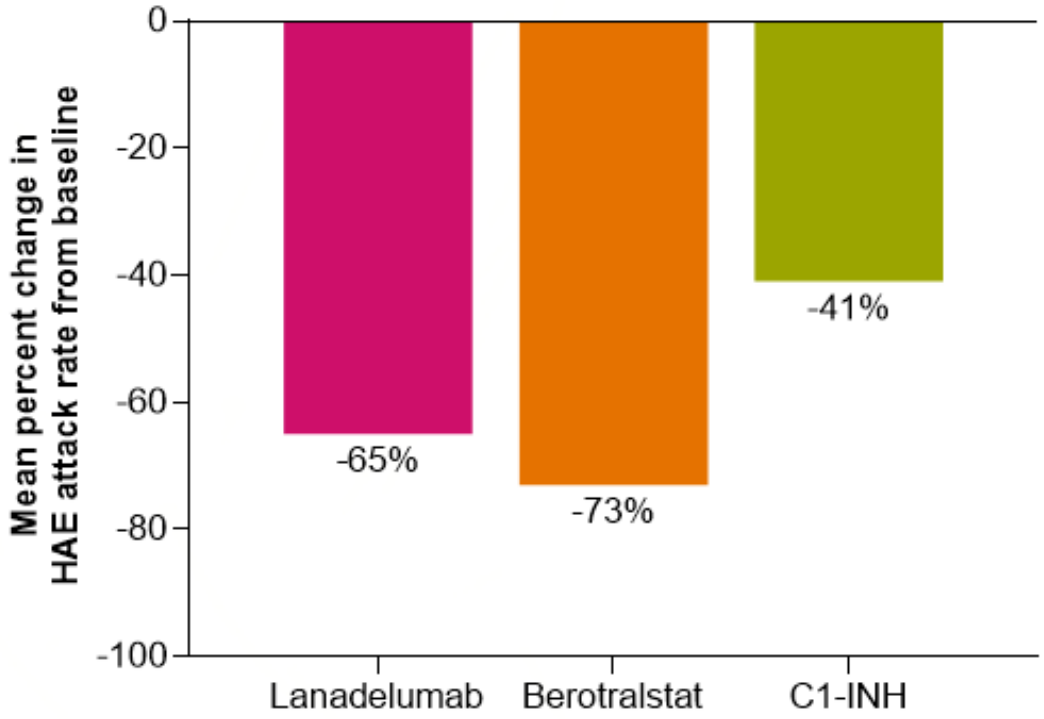
Placebo, n =	19	19	19	19	18	17	16	19	19	19	19	16	15	13	10	6	5	5	4	2
Donidalorsen 80 mg Q4W, n =	44	44	44	44	44	43	43	44	44	43	43	36	30	26	24	18	11	8	4	3
Donidalorsen 80 mg Q8W, n =	20	20	20	20	20	20	19	20	20	20	20	16	14	13	12	8	4	3	2	2

- **Q4W substantially reduced** mean **HAE attack rates:**
  - **93% improvement** from baseline at the start of OASIS-HAE[4]
- **Q8W** had a **similar effect** as **Q4W** dosing
  - **92% improvement** from baseline at the start of OASIS-HAE in HAE attack rates[4]

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. Donidalorsen 80mg SC Q8W group includes patients who were randomized to the 80mg Q8W group in the OASIS-HAE study. 4. 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]

