Corporate Presentation

November 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 is Well-Positioned for Substantial Growth

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

Realizing the Promise of our Wholly Owned Innovative Medicines[1,2]

Olezarsen

First-mover Advantage for Two Patient Populations: FCS and sHTG

Independent U.S. Launch in FCS expected by YE:2024

Blockbuster sHTG opportunity on track for Phase 3 data in H2:2025

Donidalorsen

Potential Preferred Prophylactic Treatment for HAE

August 21st, 2025 PDUFA Date
MAA submission expected soon[3]

Independent U.S. launch in HAE expected in 2025

ION582

Potential Transformational Medicine for Angelman Syndrome

Positive end of Phase 2 FDA discussion; aligned on Phase 3 design

Phase 3 development for Angelman Syndrome expected start in H1:2025

1. Timing expectations based on current assumptions and subject to change. 2. Assuming approval. 3. Granted Otsuka exclusive rights to commercialize donidalorsen in Europe and Asia Pacific regions.

Numerous Important Achievements in 2024 To Date

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]

4
Positive Phase 3 Readouts[3]

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[4]

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[5]

Donidalorsen
(OLE study)
Hereditary Angioedema (HAE)

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

ION582
(HALOS study)
Angelman Syndrome

ION224
MASH

1. WAINUA: www.wainua.com. 2. QALSODY: www.ema.Europa.eu; Biogen is responsible for commercializing QALSODY. 3. Balance (olezarsen for FCS), DEVOTE (higher dose nusinersen for SMA), OASIS-HAE and OASISplus (donidalorsen for HAE). 4. CORE, CORE2 and Essence (olezarsen for sHTG). B-Well 1 & B-Well 2 (chronic HBV). Phase 3 study for zilganersen (Alexander disease) 5. 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

—

Olezarsen
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

—

Olezarsen
U.S. FCS
EU FCS

—

Donidalorsen
U.S. HAE
EU HAE

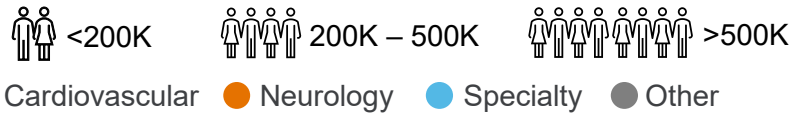
1. Timing expectations are based on current assumptions and are subject to change, timing of partnered program catalysts based on partners' most recent publicly available disclosures.

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]**
Olezarsen	IONIS	FCS		**FDA approval (2024)[5]**
		sHTG		**Ph3 data (2025)[6]**
Donidalorsen	IONIS[7]	HAE		**MAA filing (2024)**
Zilganersen	IONIS	Alexander disease		**Ph3 data (2025)**
Ulefnersen	IONIS	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. MAA filing planned for Q4:2024. 6. Data expected in H2:2025. 7. Granted Otsuka exclusive rights to commercialize donidalorsen in Europe and Asia Pacific regions.



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

Olezarsen

Independent U.S. Launch in FCS expected by YE:2024[2,3]

Building on WAINUA infrastructure

FCS field team hired and trained

Patient and caregiver support team

Further scale capabilities to realize blockbuster potential in sHTG

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. Assuming approval. 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.

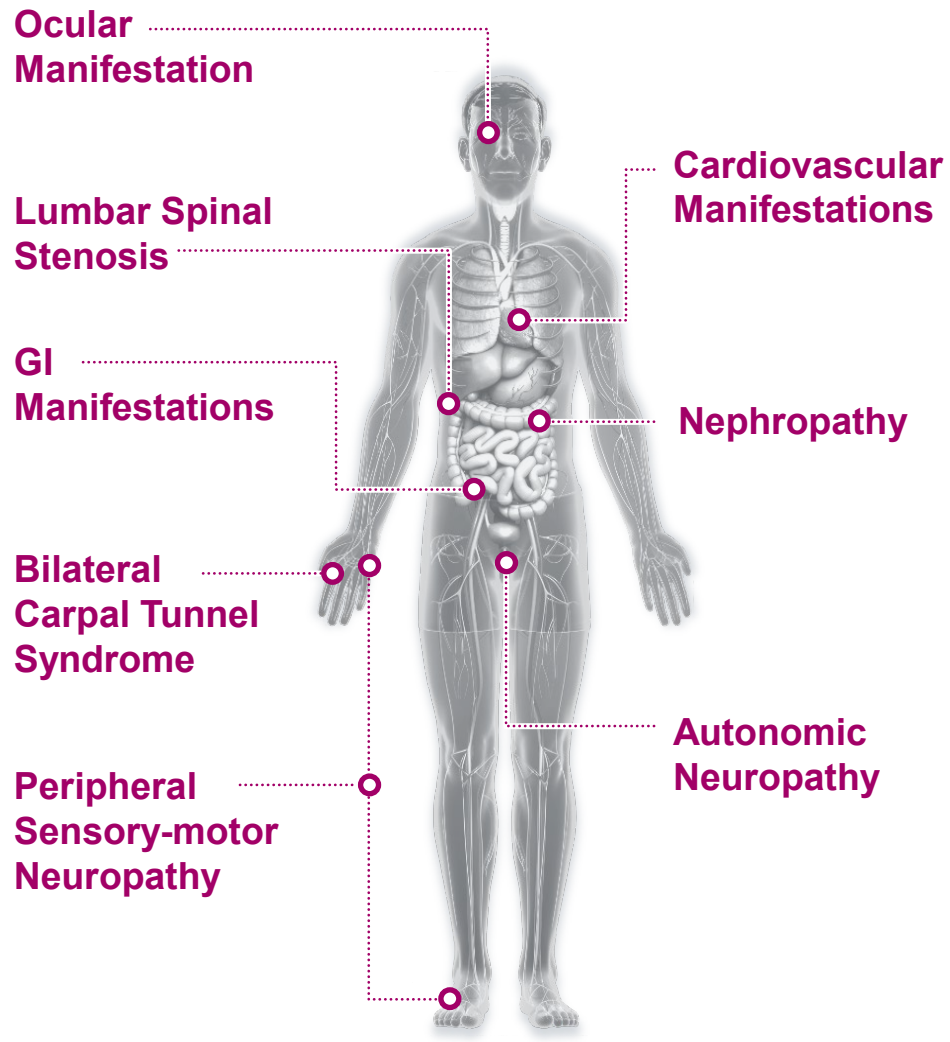
WAINUA: Positioned to Address the High Unmet Need in ATTR[1,2,3,4]

