# Q1:2025 Business Update and Financial Results

April 30, 2025

Nasdaq: IONS

Eli (with family member)
*Living with FCS*

# On Today's Earnings Call

**Brett Monia, Ph.D.**
*Chief Executive Officer*

**Kyle Jenne**
*Chief Global Product Strategy Officer*

**Beth Hougen**
*Chief Financial Officer*

**Richard Geary, Ph.D.**
*Chief Development Officer*

**Eugene Schneider, M.D.**
*Chief Clinical Development Officer*

**Eric Swayze, Ph.D.**
*Executive Vice President, Research*

**Jonathan Birchall**
*Chief Commercial Officer*

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# Forward-Looking Statements

This presentation includes forward-looking statements regarding our business, financial guidance and the therapeutic and commercial potential of our commercial medicines, additional medicines in development and technologies. Any statement describing Ionis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties including but not limited to those related to our commercial products and the medicines in our pipeline, and particularly those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. Ionis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. 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.

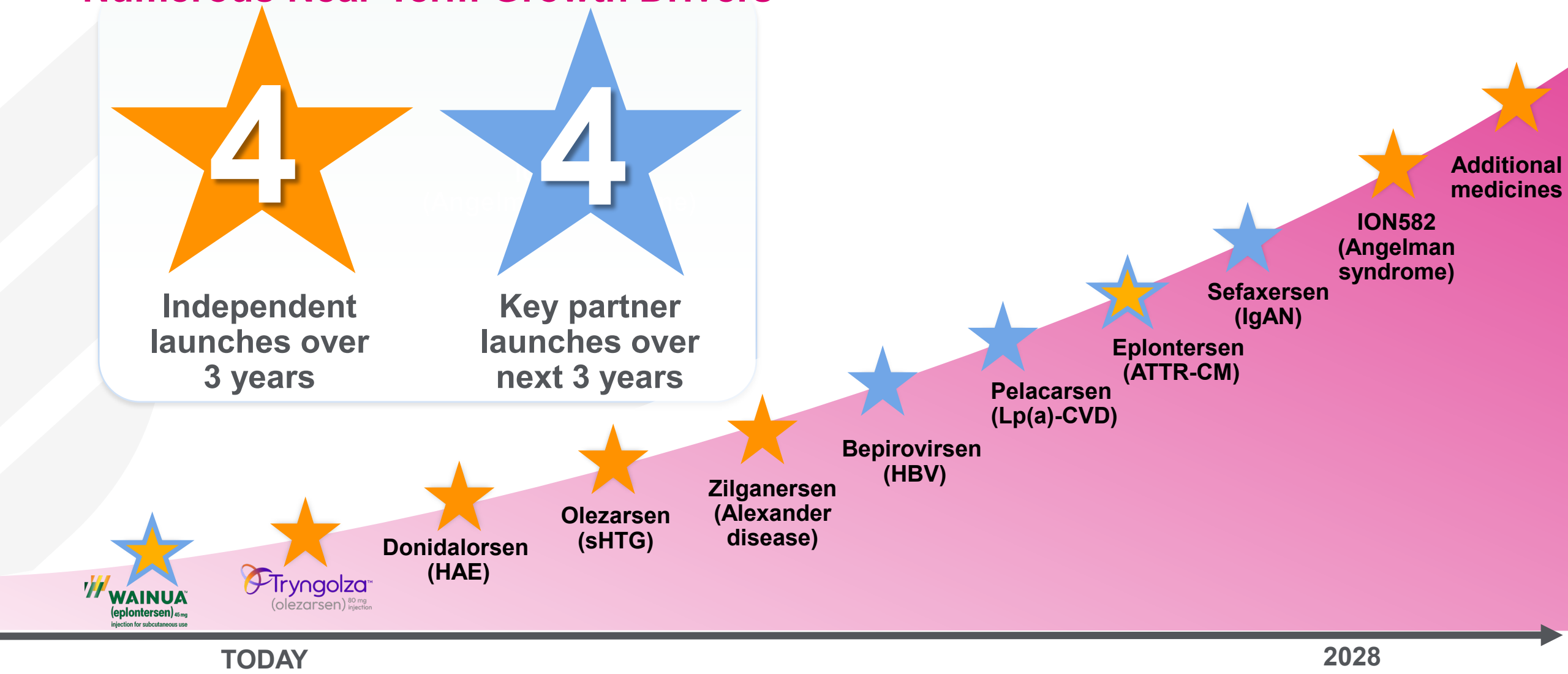
# Introduction

Brett Monia, Ph.D.