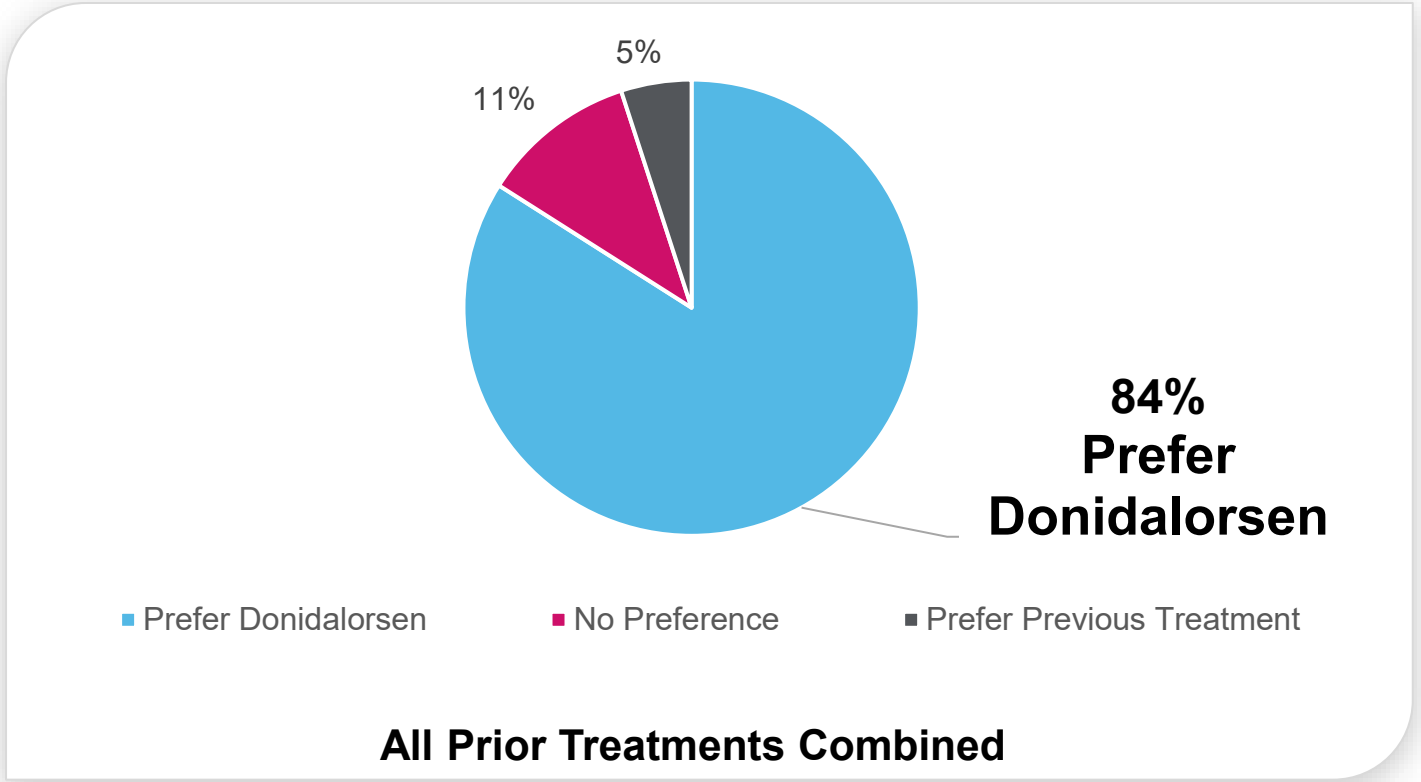


n =	31	11	22
Baseline, mean ± SD =	0.69 ± 1.09	1.80 ± 1.92	0.61 ± 0.96
Donidalorsen Q4W, mean ± SD =	0.24 ± 0.33	0.48 ± 0.53	0.36 ± 0.69

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.

Our Second Planned Independent Launch: Donidalorsen for HAE

HAE Landscape Dynamics Underscore Donidalorsen's Potential[1,2]

Well Defined Population with **>20K People with HAE** in U.S. & EU

Growing Global Market

New Treatment Options Needed

People with HAE Have Shown **Willingness to Switch**

Concentrated Prescriber Base in the US

Efficient Commercial Model

1. Market data on file. 2. Lumry et al. "Hereditary Angioedema: The Economics of Treatment of an Orphan Disease. Front. Med. 16 February 2018 Sec. Hematology Volume 5 – 2018.