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

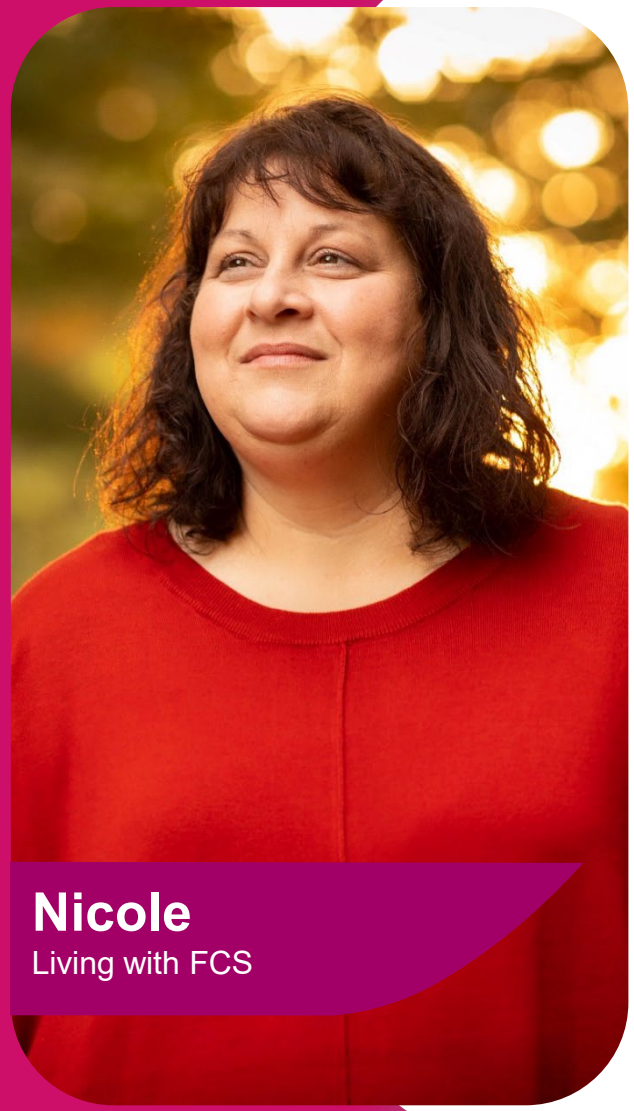
Next Steps

Data Expected in H2:2026[1]

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

Olezarsen:

Wholly Owned Blockbuster Opportunity with potential to become the **Standard-of-Care** for People with **Severely Elevated Trigylcerides**[1-3]



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

Substantial unmet need

Positive Balance (FCS) study results[4]:
- Robust reductions in apoC-III, TGs & favorable safety and tolerability
- Markedly lower rate of acute pancreatitis vs. placebo

December 19, 2024 PDUFA;
EU filing under review

1st independent launch

Phase 3 sHTG program enrollment complete; data expected in H2:2025

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

Olezarsen:

Designed to Address Two Patient Populations with Urgent Unmet Need[1,2]

Familial Chylomicronemia Syndrome

- **Rare disease opportunity**[3-5]
- **No approved treatments** in the U.S.
- **Significant risk** for acute, potentially fatal pancreatitis
- **Planned first indication** launch with **high margin potential**

Severe Hypertriglyceridemia

- **Large addressable** market[6-9]
- **Limited benefit** from current standard of care
- **Treatment guidelines** recommend preventative treatment
- **Blockbuster potential**

1. Timing expectations based on current assumptions and subject to change. 2. Assuming approval. 3. Pallazola VA, et al. *Eur J Prev Cardiol* 2020;27(19):2276-8. 4. Warden BA, et al. *J Clin Lipidol* 2020;14(2):201-6. 5. Tripathi M, et al. *Endocr Pract* 2021;27(1):71-6. 6. Sanchez et al. *Lipids in Health and Disease* 2021;20:72. 7. Berberich et al. *Lipids in Health and Disease* 2021;20:98. 8. Fan et al., *J Clin Lipidology* 2019; 13:100-108. 9. Christian et al., *Am J Cardiol* 2011;107:891-897.

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]
- EAP in U.S. for FCS underway, OLE progressing well
- U.S. Breakthrough Therapy and Orphan Drug designations
- **PDUFA December 19, 2024**; EU filing under review
- Prepared for launch in anticipation of approval[4]

Bridge
TIMI 73a

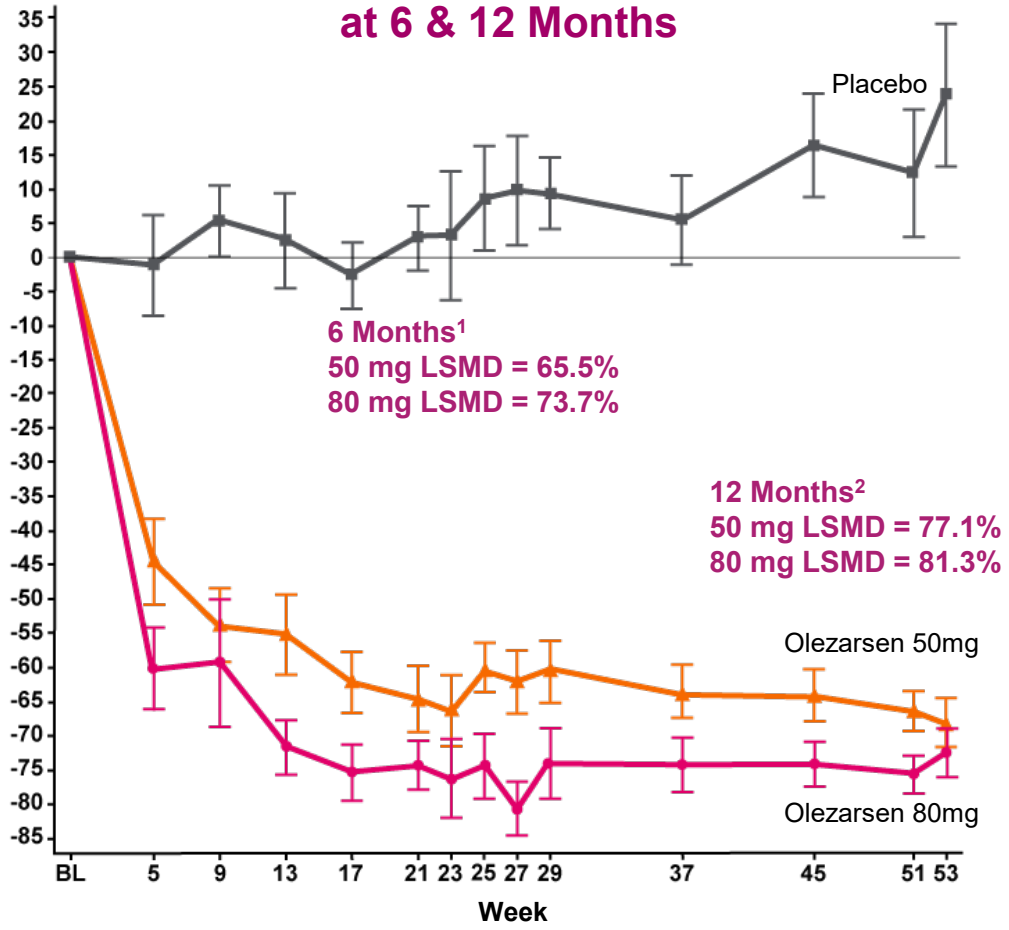
- Phase 2b study in patients with TG ≥150 mg/dL (HTG) and TG ≥500 mg/dL (sHTG)
- Supportive exposure study
- Positive data presented in late-breaker presentation at ACC, published in *NEJM*[5]
- Statistically significant reductions in apoC-III and TGs (including nearly all HTG patients achieving normal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

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. 5. Bergmark, B, et al. *N Engl J Med*. 2024.

