2025 Annual Shareholders Meeting Corporate Update

June 2025

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, 2024, 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: Pioneered the Field of Oligonucleotide Therapeutics

A Rich History **Discovering** and **Developing** Transformational RNA-Based **Medicines**

Miles and family, SMA

- Created **Industry Leading Medicinal Chemistry** and **Manufacturing** Capabilities
- **Optimized** and **Validated Delivery** to Liver and CNS for Human Therapeutics
- **Optimized** and **Validated** Multiple Mechanisms of Action Including RNase H and Splicing
- Led the Way in **Discovering** and **Developing First-in-Class Medicines** for Serious Diseases

2020: Established New Vision for Ionis

- **Maximize shareholder value as a fully integrated commercial-stage biotechnology company**
  - Build and integrate commercial organization to successfully commercialize Ionis medicines independently
  - Prioritize and advance the wholly owned pipeline to maximize commercial success
  - Build commercial capabilities to enable delivery of a steady cadence of transformational medicines well into the future
  - Prioritize and strengthen Ionis' culture of innovation
  - Maximize shareholder value
- **Strategy for commercial success**
  - Establish co-commercialization collaboration with AstraZeneca; leverage partnership to ensure global commercial success for eplontersen
  - Leverage AstraZeneca partnership to accelerate build of internal commercial capabilities
  - Establish development and commercial synergies by prioritizing cardiovascular and neurology therapeutic franchises
  - Focus initially on U.S., with plans to expand outside the U.S. with future medicines
- **Expand and diversify our technology**
  - Strengthen differentiation from emerging competition
  - Expand the scope of our technology to deliver more medicines to patients with commercial success
  - Solidify our leadership in RNA-based therapeutics
- **Drive substantial and sustained revenue growth and positive cash flow**

Ionis Evolution: Strong Progress to Achieve our Vision

- **Strengthened the organization to support commercial success**
  - Built an innovative and scalable commercial organization with highly experienced commercial leadership
  - Strengthened key functional areas across the organization to support commercialization (*e.g.,* late-stage development, communications, finance, legal, compliance)
- **Steady cadence of positive Phase 3 outcomes** (ATTRv-PN, FCS, HAE and moderate HTG)
- **Three transformational medicines approved and launched with one additional expected near-term**
  - **QALSODY** first medicine approved for a genetic form of ALS[1]
  - **WAINUA** Ionis' first launch of a co-commercialized medicine[2]
  - **TRYNGOLZA** Ionis' first independent commercial launch[3]
  - **Donidalorsen** Ionis' expected second independent commercial launch[4,5]
- **Expanded and diversified technology**[6]
  - Expanded platform (siRNA, MsPA backbone, DNA editing) to optimize potency, durability and delivery
  - Optimized targeted delivery to muscle (skeletal and cardiac muscle) and to cross blood brain barrier
  - Strengthened leading franchise in cardiology and neurology while enabling potential new therapeutic areas (pulmonary and renal)

1. QALSODY, SOD1-ALS, Biogen. 2. WAINUA, ATTRv-PN, AstraZeneca. 3. TRYNGOLZA, FCS, see Full Prescribing Information 4. Donidalorsen, HAE, PDUFA 8/21/25, assuming approval. 5. Timing expectations are based on current assumptions and are subject to change. 6. Based on current preclinical data.

Ionis Today: A Fully Integrated Commercial-stage Biotech Poised to Deliver Sustained and Substantial Shareholder Value[1,2]

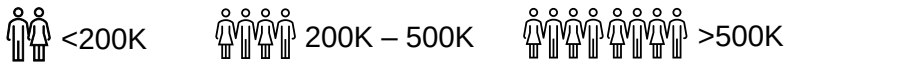
- **Industry leading neurology franchise**
  - Transformational medicines making a difference in the lives of patients: SPINRAZA, QALSODY and WAINUA
  - New potentially transformational medicines advancing towards the market: ION582 (Angelman Syndrome), IONIS-MAPT$_{Rx}$ (Alzheimer's disease), zilganersen (Alexander disease)
  - Technology advancements on brink of clinical testing to further strengthen leadership in neurology
- **Large and expanding cardiovascular disease pipeline**
  - Key late-stage programs: eplontersen (ATTR-CM), olezarsen (FCS and sHTG), pelacarsen (Lp(a)-CVD)
  - Technology advancements on brink of clinical testing to further strengthen our cardiovascular franchise[3]
- **Rich late-stage pipeline poised to deliver a steady cadence of near-term value driving events**
  - Ten Phase 3 studies on track for data in 2025-2028
  - Broad and severe/rare patient populations
  - Wholly owned and partnered programs

1. Based on current estimates, subject to change. 2. 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. 3. Based on current preclinical data.

Rich Late-Stage Pipeline with Multi-Billion Dollar Potential[1]

		Indication	Prevalence[2]	Next Events[3]
TRYNGOLZA (olezarsen)	IONIS[4,5]	FCS		**U.S. launch progress (2025)** **EU approval (2025)**
		sHTG		**Ph3 data (2025)**[6]
Donidalorsen	IONIS[4,7]	HAE		**U.S. approval & launch (2025)**[8]
Zilganersen	IONIS	Alexander disease		**Ph3 data (2025)**[9]
ION582	IONIS	Angelman Syndrome		**Ph3 first patient dosed (2025)** **Ph3 complete enrollment (2026)**
WAINUA (eplontersen)	IONIS AstraZeneca	ATTR-CM		**Ph3 data (2026)**[10]
Pelacarsen	NOVARTIS	Lp(a) CVD		**Ph3 data (2026)**[11]
Bepirovirsen	GSK	HBV		**Ph3 data (2026)**
Sefaxersen	Roche	IgA nephropathy		**Ph3 data (2026)**
Ulefnersen	Otsuka	FUS-ALS		**Ph3 data (2026)**
Tofersen	Biogen	Presymptomatic SOD1-ALS		**Ph3 data (2028)**

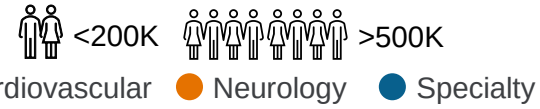
1. Assuming approval. Peak sales estimates based on current estimates and subject to change. 2. Market data on file. 3. Timing expectations are based on current assumptions and are subject to change. 4. Granted Theratechnologies exclusive rights to commercialize olezarsen and donidalorsen in Canda. 5. Granted Sobi exclusive olezarsen commercial rights outside the U.S., Canada and China 6. Olezarsen sHTG data expected in Q3:2025. 7. Granted Otsuka exclusive rights to commercialize donidalorsen in Europe and Asia Pacific regions. 8. U.S. PDUFA 8/21/25, MAA submission completed in Q4:2024. 9. Data expected H2:2025. 10. Data expected H2:2026. 11 Data expected H1:2026.