Donidalorsen: Clinical Results Support Potential to be a Preferred Choice for People with HAE[1,2]

Lauren & Lindsey
Sisters Living with HAE

- Potential first-in-class RNA-targeted medicine
- Substantial and sustained attack rate reduction with long-term durability and disease control demonstrated in the studies
- Strong patient preference results with data to inform potential switching
- Favorable safety and tolerability profile in the studies
- Data support monthly or every two-month self-administration with an autoinjector

1.Based on data generated to date including Phase 2, Phase 2 OLE, Phase 3 and Phase 3 OLE + Switch data. 2. Assuming approval.

Pelacarsen: Addressing a Major Independent Risk Factor for CVD and Aortic Stenosis[1]

Lp(a) Driven Cardiovascular Disease

- Lp(a): independent, genetic, causal risk factor for CVD, mediating MI, stroke and peripheral artery disease
- Lp(a) levels determined genetically, not influenced by diet or lifestyle
- 1 in 5 people worldwide have elevated Lp(a)
- Currently no approved therapies to treat elevated Lp(a)

Pelacarsen

- Targets Apo(a), the root cause of Lp(a)-driven CVD

>8 million

Patients with CVD & elevated Lp(a) worldwide[2]

Phase 3 Lp(a) HORIZON Study

- >8,000 patients with elevated Lp(a) levels and established CVD
- Achieved full enrollment in July 2022
- On track for data in 2025

Lp(a) Horizon Outcomes Study

Eligible for:

Additional milestone payments

Royalties in the mid-teens to low 20% on net sales[3]

1. Novartis licensed pelacarsen in 2019 and as a result is responsible for development and commercialization, assuming approval. 2. Market data on file. 3. Royalty Pharma to receive 25% of any future royalty payments on pelacarsen.

Leading Neurology Franchise

3

Approved Medicines[1]

13

Medicines in Clinical Development

6

Wholly Owned Medicines in Clinical Development[2]

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)

ION582
Angelman syndrome (UBE3A-ATS)

ION717
Prion disease (PRNP)

ION356
Pelizaeus-Merzbacher Disease (PLP1)

ION440
MECP2 duplication syndrome (MECP2)

ION269
Alzheimer's disease (APP)

ION306
SMA (SMN2)

Ulefnersen
FUS-ALS (FUS)

Tofersen
Presymptomatic SOD1-ALS (SOD1)

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

ION859
Parkinson's disease (LRRK2)

Tominersen
Huntington's disease (HTT)

ION464
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), ION582 (Angelman syndrome), ION717 (Prion disease), ION356 (PMD), ION440 (MECP2 Duplication syndrome) and ION269 (APP).

ION582:

A **Promising** New Investigational Medicine for **Angelman Syndrome** from Ionis' **Wholly Owned** Neurology P**ipeline**[1]

Jackson
Living with Angelman Syndrome

Positive Early Results Seen in the HALOS Study[1]

- Consistent and meaningful improvements in key areas of clinical function, including communication, cognition and motor function
- Evidence of consistent improvements across age groups and genotypes
- Favorable safety and tolerability profile

Phase 3 Study Start Planned for H1:2025[2]

- FDA alignment on Phase 3 study design
- Robust global 2:1 randomized pivotal study evaluating 2 doses of ION582 compared to placebo in broad AS population

Priority Wholly Owned Opportunity

- Significant transformational potential
- Strengthens Ionis' wholly owned neurology pipeline