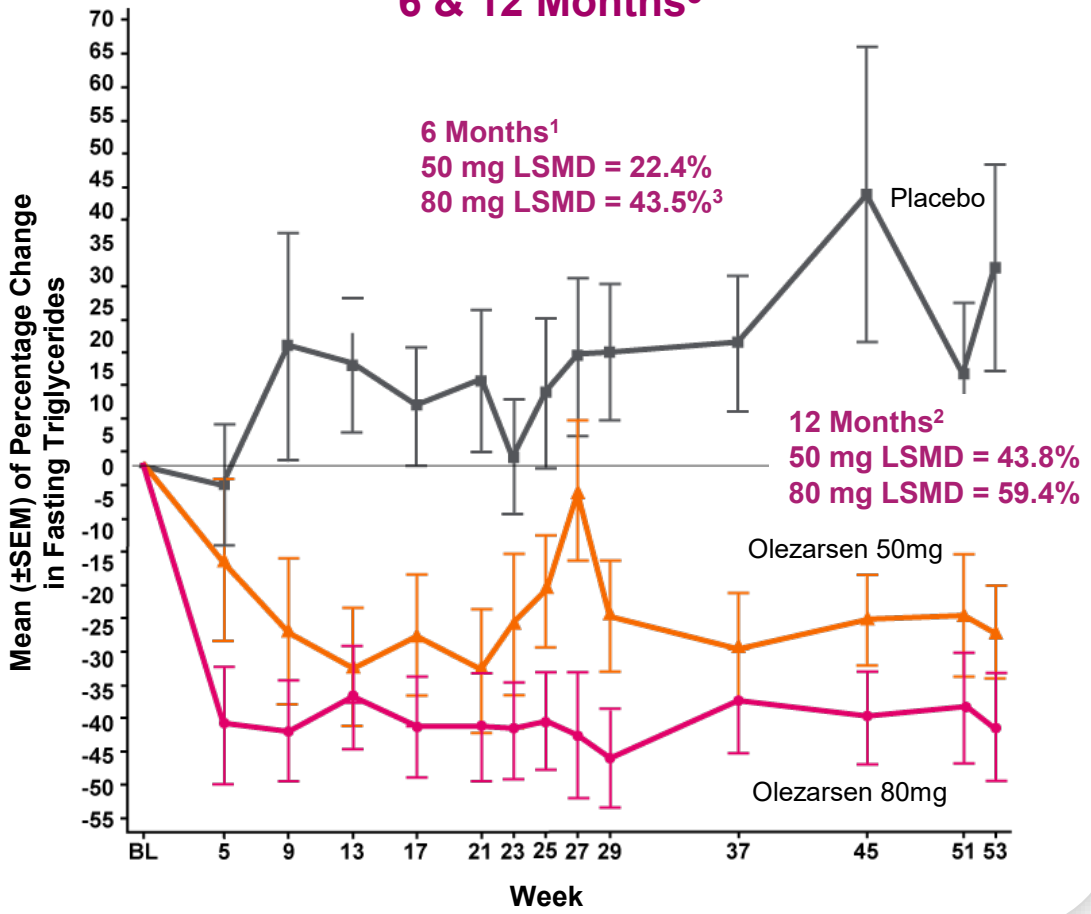
Olezarsen Treatment Resulted in Robust Reductions in ApoC-III and Triglycerides at 6 and 12 Months

Balance
a familial chylomicronemia syndrome study

Mean Change (%) in ApoC-III at 6 & 12 Months



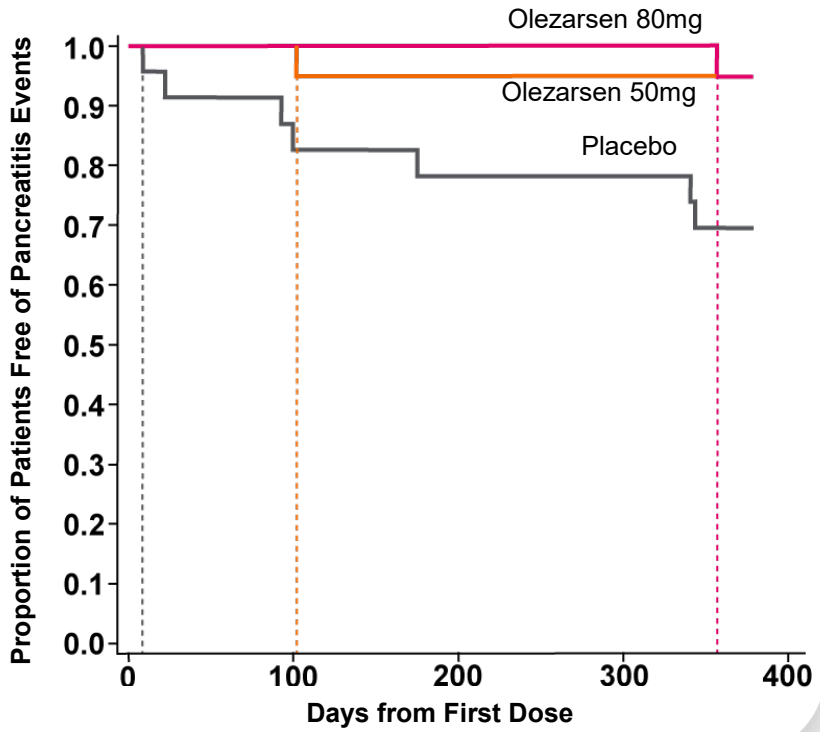
Mean Change (%) in TGs at 6 & 12 Months[3]



LSMD, Least squares mean difference. 1. Average of weeks 23, 25, and 27. 2. Average of weeks 51 and 53. 3. Olezarsen 80 mg dose ($p<0.001$); 50 mg dose ($p=0.078$).

Olezarsen Treatment Resulted in Substantial and Clinically Meaningful Difference in Acute Pancreatitis Events

Time to first pancreatitis event



Pancreatitis events

	Placebo (n=23)	Olezarsen 50 mg (n=21)	Olezarsen 80 mg (n=22)
Pancreatitis events, n	11	1	1
First Pancreatitis event, study day	9	102	357

Selected prespecified secondary endpoints

Adjudicated Acute Pancreatitis Endpoint (Week 1-53)	**Event Rate per 100 PY (95% CI)**		**Mean Rate Ratio* (95% CI)**
	Placebo (n=23)	**Pooled Olezarsen**	
Full analysis set	36.3 (14.7, 89.7)	4.37 (0.942, 20.3)	0.12 (0.022, 0.656)
Patients with previous history within 10 years prior to screening	66.2 (30.5, 144)	6.73 (1.61, 28.1)	0.10 (0.020, 0.506)
Patients with ≥2 events within previous 5 years prior to enrollment	119 (61.2, 230)	16.6 (4.05, 67.9)	0.14 (0.029, 0.669)