Advancing Ionis' Independent Late-Stage Pipeline with Multi-Billion Dollar Potential[1,2]

	Indication	Prevalence[3]	Next Events[4]
TRYNGOLZA (olezarsen)	Familial Chylomicronemia syndrome		**U.S. launch progress (2025)** **EU approval (2025)**
	Severe Hypertriglyceridemia		**Ph3 data (2025)[5]**
Donidalorsen	Hereditary Angioedema		**U.S. approval & launch (2025)[6]**
Zilganersen	Alexander disease		**Ph3 data (2025)[7]**
ION582	Angelman Syndrome		**Ph3 first patient dosed (2025)** **Ph3 complete enrollment (2026)**

4 More Independent Launches in Next 3 Years with More to Follow[1,4]



1. Assuming approval. 2. Peak sales estimates based on current estimates and subject to change. 3. Market data on file. 4. Timing expectations are based on current assumptions and are subject to change. 5. Olezarsen sHTG (CORE and CORE2) data expected in Q3:2025. 6. PDUFA August 21,2025. MAA submission completed in Q4:2024. 7. Data expected in H2:2025.

Tryngolza™ (olezarsen) 80 mg injection

The first FDA-approved therapy for adults with FCS

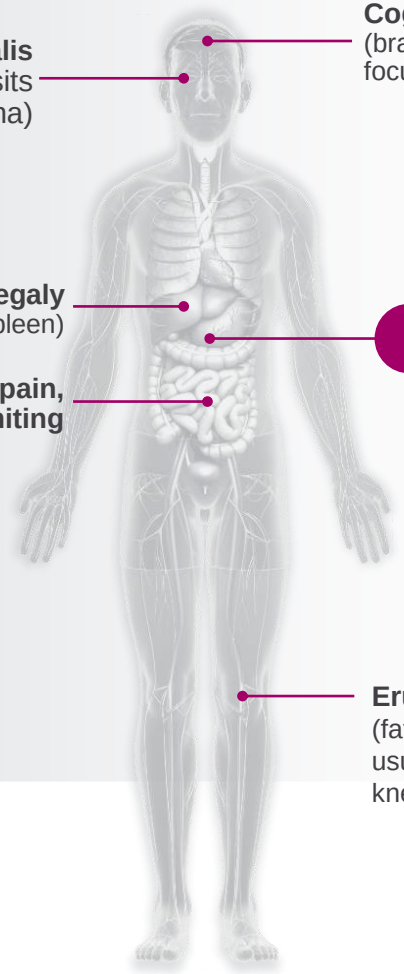
NOW APPROVED

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 risk of potentially fatal acute pancreatitis, 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]



Lipemia Retinalis (fatty deposits in the retina)

Cognitive symptoms (brain fog, fatigue, lack of focus, memory loss)

Hepatosplenomegaly (enlarged liver and spleen)

Acute pancreatitis

Severe abdominal pain, nausea & vomiting

Eruptive xanthomas (fatty deposits under the skin, usually on buttocks, trunk, knees, and elbows)

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.

TRYNGOLZA FCS Launch Off to Encouraging Start[1,2]

Over $6 million in revenue in first full quarter of launch[2]

Robust efficacy and safety

- Significant and sustained triglyceride reductions
- Substantial reduction in acute pancreatitis events

Convenience of once-monthly self-administration with an autoinjector

Strong Patient Uptake

Prescriptions generated from:

- ✓ U.S. EAP and OLE patients
- ✓ Previously diagnosed patients
- ✓ Newly identified patients

Positive Physician Engagement

Good initial breadth of prescribers:

- ✓ Prescriptions from across the country
- ✓ 50% cardiologists, 25% endocrinologists, 25% from lipidologists and internal medicine

Favorable Payer Dynamics

- ✓ Coverage split: ~60% commercial, ~40% government[2]
- ✓ Clinically diagnosed and genetically confirmed patients
- ✓ Nearly 90% of patients had $0 out-of-pocket costs

1. TRYNGOLZA is approved in the U.S. for Familial Chylomicronemia Syndrome in adults as an adjunct to diet; see Full Prescribing Information. 2. For the quarter ended March 31, 2025.

Severe Hypertriglyceridemia (sHTG):
A Serious, Prevalent Condition with High Unmet Need[1-7]

Defined by **triglyceride** levels **over 500 mg/dL** and increased risk of **acute, potentially fatal pancreatitis**

Broad population, **impacting ~1% of people in the U.S.**

High unmet need:

Poorly managed with current treatments, including fibrates, omega-3s, statins and GLP-1s

"We've all seen patients with their first acute pancreatitis episode absolutely destroy their pancreas. Pancreatitis is more frightening than even a heart attack, harder to deal with." – Dr. Seth Baum[8]

1. Sanchez et al. Lipids in Health and Disease 2021;20:72. 2. Berberich et al. Lipids in Health and Disease 2021;20:98. 3. Fan et al., J Clin Lipidology 2019; 13:100-108. 4. Christian et al., Am J Cardiol 2011;107:891-897. 5. Simha V. BMJ. 2020;371:m3109. 6. Yang AL, et al. Pancreatology. 2020;20(5):795-800. 7. Aquest Research, 2021. 8. Seth Baum, M.D., MASPC, FACC, FAHA, FNLA chief medical officer, Flourish Research and clinical affiliate professor of cardiology, Florida Atlantic University.

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 safety study in patients w/ TG ≥150 mg/dL (HTG)[2]
- Results to be used to support olezarsen exposure database
- Nearly 1,500 patients
- **Reported positive topline efficacy and safety data**

On Track for Data from CORE + CORE2 Studies in Q3:2025[1]

1. Timing expectations and peak sales estimates based on current assumptions and subject to change. 2. Conducted in TG ≥150-500 mg/dL with or at risk for ASCVD or TG ≥500 mg/dL.

Essence Study Topline Results: Robust Efficacy and Favorable Safety

Innovative Study Design

- Largest study ever conducted for an RNA-targeted treatment to reduce triglycerides
- Opportunity to fully explore the lipid benefits of olezarsen in people with hypertriglyceridemia and support the exposure database for olezarsen

Strong Clinical Profile

- Significant 61% (80 mg) and 58% (50 mg) reduction in TGs vs. placebo at 6 months[1]
- Met all key secondary endpoints[2]
- Vast majority of participants reached TG reductions to normalized levels
- Favorable safety and tolerability[3]

Looking Ahead: CORE & CORE2[4]

- Additional data to be presented at a medical congress
- Data from CORE and CORE2 studies in patients with sHTG expected in Q3:2025

1. Primary endpoint; achieved statistically significant placebo-adjusted 61% and 58% reductions in fasting TG levels, on top of standard of care, at 6 months with the 80 mg and 50 mg monthly doses, respectively (p <0.0001).
2. The most common treatment- emergent adverse event that occurred more frequently than placebo in the olezarsen groups were injection site reactions, with the majority mild in severity. 3. Key secondary endpoints included percent changes in triglyceride levels at 12 months, proportion of patients who achieve fasting TG<150 mg/dL and percent changes in other lipid parameters, including apoC-III, remnant cholesterol, non-HDL-C and apoB, compared to placebo over the treatment period. 4. Timing expectations are based on current assumptions and are subject to change.