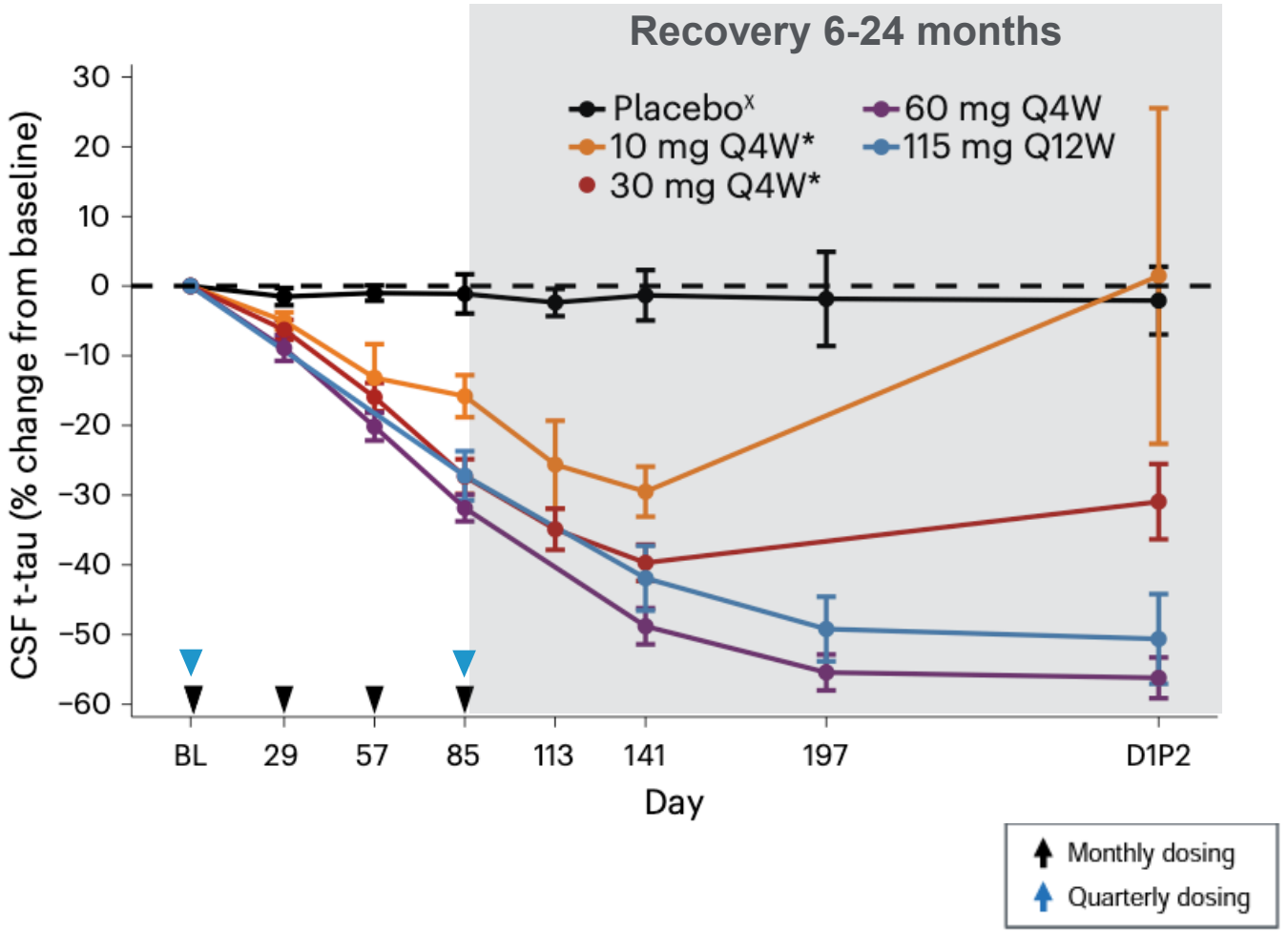
1. Based on data generated to date from the Phase 1/2a HALOS study of ION582. 2. Timing expectations based on current assumptions and subject to change.