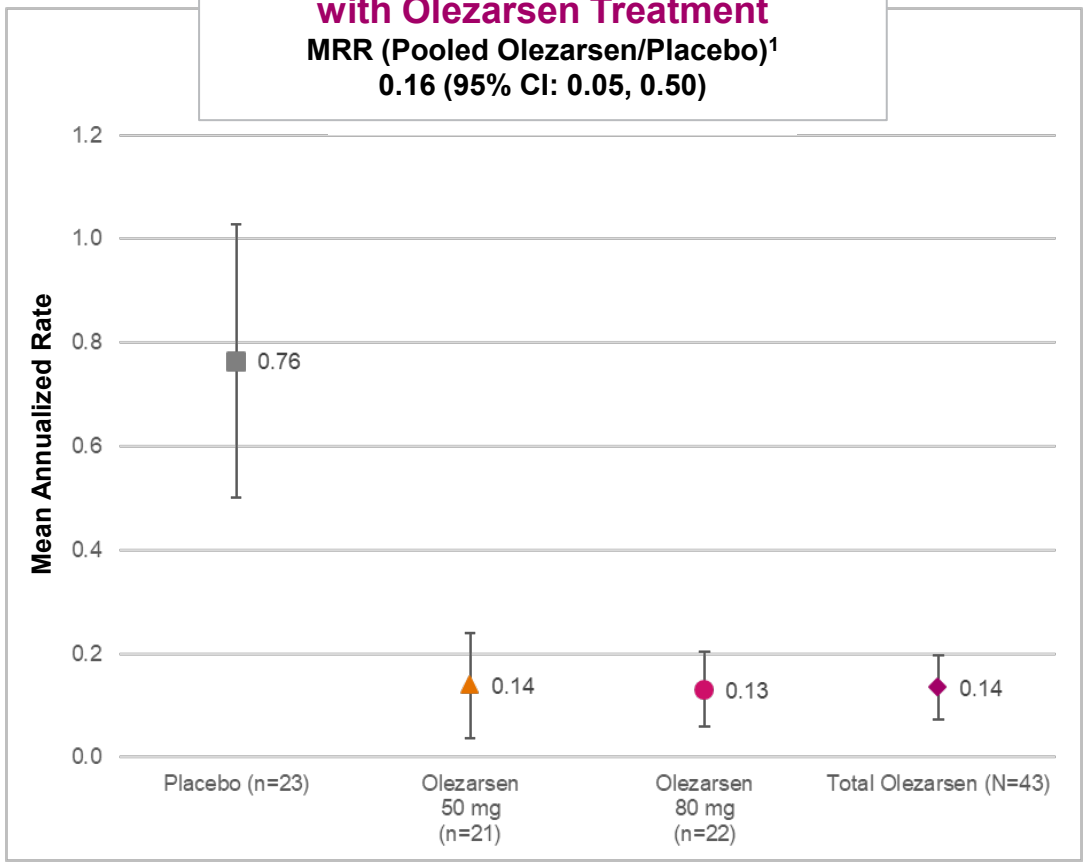
*Pooled olezarsen vs placebo; exposure-adjusted event rate in the treatment group divided by the exposure-adjusted event rate in the placebo group; a ratio of 1 would indicate no difference. Abbreviations: CI, confidence interval; PY, patient-year.

84% Reduction in All-Cause Hospitalizations and Inpatient Days Reduced by >6 Days with Olezarsen Treatment

Balance
a familial chylomicronemia syndrome study

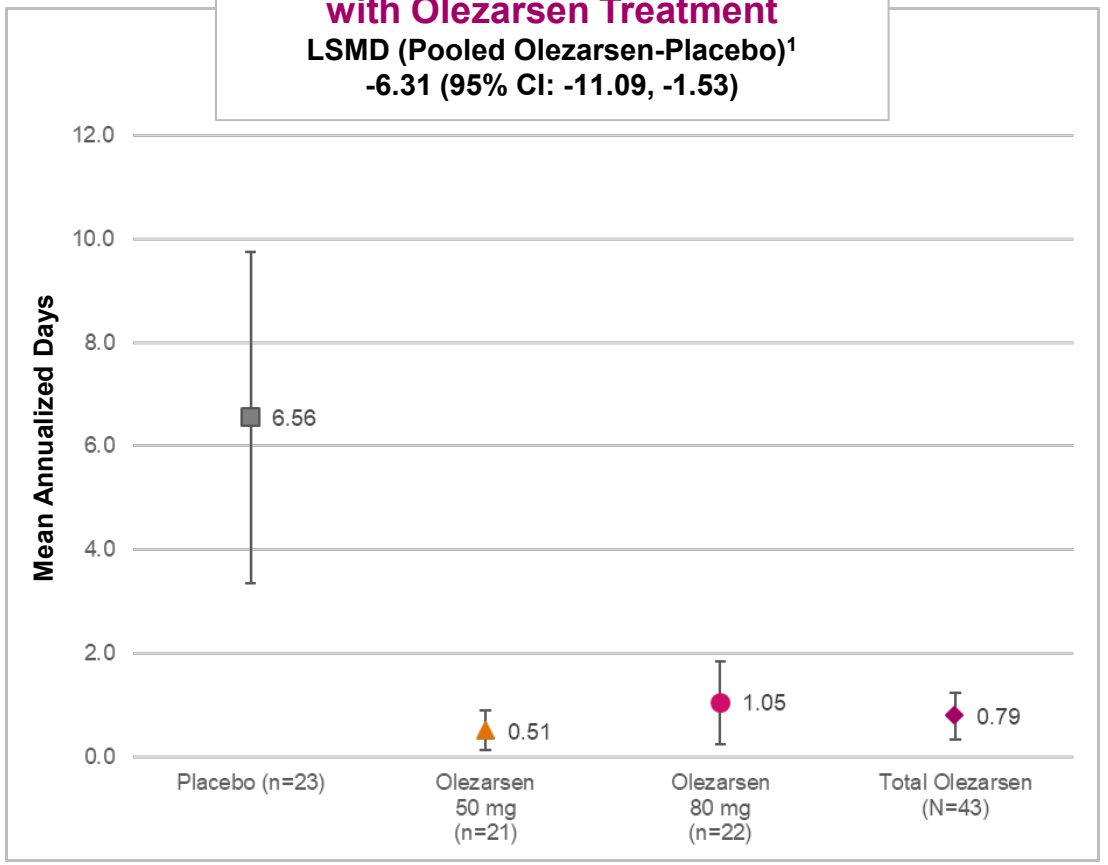
All-Cause Hospitalizations with Olezarsen Treatment

MRR (Pooled Olezarsen/Placebo)[1]
0.16 (95% CI: 0.05, 0.50)



Total Inpatient Days with Olezarsen Treatment

LSMD (Pooled Olezarsen-Placebo)[1]
-6.31 (95% CI: -11.09, -1.53)



MRR, mean rate reduction; LSMD, Least squares mean difference.

Favorable Safety and Tolerability Profile

- More TEAEs and SAEs in placebo-treated patients, primarily driven by more pancreatitis events in the placebo group
- No serious TEAEs related to study drug
- No clinically meaningful changes in platelet count or in measures of hepatic and renal function
- Low incidence of mild injection site reactions
- 1 death occurred in the 50 mg olezarsen group that was assessed as unrelated to study drug

TEAEs, n (%)	Placebo (n=23)	Olezarsen 50 mg (n=21)	Olezarsen 80 mg (n=22)
Any	22 (95.7)	18 (85.7)	19 (86.4)
Related to study drug	5 (21.7)	6 (28.6)	7 (31.8)
Mild	3 (13.0)	6 (28.6)	3 (13.6)
Moderate	0	0	4 (18.2)
Severe	2 (8.7)	0	0
Leading to treatment discontinuation	0	1 (4.8)	2 (9.1)
Leading to death	0	1 (4.8)	0
Any serious	9 (39.1)	4 (19.0)	3 (13.6)
Serious related to study drug	0	0	0

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.