Olezarsen: Potential to Change the sHTG Treatment Paradigm[1,2]

sHTG launch on track for 2026[3]

- **High unmet need and blockbuster potential[4]**
- **First mover advantage in FCS and sHTG[3]**
- **Encouraging early FCS launch progress[5]**
- **Robust efficacy and safety data reported in Phase 3 Essence study**
- **Pivotal CORE/CORE2 Data Q3 2025[3]**

1. Assuming approval. 2. Granted Sobi exclusive olezarsen commercial rights outside the U.S., Canada and China; Granted Theratechnologies exclusive rights to commercialize olezarsen and donidalorsen in Canda.
3. Timing expectations are based on current assumptions and are subject to change. 4. Peak sales estimates based on current estimates and subject to change. 5. For the quarter ended March 31, 2025.

Donidalorsen: A Potential Advance in Prophylactic Treatment of HAE

Hereditary Angioedema (HAE) Disease Overview[1-6]

A rare, chronic and potentially life-threatening **genetic disease** that can impact multiple family members

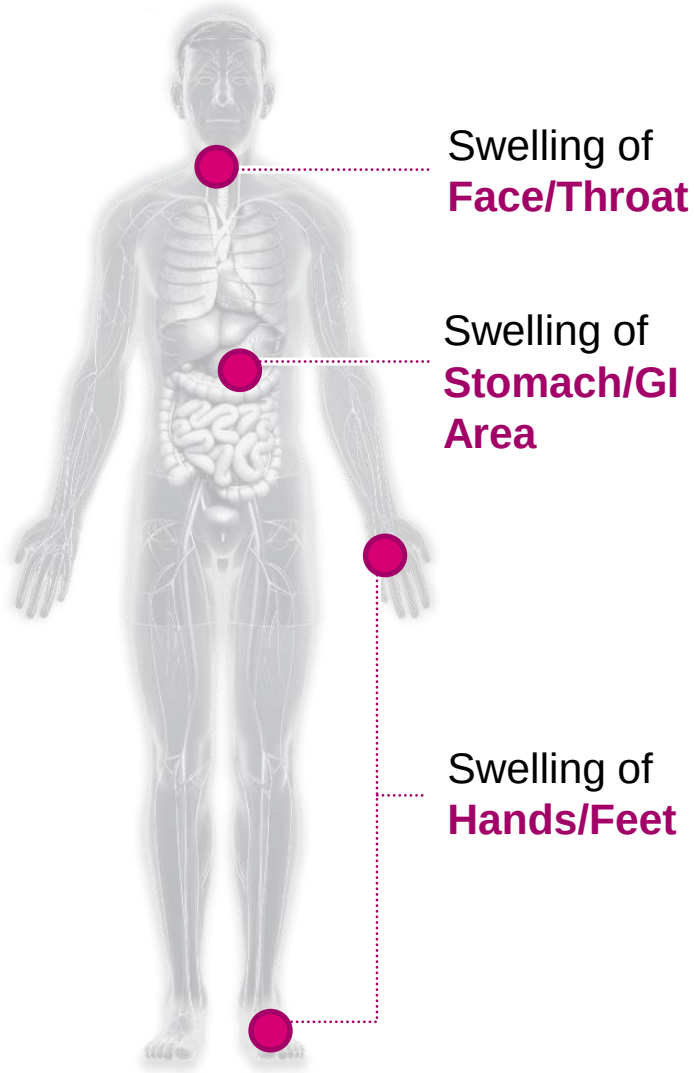
Patients experience recurring, unpredictable, severe **swelling attacks**, commonly affecting the hands, feet, stomach, face and throat

Most patients experience their first attack **before age 18**, with attacks reported in children **as young as 1 year**

>20K

People in the US and Europe with HAE[1]

Estimated incidence of 1:50,000



1. Busse, P.J. and Christiansen, S.C., 2020 NEJM ; 2. Busse 2020 J Allergy Clin Immunol Pract; 3. HAEI; 4. HAEA. 5. Banerji, A. et al., 2020 Ann Allergy Asthma Immunol; 6. Banerji, A. et. al. 2015 Allergy & Asthma.

New Treatment Options for HAE Needed[1]

Harris Poll and Patient Reported Survey Results Reinforce Need for New Therapies

Patients reported that HAE continues to **negatively impact their lives** despite current treatment options

91%	of patients surveyed expressed interested in trying a **new prophylactic therapy**
89%	of patients reported **missed or avoided activities** of daily living past 12 months
65%	of patients reported they **still have not found the best prophylactic therapy** for them
>20%	of patients **switch to alternative treatments** in the U.S. annually

1. Ionis-sponsored Harris Poll results; Sandra C. Christiansen MD , Joyce Wilmot MS , Anthony J. Castaldo MPA , Bruce L. Zuraw MD , For the US Hereditary Angioedema Association (HAEA) Medical Advisory Board members, The US HAEA Scientific Registry: Hereditary Angioedema Demographics, Disease Severity, and Comorbidities, Annals of Allergy, Asthma Immunology (2023).

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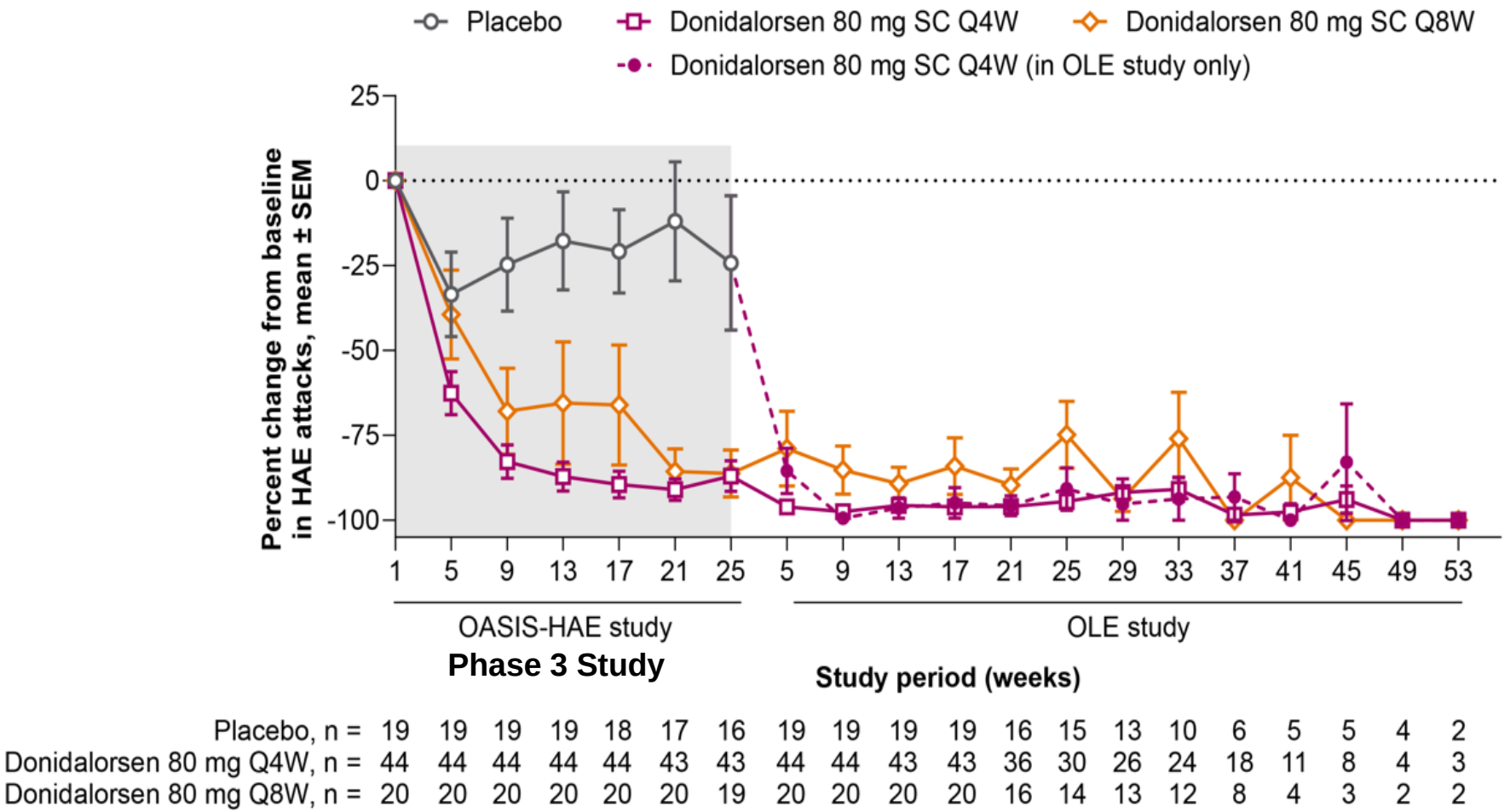
Sustained Reduction in HAE Attacks that Continue to Improve with Extended Donidalorsen Treatment[1,2,3]