IONIS-MAPT$_{Rx}$: Rapid, Substantial and Sustained Reduction in Tau in CSF in Phase 1b Study[1]

MAPT$_{Rx}$ (BIIB80) is designed to **reduce production and thus aggregation of tau protein** associated with disease in Alzheimer's disease

Total tau in the CSF **continued to decline 16 weeks post-last dose** of BIIB080 in 4-and 12-week cohorts

Generally well-tolerated at all doses and dose frequencies



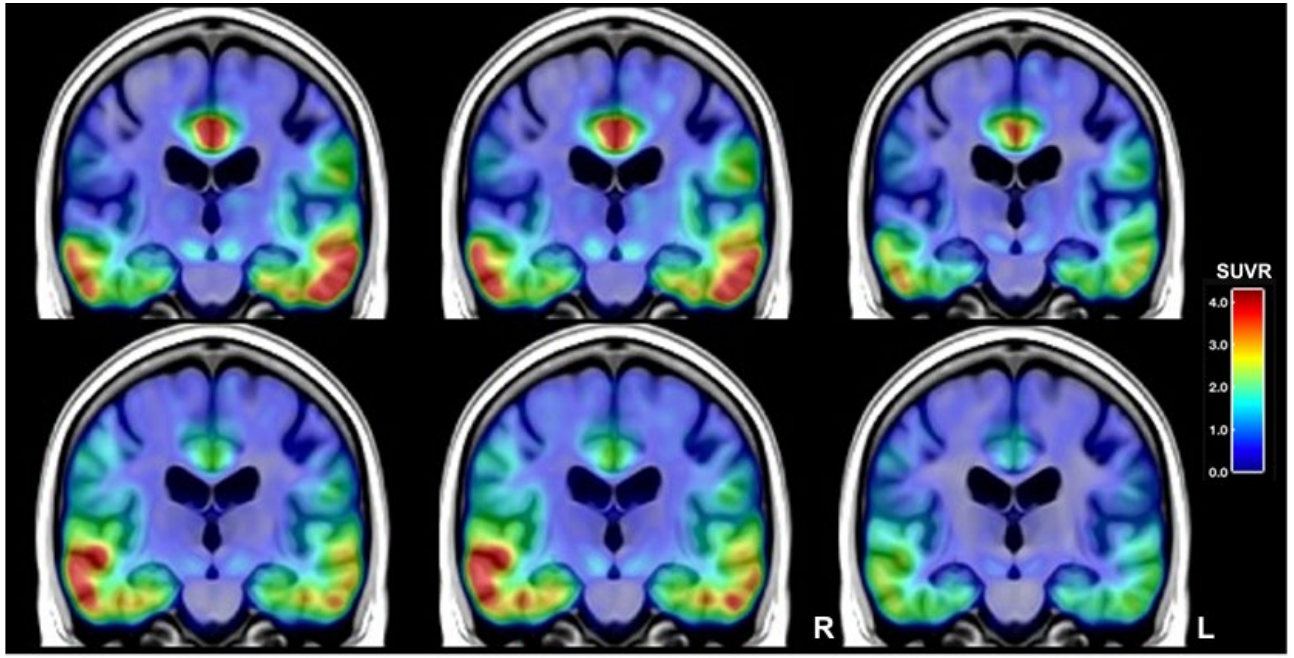
1. Mummery et al., Nat Med, 2023; AD = Alzheimer's disease; CSF = cerebrospinal fluid; Q4W = every 4-week dosing; Q12W = every 12-week dosing; t-tau = total tau

IONIS-MAPT$_{Rx}$: Consistent Reduction in Tau Burden Across All Brain Regions

Screening → Placebo → **Week 25** → 115mg Q12W → **Week 100**

2380-4011
67 y/o
Male
CDR= 0.5
MMSE= 26

2176-4009
71 y/o
Male
CDR= 0.5
MMSE= 26



CELIA Phase 2 Study in patients with early AD fully enrolled; Data expected in 2026[2,3]

Phase 1b Tau PET Results[1]

Patients initially on placebo then MAPT$_{Rx}$ (BIIB080) showed **reduced tau burden following treatment**

Reduced tau burden at all doses and dose frequencies in the long-term extension study

Generally **well-tolerated at all doses and dose frequencies**

1. Collins et al., AD/PD 2023 CDR Clinical Dementia Rating scale; MMSE Mini Mental State Examination; SUVR standard uptake valueratio; CELIA Study (Biogen conducting): Clinialtrials.gov/NCT05399888 2. Timing based on current estimates and subject to change.
3. Biogen disclosed CELIA trial update reducing number of patients in August 2024.