Bridge Study: Significant Reductions in ApoC-III and Triglycerides in HTG and sHTG Patients Treated with Olezarsen

Bridge TIMI 73a

Olezarsen 80mg:

- 93% of patients with HTG achieved normal levels at 6 months (<150mg/dL)
- ApoC-III: 73% (6 months) and 71% (12 months) reduction vs. placebo[1]
- Triglycerides: 53% (6 months) and 55% (12 months) reduction vs. placebo[1]
- Favorable safety and tolerability

Olezarsen 80mg, sHTG subgroup:

- ApoC-III: 86% (6 months) and 91% (12 months) reduction from baseline[2]
- Triglycerides: 83% (6 months) and 86% (12 months) reduction from baseline[2]
- Favorable safety and tolerability

Looking ahead: CORE & CORE2

- Data in CORE and CORE2 studies in patients with sHTG expected to be similar to sHTG patient data from Bridge based on normal LPL activity

1. Placebo-adjusted, p<0.001. 2. Not placebo-adjusted; placebo changes in apoC-III of -14% and -31% and in triglycerides of -35% and -48% observed at 6 and 12 months, respectively.

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 **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]

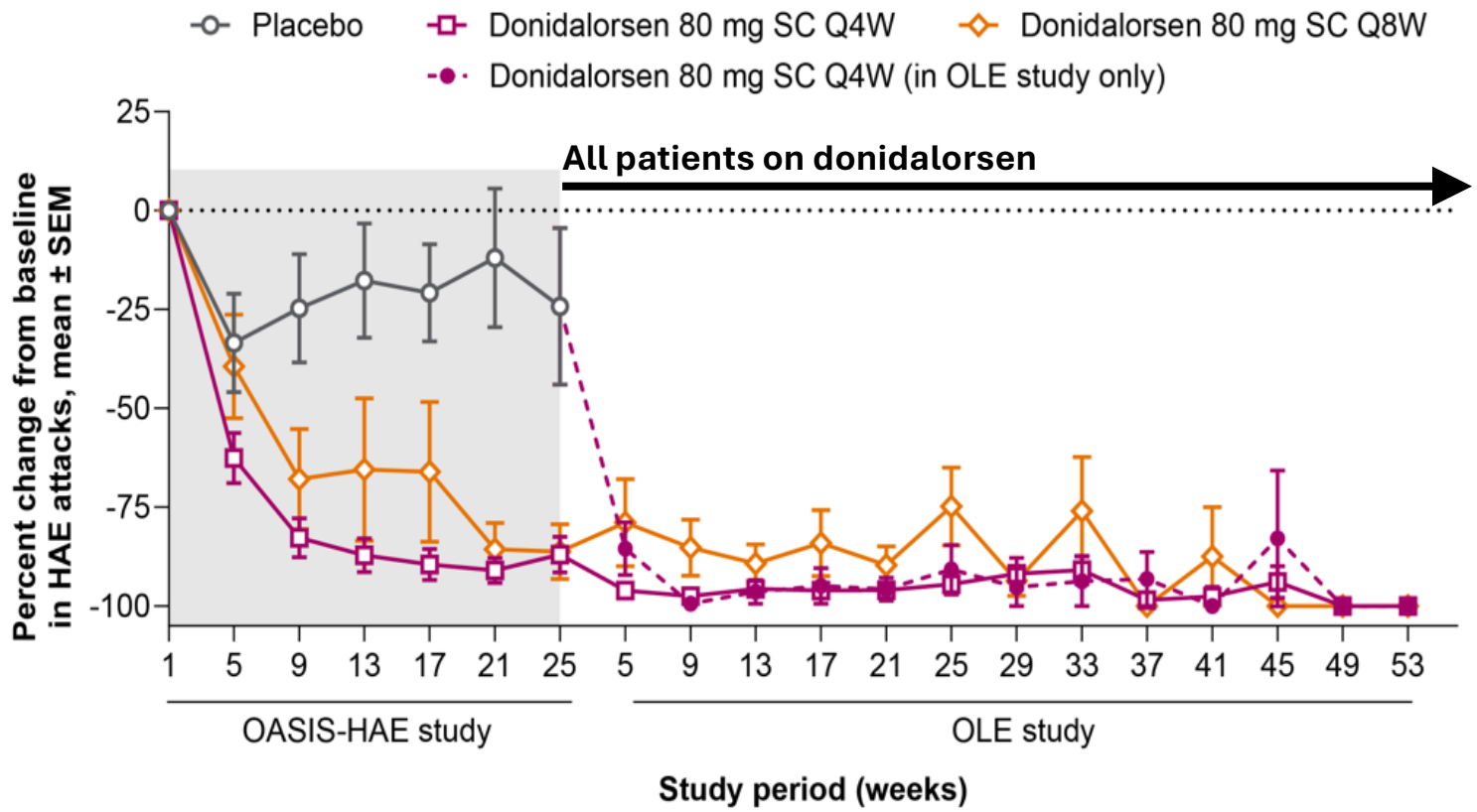
OASIS plus

- 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]



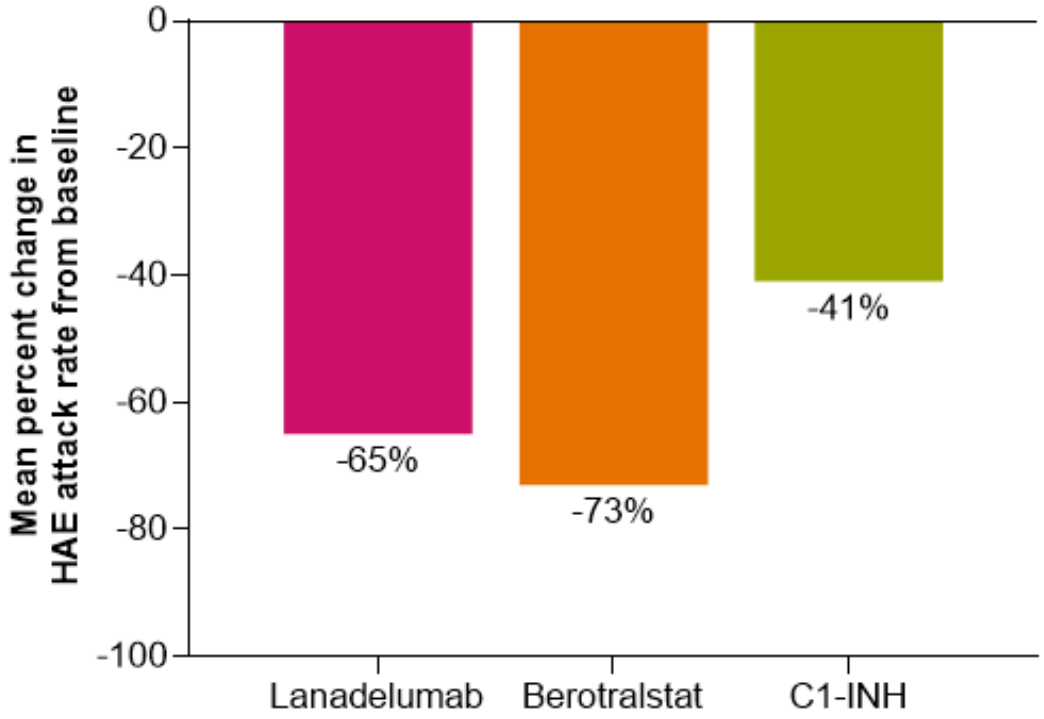
Placebo, n =	19	19	19	19	18	17	16	19	19	19	19	16	15	13	10	6	5	5	4	2
Donidalorsen 80 mg Q4W, n =	44	44	44	44	44	43	43	44	44	43	43	36	30	26	24	18	11	8	4	3
Donidalorsen 80 mg Q8W, n =	20	20	20	20	20	20	19	20	20	20	20	16	14	13	12	8	4	3	2	2