- **Q4W substantially reduced** mean **HAE attack rates:**
  - **93% improvement** from baseline at the start of OASIS-HAE Phase 3 study[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.

Switch Study Design

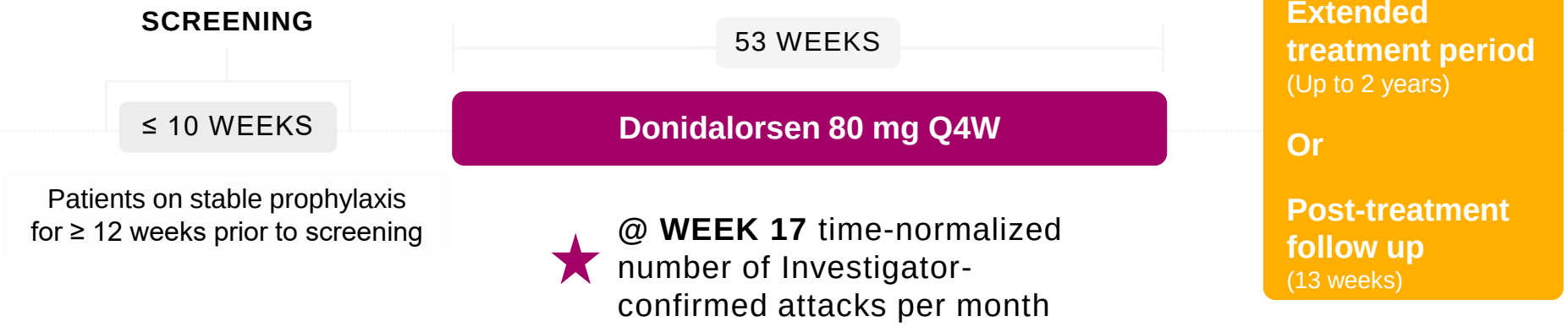
Design

An open label study **in HAE patients** who switched from an approved **prophylactic treatment** (lanadelumab, berotralstat or C1-INH) to treatment with **donidalorsen Q4W**

Objectives

Designed to:

- Provide guidance to safely switch patients to donidalorsen
- Generate long-term donidalorsen efficacy and safety data
- Understand patient preference



★ Primary Endpoint Readout

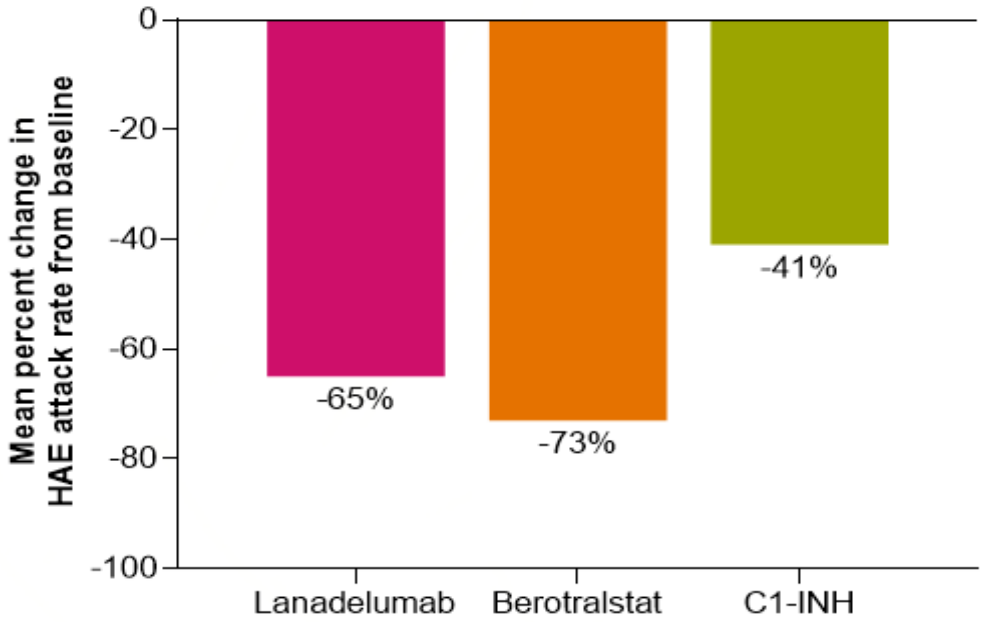
1. NCT05392114.

Positive Results from Donidalorsen Switch Study[1]

84%

of
Switch Patients
Surveyed
Preferred
Donidalorsen

% Reduction in HAE Attack Rate Following Switch to Donidalorsen[1-4]



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

Donidalorsen substantially reduced HAE attack rates after switching

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).

Donidalorsen: Positioned for Success in HAE

Robust Product Profile, Attractive Market Dynamics, Clear Unmet Need[1-3]

Robust Clinical Profile[1]

- Substantial and sustained reductions in HAE attacks up to >3 years
- Favorable safety and tolerability
- Patient-friendly monthly or every two-month self-administration

Well Defined Population: >20K HAE patients in U.S. & EU[4]

- Switch data demonstrates >80% preference for donidalorsen[5]
- HAE patients show willingness to switch
- New patient growth expected from global markets

Efficient Launch Approach

- Concentrated prescriber base with ~1,000 allergist/immunologists manage >70% of HAE patients[6]
- Planned <100-person field team including sales and patient support

PDUFA August 21, 2025, MAA under review[7]

1. Based on data generated to date including Phase 2, Phase 2 OLE, Phase 3 and Phase 3 OLE + Switch data. 2. Lumry et al. "Hereditary Angioedema: The Economics of Treatment of an Orphan Disease. Front. Med. 16 February 2018 Sec. Hematology Volume 5 – 2018. 3. Granted Otsuka exclusive rights to commercialize donidalorsen in Europe and Asia Pacific regions; Granted Theratechnologies exclusive rights to commercialize olezarsen and donidalorsen in Canda. 4. Market data on file. 5. Switch preference data represents percentage of switch patients surveyed, total n=55 assessed at week 17, as of 2/28/24, who indicated donidalorsen preference vs. prior prophylactic treatment. 6. Ionis secondary market research (2021). 7. Timing based on current estimates and subject to change.