Advancing and Expanding our Wholly Owned Neurology Franchise[1]

Pediatric Neurology

Zilganersen
Alexander Disease
Pivotal study fully enrolled; data planned in 2025

ION582
Angelman Syndrome
Pivotal study to start in H1:2025

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

ION440
MECP2 Duplication Syndrome
First in patient study underway

Dementia

ION717
Prion Disease
(PRNP)
First in patient study underway

ION269
Alzheimer's disease
(APP)
First in patient study underway[2]

Future Wave

Neuromuscular and Peripheral Neuropathies

Movement Disorders

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. 2. Initially being studied in adults with Down syndrome (DS) who have a genetic risk of developing Alzheimer's disease (AD).

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

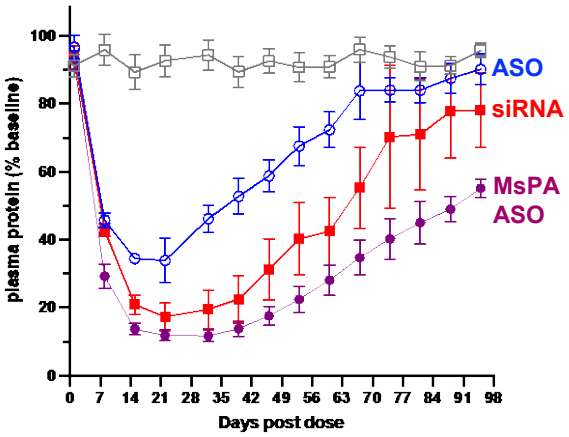
Leading Medicinal Chemistry Platform

Technology Advancements Powering Future Medicines

Expanding Technology Platform

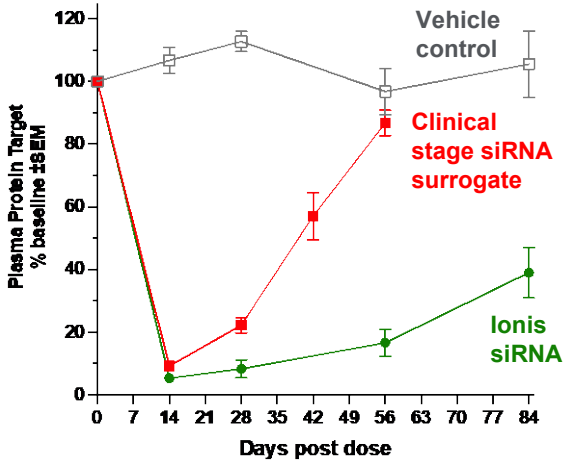
MsPA Backbone

Enables Less Frequent Dosing[1,2]



Ionis siRNA

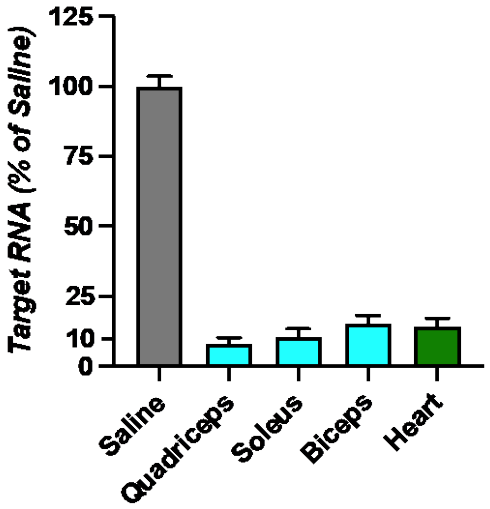
Demonstrates Competitive Profile[2,3]