- **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]

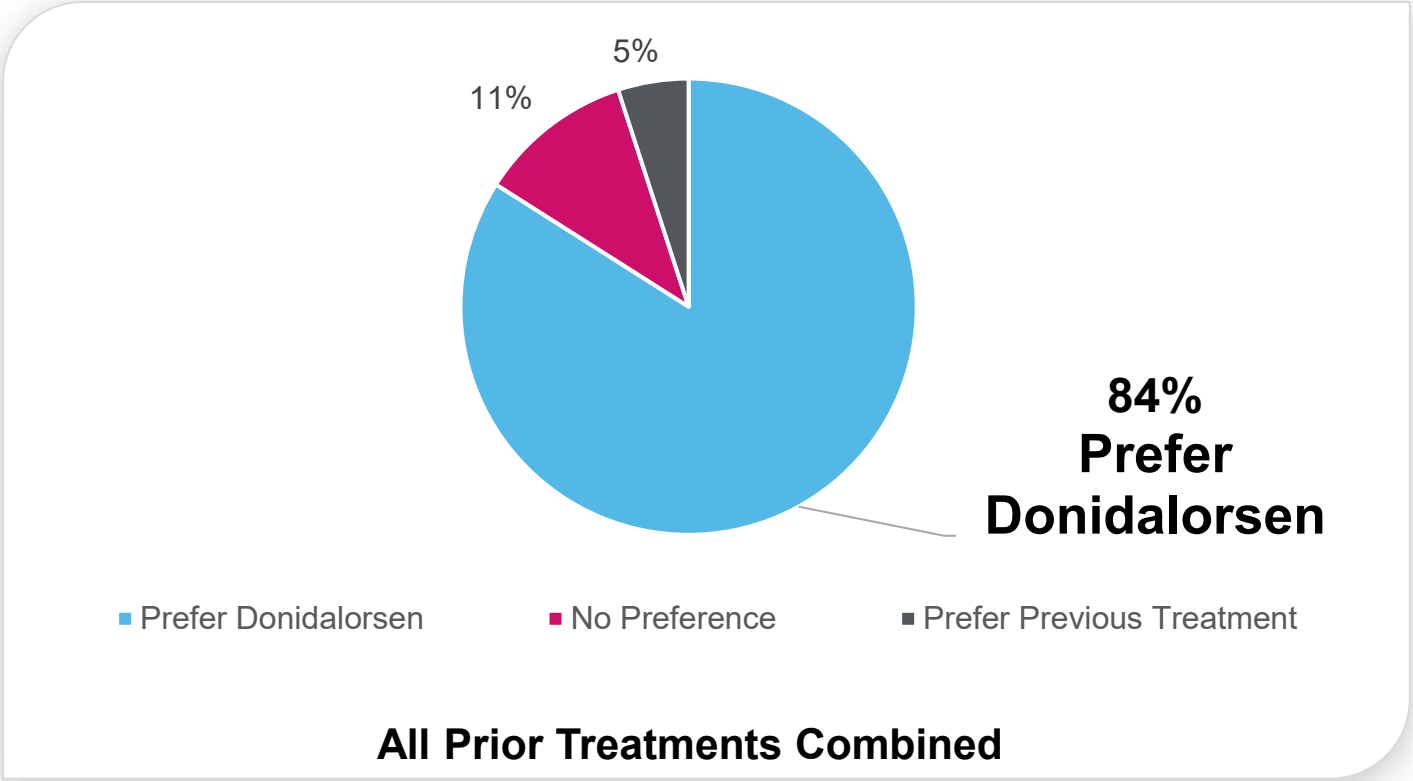


n =	31	11	22
Baseline, mean ± SD =	0.69 ± 1.09	1.80 ± 1.92	0.61 ± 0.96
Donidalorsen Q4W, mean ± SD =	0.24 ± 0.33	0.48 ± 0.53	0.36 ± 0.69

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

7

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)

Ulefnersen
FUS-ALS
(FUS)

ION582
Angelman syndrome
(UBE3A-ATS)

ION717
Prion disease
(PRNP)

ION356
Pelizaeus-Merzbacher
Disease (PLP1)

ION440
MECP2 duplication
syndrome (MECP2)

ION269
Alzheimer's disease
(APP)

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)

ION306
SMA (SMN2)

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), 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

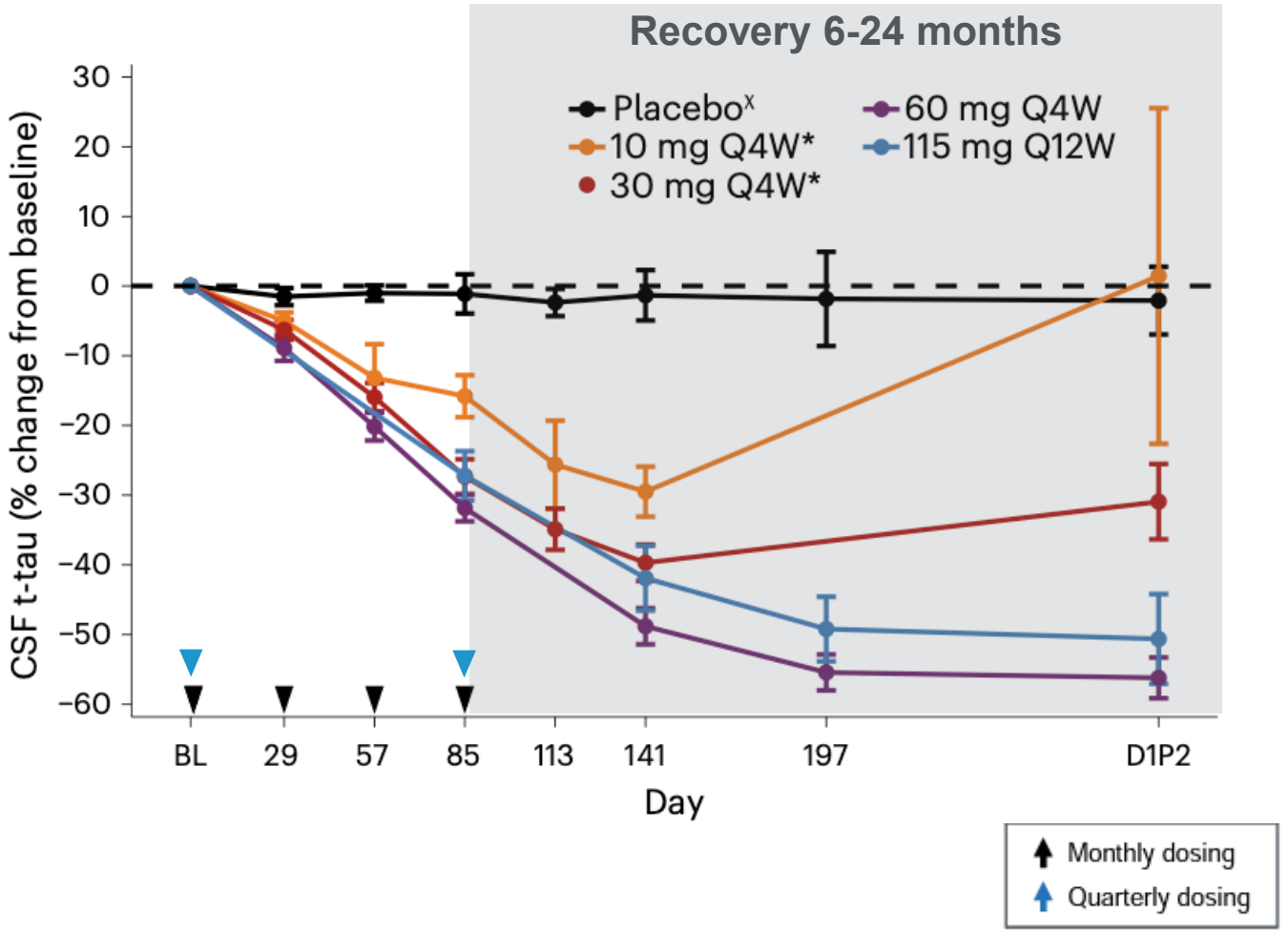
1. Based on data generated to date from the Phase 1/2a HALOS study of ION582. 2. Timing expectations based on current assumptions and subject to change.