WAINUA (eplontersen): A Novel Treatment for ATTR-Amyloidosis

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

ATTR

ATTR is a **systemic, progressive and fatal** disease

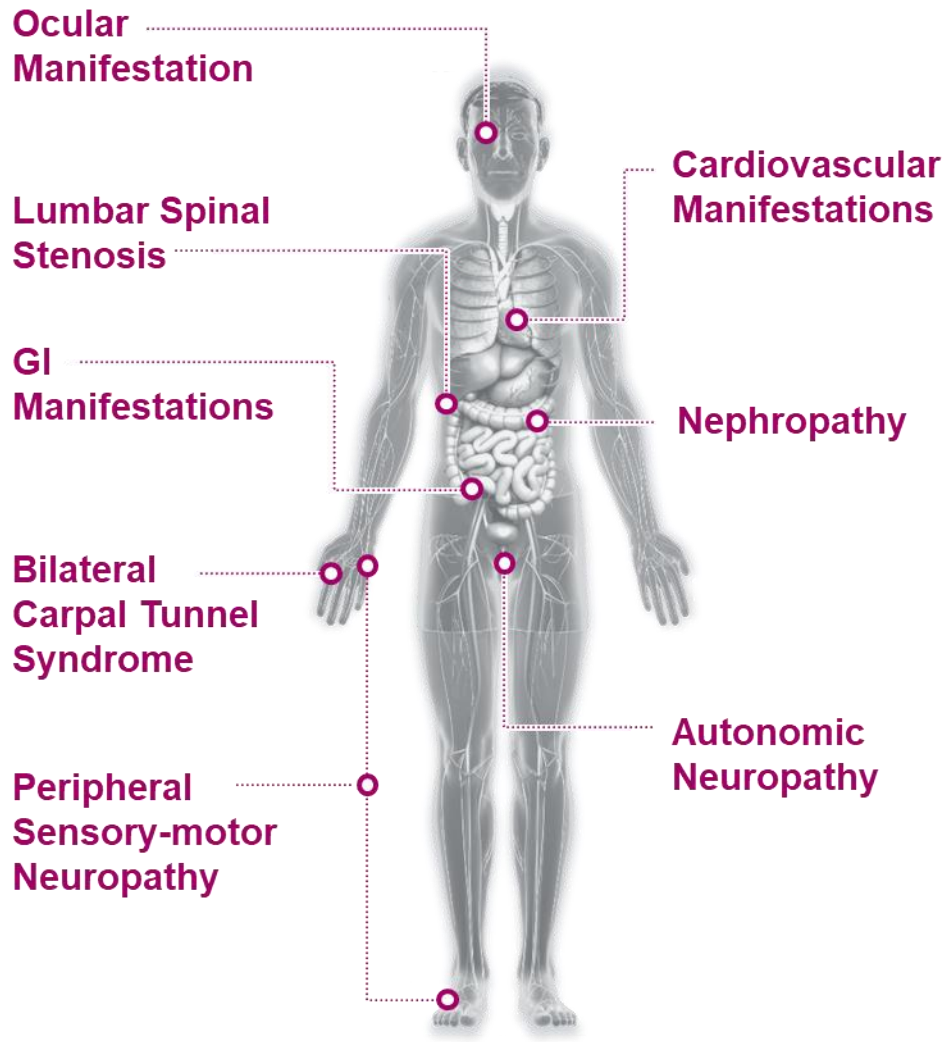
ATTR is caused by **accumulation of misfolded protein that can occur in multiple tissues**, including heart, nerves and GI tract

Patients experience a **rapid loss of independence and quality of life** before succumbing to their disease

~500K
ATTR
patients worldwide

300-500K
wtATTR[5] & ATTRv[6]

~40K
ATTRv-PN[7] &
ATTRv-Mixed[8]



amyloidosis.org (https://amyloidosis.org/facts/familial/; https://amyloidosis.org/facts/wild-type/
NOTE: For illustrative purposes only. 1. Conceição I et al. *J Peripher Nerv Syst*. 2016;21:5-9. 2. Ando Y et al. *Orphanet J Rare Dis*. 2013;8:31. 3. Gertz MA. *Am J Manag Care*. 2017;23:S107-S112. 4. Maurer MS et al. *Circulation*. 2017;135:1357-1377.5 wtATTR: wild-type ATTR. 6. ATTRv: hereditary ATTR. 7.ATTRv-PN: Hereditary TTR Amyloid Polyneuropathy. 8. ATTRv-Mixed: include ATTRv with mixed phenotype.

WAINUA: First Ionis Co-commercialized Medicine

ATTRv-PN Launch Delivering Growth[1]

WAINUA: Approved in the U.S. on December 21, 2023, for the treatment of Hereditary ATTR Polyneuropathy, a systemic, progressive and fatal disease

Continued increasing demand from existing patients and new patient starts[2]

Encouraging patient mix and breadth of prescribers

Physicians and patients report positive patient experience:

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

1. WAINUA: www.wainua.com; co-developing and commercializing in the U.S. with AstraZeneca. Now approved under brand name WAINZUA in the E.U. 2. WAINUA product sales through Q1 2025.

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.