Optimizing Delivery for New Therapeutic Opportunities

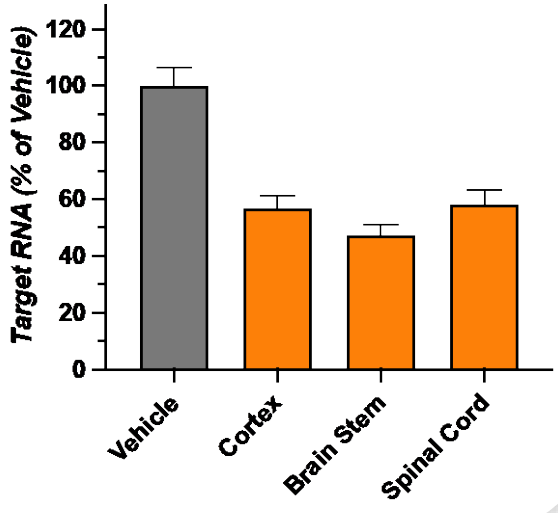
Bicycle-siRNA

Target Reduction in Muscle[1]



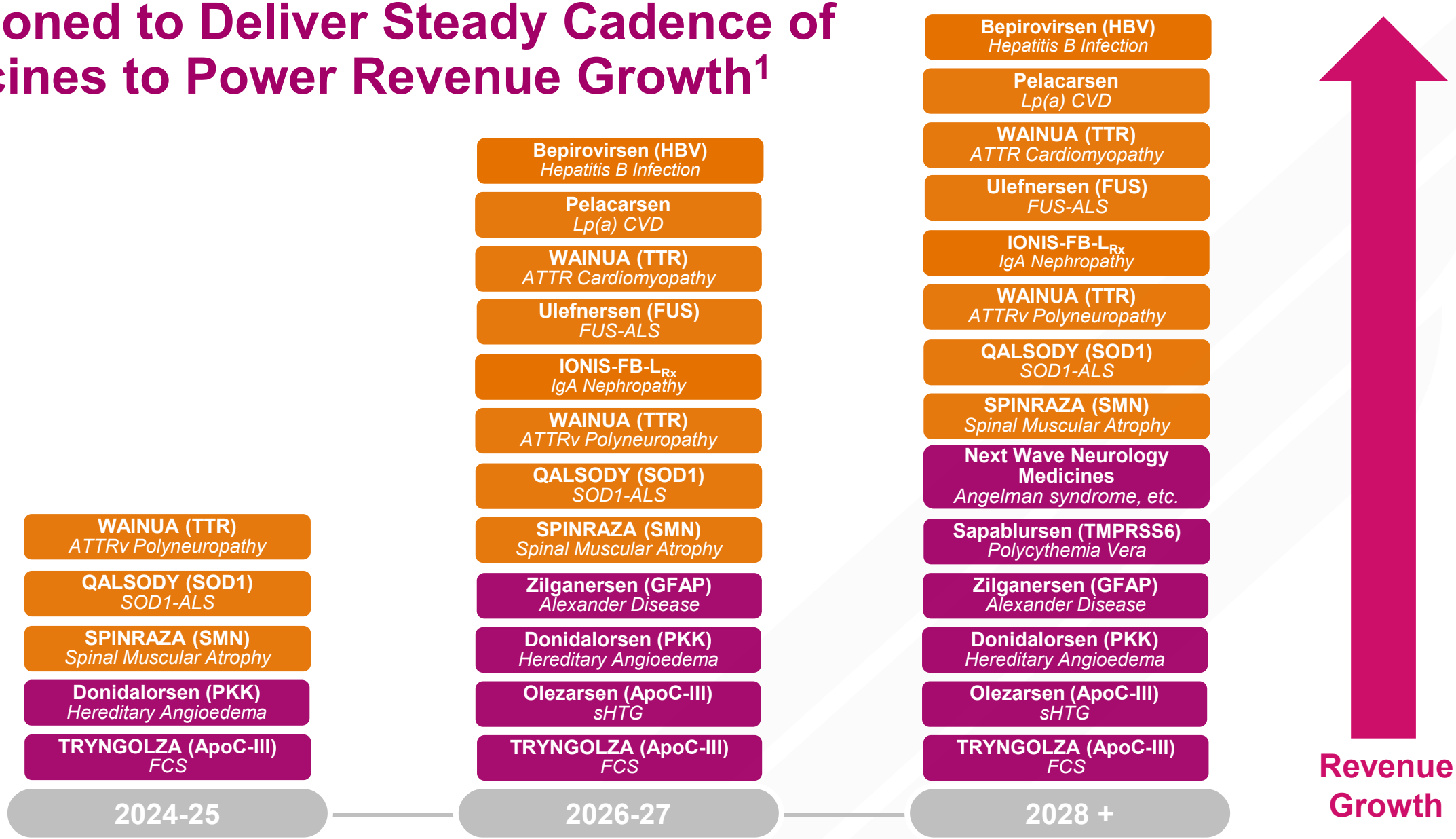
Bicycle ASO

Target Reduction in CNS (Systemic Dosing)[3]



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

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



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

Q3:2024 YTD Financial Highlights[1]

On Track to Achieve 2024 P&L Guidance; Increased Cash Guidance to ~$2.2 Billion

$479M

Revenue

Commercial Revenue: $207M

- SPINRAZA comprised largest component
- New stream of royalty revenue from WAINUA launch with substantial and sustained sequential quarterly growth

R&D Revenue: $272M

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

---

$749M

Operating Expenses[2]

R&D Expenses[2]: $589M

- Flat YoY as several late-stage studies have ended and other late-stage studies are now fully enrolled

SG&A Expenses[2]: $154M

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