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



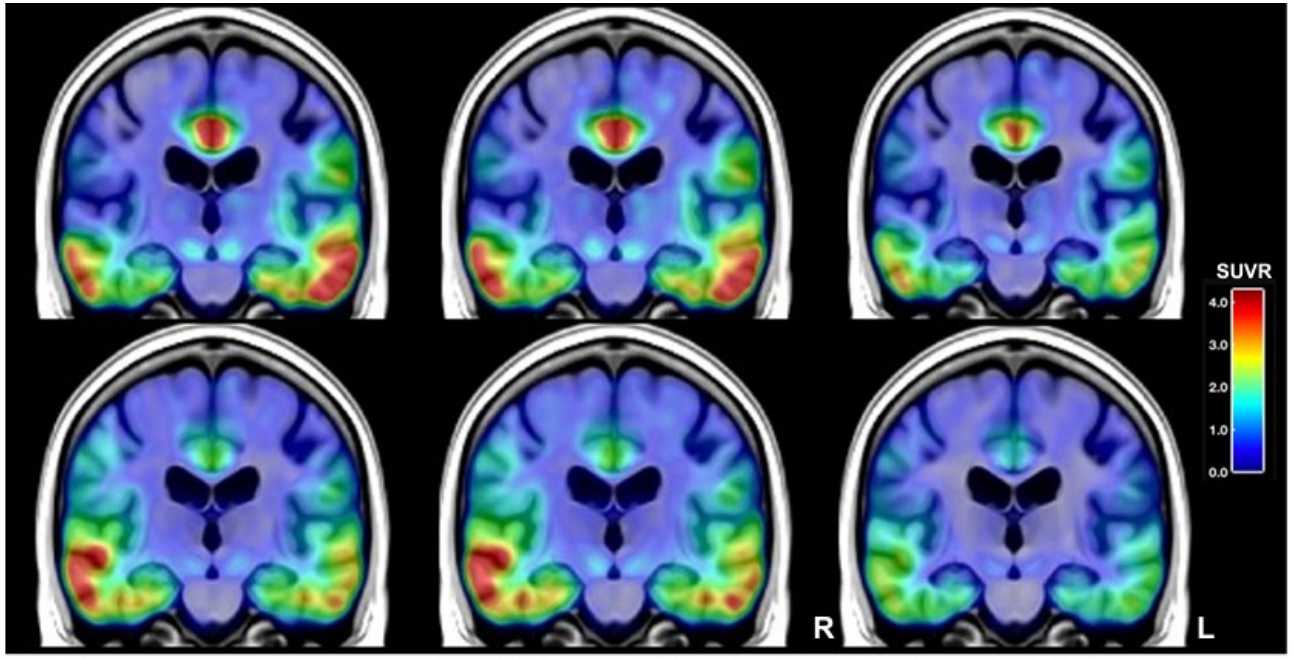
1. Mummery et al., Nat Med, 2023; AD = Alzheimer's disease; CSF = cerebrospinal fluid; Q4W = every 4-week dosing; Q12W = every 12-week dosing; t-tau = total tau

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

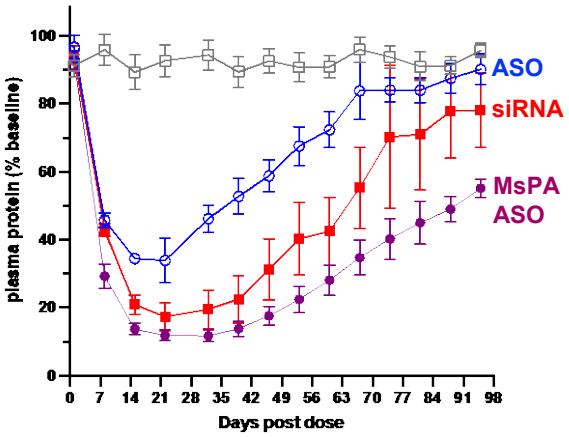
Leading Medicinal Chemistry Platform

Technology Advancements Powering Future Medicines

Expanding Technology Platform

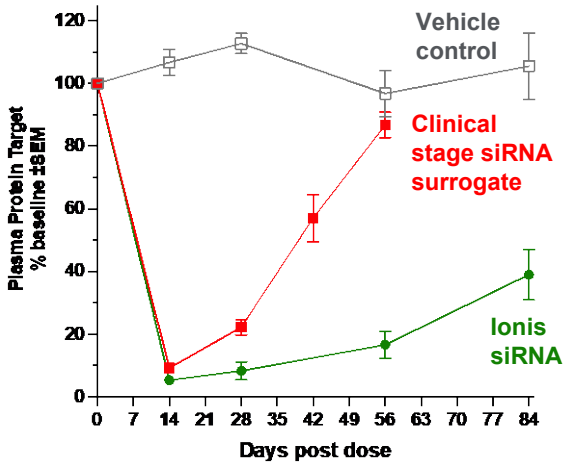
MsPA Backbone

Enables Less Frequent Dosing[1,2]