Leading Cardiology Franchise

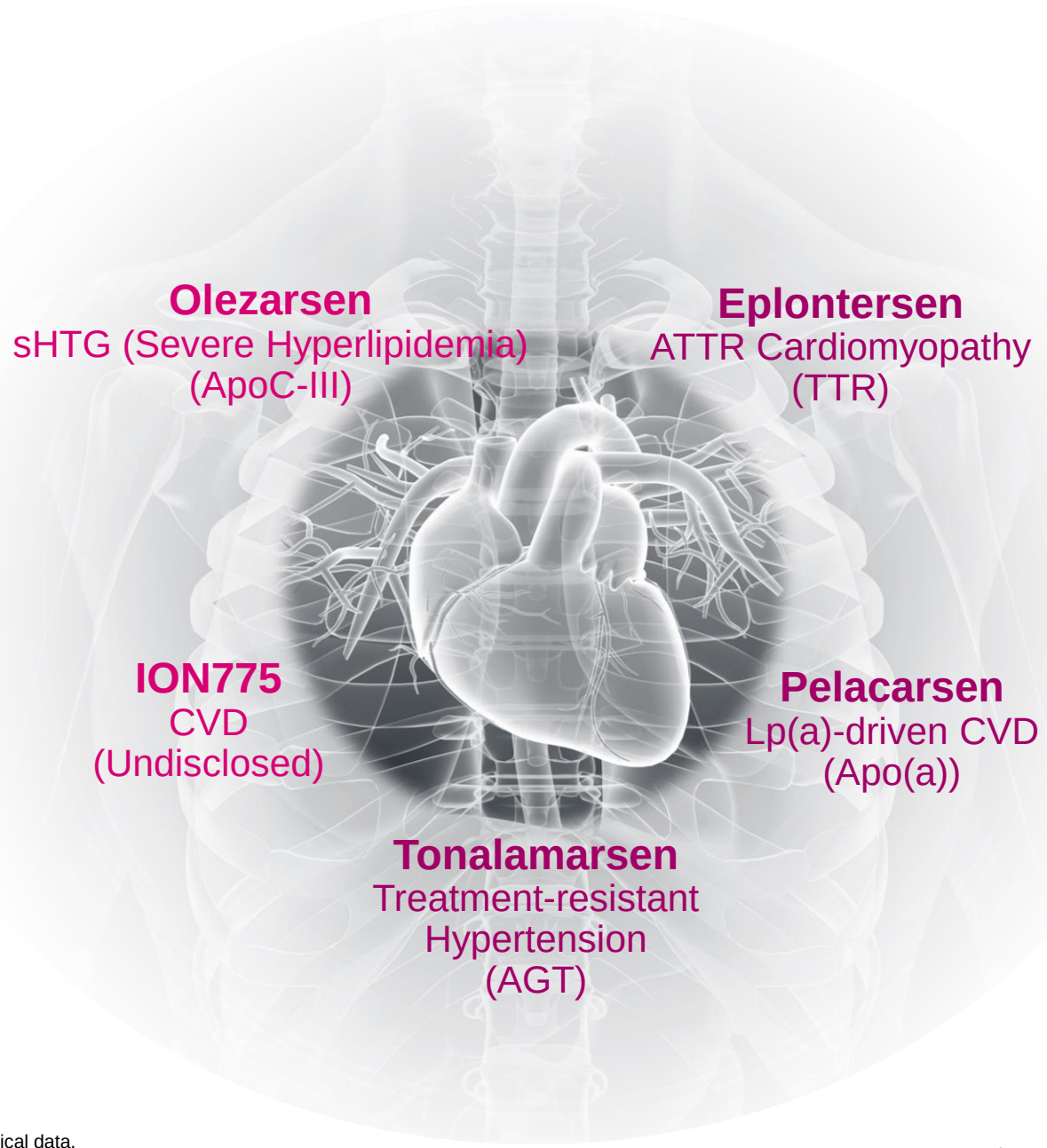
5 Medicines in clinical development

3 Phase 3 studies; two CVOTs

2 Wholly owned medicines in clinical development[1]

2 Key Technology Advancements[2]

- Semi-annual or annual SC dosing (follow-ons, new programs)
- Targeted delivery to cardiac myocytes for broad range of CV indications



1. Wholly owned programs include: olezarsen (sHTG) and ION775 (undisclosed target, CVD). 2. Based on current preclinical data.

Pelacarsen: Addressing a Major Independent Risk Factor for CVD[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 high Lp(a) and established CVD
- Study enrolled high-risk, high Lp(a) population with significant CV risk despite stable lipid-lowering treatment[3]
- Baseline demographics support potential for robust data[3]
- **Data expected H1:2026; regulatory filing H2:2026[4]**

Lp(a) Horizon Outcomes Study

Eligible for:

Additional milestone payments

Royalties in the mid-teens to low 20% on net sales[5]

1. Novartis licensed pelacarsen in 2019 and as a result is responsible for development and commercialization, assuming approval. 2. Market data on file. 3. Lp(a) HORIZON study design and baseline demographics published in the *American Heart Journal*. 4. Timing expectations based on current assumptions and subject to change. 5. Royalty Pharma to receive 25% of any future royalty payments on pelacarsen.

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Leading Neurology Franchise

3 **Approved Medicines**[1]

13 **Medicines in Clinical Development**

8 **Wholly Owned Medicines in Clinical Development**[2]

3 **Key Technology Advancements**[3]

- Semi-annual or annual IT dosing
- Systemic administration (BBB)
- Muscle-delivery (neuromuscular diseases)

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)

ION464
Multiple System Atrophy
(alpha-synuclein)

ION859
Parkinson's disease
(LRRK2)

ION717
Prion disease
(PRNP)

ION356
Pelizaeus-Merzbacher Disease (PLP1)

ION440
MECP2 duplication syndrome (MECP2)

Ulefnersen
FUS-ALS
(FUS)

Tofersen
Presymptomatic SOD1-ALS
(SOD1)

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

Tominersen
Huntington's disease
(HTT)

ION306
SMA (SMN2)

ION269
Alzheimer's disease
(APP)

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), ION464 (MSA), ION859 (PD), ION717 (Prion disease), ION356 (PMD), ION440 (MECP2 Duplication syndrome) and ION269 (APP). 3. Based on current preclinical data.

IONIS

Zilganersen for the Treatment of Alexander Disease, a Devastating Neurological Disease with No Approved Treatments

Lilas
Living with Alexander disease
(shown with her brother)

Rare leukodystrophy of significant unmet need

- Prevalence: ~1 in 1-3 million[1]
- Accounts for ~2-8% of leukodystrophies, although likely underreported[2]
- No approved disease modifying treatments

Fatal and progressive childhood neurological disorder

- Characterized by cognitive and gross/fine motor impairment, speech difficulties, ataxia and seizures
- Median survival between 14 and 25 years[3,4]
- ~65% of cases occur in childhood[5]

On track for pivotal data H2’2025[6,7]

- Global, placebo-controlled study in ~50 patients, ages 2-65
- Open-label sub-study in patients <2 years conducted at select sites
- Primary endpoint is change in gait speed (10MWT) at week 61
- Multiple secondary endpoints evaluating clinical measures of AxD

1. Yoshida T, Sasaki M, Yoshida M, et al. Nationwide survey of Alexander disease in Japan and proposed new guidelines for diagnosis. J Neurol. 2011;258(11):1998-2008; 2. Heim et al., Am J Med Genet 1997; 71:475-478 and Cohen et al., Ann Hum Genet 2020; 84:11–28. Messing, Albee. Alexander Disease: A Guide for Patients and Families. Colloquium Series on Neuroglia in Biology and Medicine: From Physiology to Disease. Vol. 3. No. 1. Morgan & Claypool Life Sciences, 2017; 4. Prust M, et al. GFAP mutations, age at onset, and clinical subtypes in Alexander disease. Neurology. 2011;77(13):1287-1294. 5. Srivastava et al., 1993; 6. clinicaltrials.gov/NCT04849741. 7. Timing expectations based on current assumptions and subject to change.

Angelman Syndrome: Severe Neurodevelopmental Disorder with a Clear Unmet Medical Need

Severe, Rare Neurodevelopmental Disorder[1-5]

- Estimated 1 in 21,000 people with Angelman syndrome worldwide
  - >100,000 people in major geographies
- Caused by loss of function of the *UBE3A* gene
- Symptom onset and diagnosis ~2 years old
- Not progressive, associated with normal life expectancy

Significant Burden on People with Angelman Syndrome and their Caregivers[6]

- Profound developmental and cognitive delay
- Results in need for lifelong, fulltime supervision

Clear Unmet Medical Need[6,7]

- No approved disease-modifying treatments
- Current standard-of-care treatments for symptom management only

1. Yakoreva et al. *A Eur. J. Hum*. Genet. (2019). 2. Luk. *Eur. J. Méd. Genet*. (2016). 3. Mertz et al. *Am. J. Méd. Genet. Part A* (2013). 4. Wheeler et al. *J Neurodev Disord*. (2023). 5. Major geographies include U.S., EU, UK, Canada, Brazil, Japan and China. 6. Clayton-Smith. *J Med Genet* (2003). 7. Besten, et al. *Am. J. Méd. Genet. Part A* (2021).