1. For the nine months ended September 30, 2024. 2. Non-GAAP – please see reconciliation to GAAP in Q3 2024 press release.

On Track to Achieve 2024 P&L Financial Guidance

Increased Cash Guidance to ~$2.2B Reflects Equity Offering Proceeds

Revenue	Operating Loss	Cash
>$575 million	<$475 million[1]	~$2.2 billion
		Prior: $1.7 billion

Expectations for 2024:

Revenue: Substantial and sustained

- **Commercial:** Significant SPINRAZA royalties; growing 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 Q3 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' current large Phase 3 studies are fully enrolled
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

Clear Path to Drive Value Creation

Foundation

Robust Innovative Pipeline Positions Ionis to Drive Value

Invest

Invest to Bring Important Medicines to Patients

—

Advancing Pipeline and Technology to Drive Steady Cadence of New Medicines

Growth

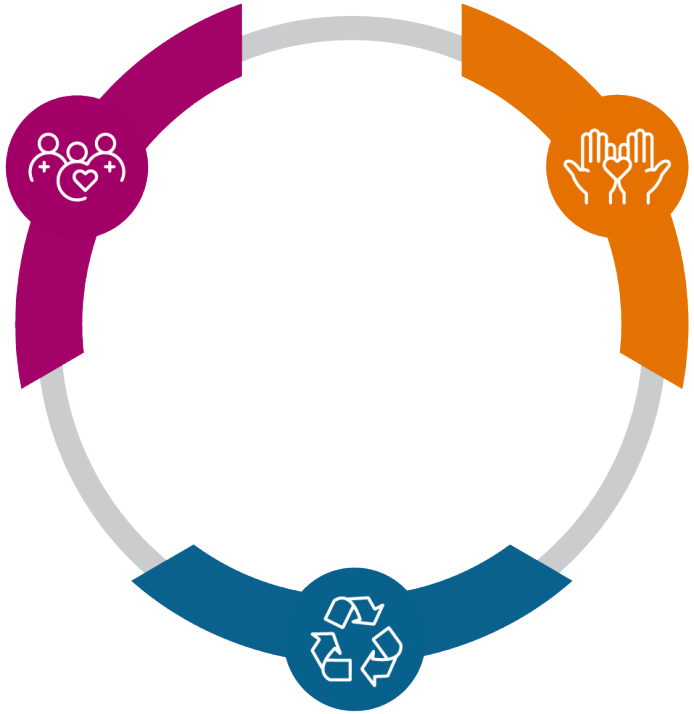
Positive Cash Flow Powered by Substantial Revenue Growth

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.

IONIS®