Ionis siRNA

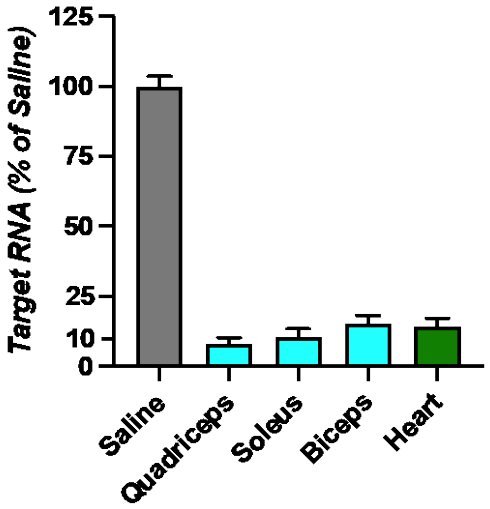
Demonstrates Competitive Profile[2,3]



Optimizing Delivery for New Therapeutic Opportunities

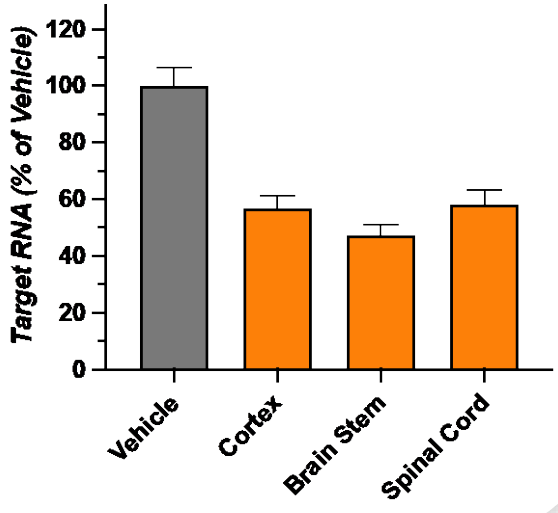
Bicycle-siRNA

Target Reduction in Muscle[1]



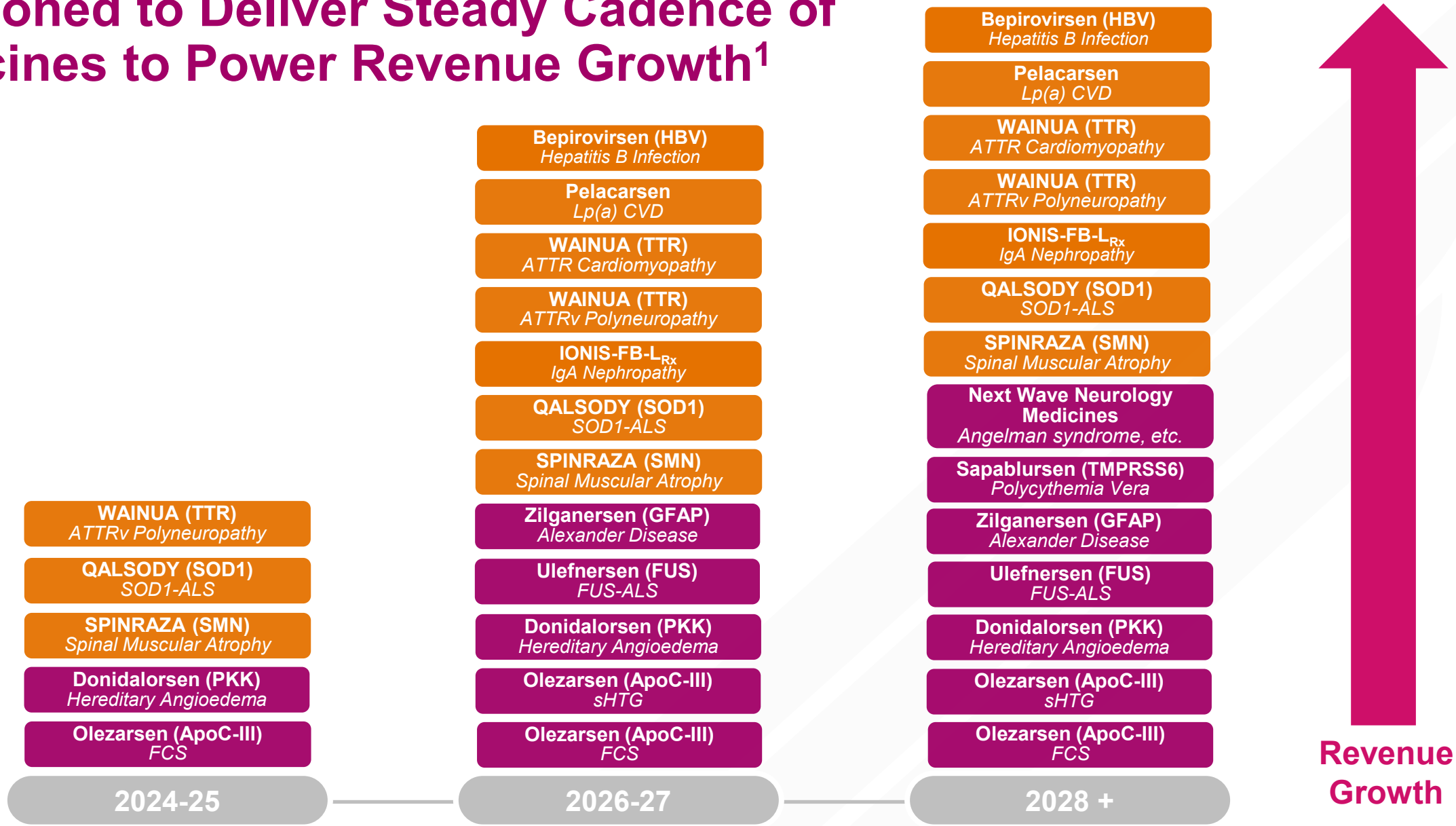
Bicycle ASO

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

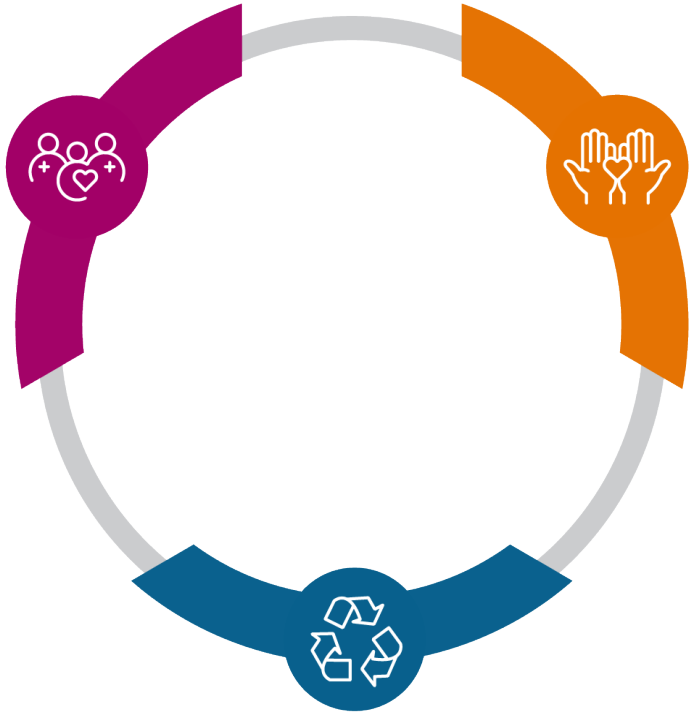
Positive Cash Flow Powered by Substantial Revenue Growth

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®