ION582: A Promising New Investigational Medicine for Angelman Syndrome

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

Robust Pivotal Phase 3 Study Now Recruiting[2]

- First patient dosed imminent
- Full enrollment expected next year[3]
- Children and adults and both deletion and mutation genotypes
- Global, randomized (2:1), 40mg and 80mg ION582 quarterly vs. placebo

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. REVEAL Trial, clinicaltrials.gov/NCT06914609. 3. Timing expectations based on current assumptions and subject to change.

2025 and 2026 Key Value-Driving Events[1]

Phase 3 **Clinical Events**

2025

ION582
Study start
(Angelman syndrome)

Zilganersen
Data
(Alexander disease)

Olezarsen
✓ Essence Data
(HTG)

Olezarsen
CORE & CORE2 Data
(sHTG)

2026

Pelacarsen
Lp(a) HORIZON data
(Lp(a)-CVD)

Bepirovirsen
B-Well data
(HBV)

Eplontersen
CARDIO-TTRansform data
(ATTR-CM)

Sefaxersen
IMAGINATION data
(IgAN)

ION582
Enrollment completion
(Angelman syndrome)

Ulefnersen
FUSION data
(FUS-ALS)

Regulatory **Actions**

2025

Donidalorsen
U.S. approval
(HAE)

TRYNGOLZA
EU approval
(FCS)

WAINZUA
✓ EU approval
(ATTRv-PN)

Olezarsen
U.S. Submission
(sHTG)

Higher Dose Nusinersen
✓ U.S. & EU submissions
U.S. approval
(SMA)

2026

Donidalorsen
EU approval
(HAE)

Olezarsen
U.S. Approval
(sHTG)

Pelacarsen
U.S. Submission
(Lp(a)-CVD)

Bepirovirsen
Submission(s) & approval(s)
(HBV)

Zilganersen
U.S. submission & approval
(Alexander disease)

Product **Launches**

2025

Donidalorsen
U.S.
(HAE)

TRYNGOLZA
EU
(FCS)

✓ **TRYNGOLZA**
U.S.
(FCS)

✓ **WAINZUA**
EU
(ATTRv-PN)

2026

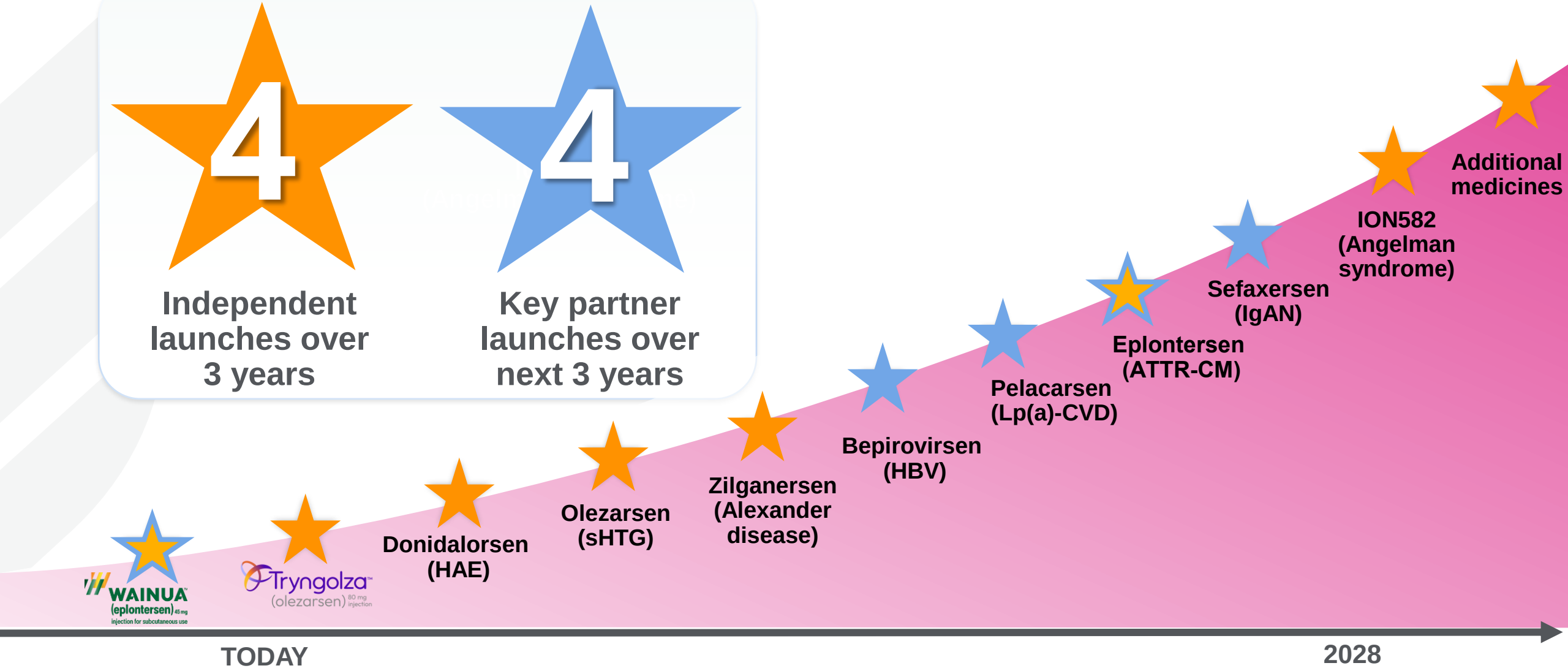
Olezarsen
U.S.
(sHTG)

Zilganersen
U.S.
(Alexander disease)

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 checkmark indicates event was achieved.

Inflection 2025: Poised to Deliver a Steady Cadence of New Medicines

Numerous Near-Term Growth Drivers[1,2]

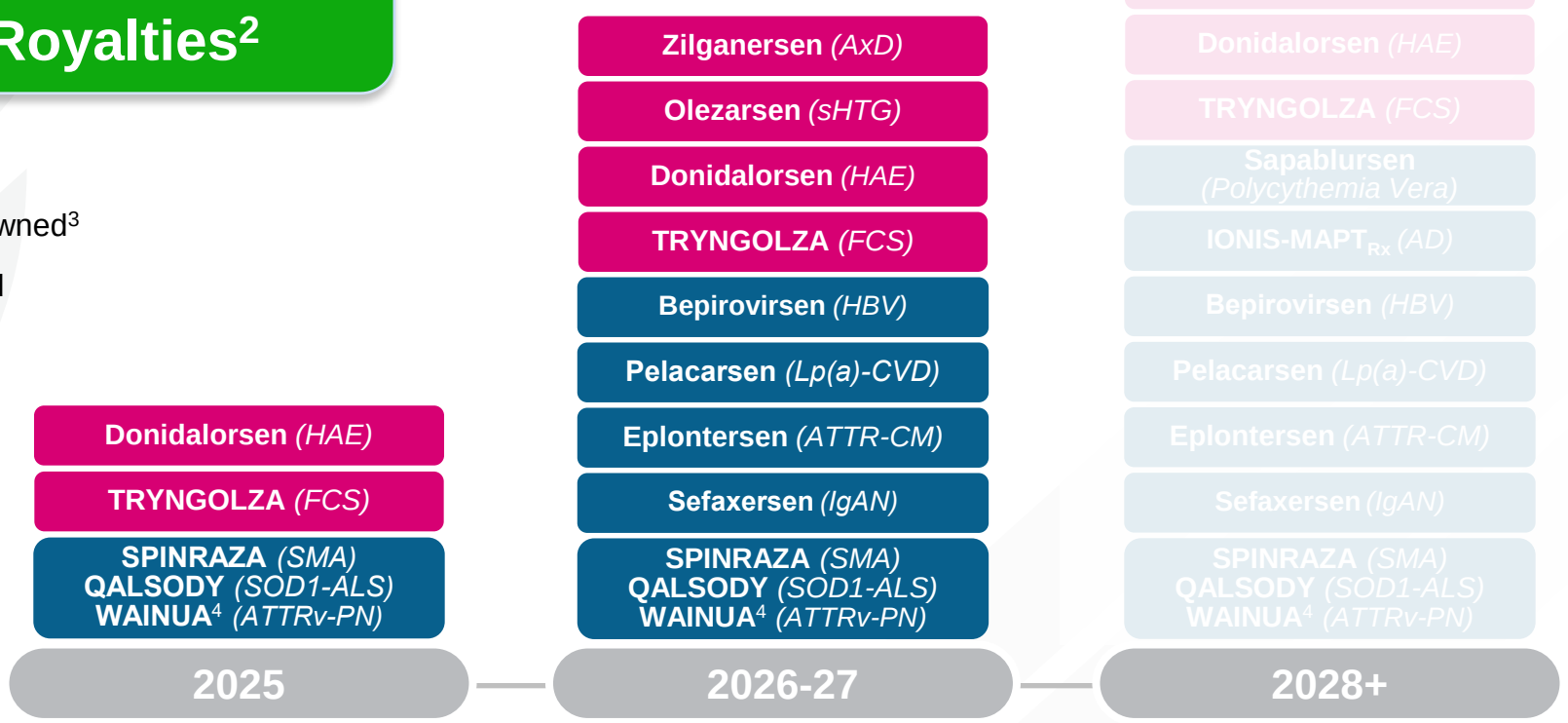


1. Assuming approval. 2. Timing expectations are based on current assumptions and are subject to change.

Steady Cadence of Expected Launches to Power Revenue Growth and Positive Cash Flow[1]

>$5B
in Potential Annual Peak Product Revenue + Royalties[2]

- Wholly Owned[3]
- Partnered



>$3B
in Potential Annual Peak Product Revenue[2]

>$2B
in Potential Annual Peak Royalties[2]

Revenue Growth

1. Assuming approval. Estimated timing of potential U.S. approval based on current assumptions and subject to change. 2. Peak sales estimates based on current estimates and subject to change. Partnered royalties based on public disclosure made by the respective partner and Ionis' contractual royalty rates for each medicine. 3. Granted Sobi exclusive rights to commercialize olezarsen in most countries outside of the U.S. Granted Otsuka exclusive rights to commercialize donidalorsen in Europe and Asia Pacific regions. Granted Theratechnologies exclusive rights to commercialize TRYNGOLZA and donidalorsen in Canada. 4. Approved, under brand name WAINZUA in the EU.

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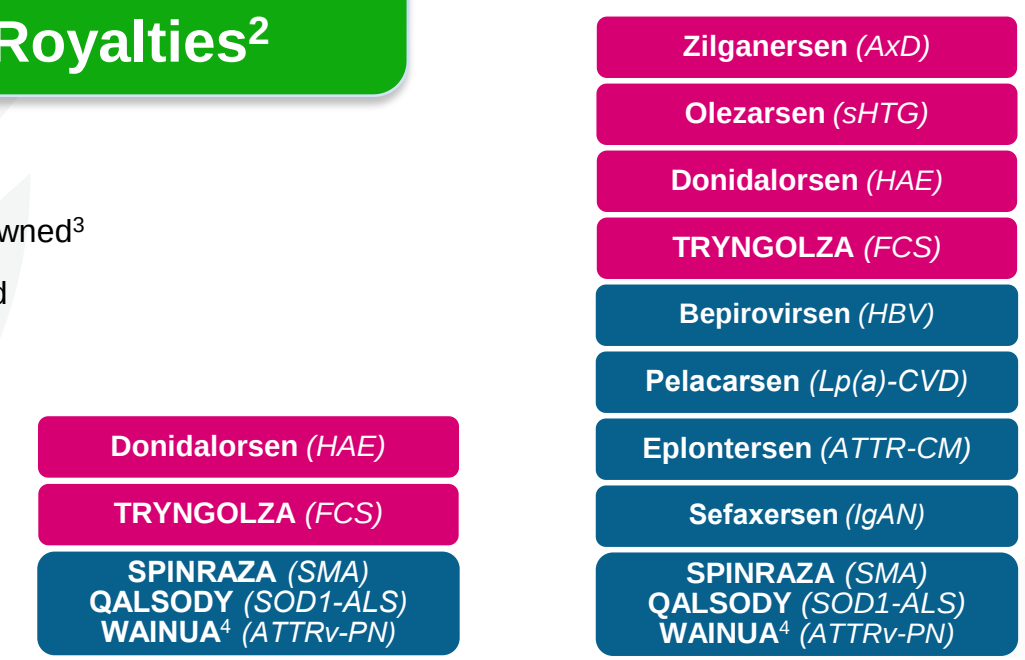

>$3B
in Potential Annual Peak Product Revenue[2]

>$2B
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Revenue Growth

1. Assuming approval. Estimated timing of potential U.S. approval based on current assumptions and subject to change. 2. Peak sales estimates based on current estimates and subject to change. Partnered royalties based on public disclosure made by the respective partner and Ionis' contractual royalty rates for each medicine. 3. Granted Sobi exclusive rights to commercialize olezarsen in most countries outside of the U.S. Granted Otsuka exclusive rights to commercialize donidalorsen in Europe and Asia Pacific regions. Granted Theratechnologies exclusive rights to commercialize TRYNGOLZA and donidalorsen in Canada. 4. Approved, under brand name WAINZUA in the EU.

Accelerating Value Through Innovation

Proven and **prolific discovery** and **development engine**

Pipeline delivering at all stages

Scalable innovative **commercial organization**

Increased 2025 financial guidance; clear path to **positive cash flow**[1]

Improving the **lives** of **millions of patients** with **transformational medicines**[2]

1. Based on current assumptions and are subject to change. 2. Market data on file, assuming approval.

Q&A Session

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

Delivering Accelerated Value