Chief Executive Officer

# 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.

# Bringing Important Medicines to Patients

Kyle Jenne

Chief Global Product Strategy Officer

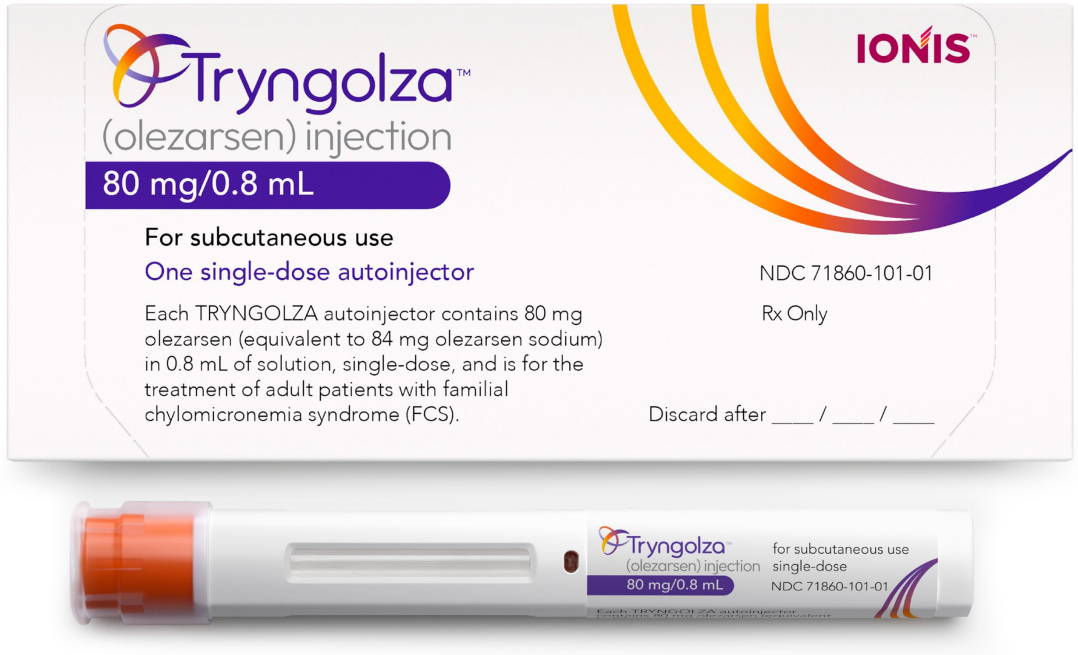
# Advancing Ionis' Independent Late-Stage Pipeline with Blockbuster Potential

| | Indication | Prevalence[1] | Anticipated Next Event[2] |
|---|---|---|---|
| **TRYNGOLZA (olezarsen)** | Familial Chylomicronemia syndrome (FCS) |  | **EU approval (2025)** |
| | Severe Hypertriglyceridemia (sHTG) |  | **Ph3 data (2025)[3]** |
| **Donidalorsen** | Hereditary Angioedema (HAE ) |  | **U.S. approval (2025)[4]** |
| **Zilganersen** | Alexander disease (AxD) |  | **Ph3 data (2025)[5]** |


● Cardiovascular ● Neurology ● Specialty

1. Market data on file. 2. Timing expectations are based on current assumptions and are subject to change. 3. Olezarsen sHTG (CORE and CORE2) data expected in Q3:2025. 4. PDUFA August 21,2025. MAA submission completed in Q4'24. 5. Data expected in H2:2025.

# TRYNGOLZA: First and Only FDA-Approved Treatment for FCS[1]




- ✓ **Robust efficacy and safety**
  - ✓ Significant and sustained triglyceride reductions
  - ✓ Substantial reduction in acute pancreatitis events
- ✓ **Convenience of once-monthly self-administration with an autoinjector**

**Over $6 million** in net product **sales** in **first** full **quarter** of **launch**[2]

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.

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

## 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

> ***I was over the moon! This is the lowest my patient's TG levels have ever been!***
>
> - Recent TRYNGOLZA Prescriber

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.

# Building on TRYNGOLZA Early Launch Momentum for Sustained Success[1]

**Patient Finding is Critical**

Most of the **3,000** estimated U.S. FCS **patients remain unidentified** and **undiagnosed**[2-6]

**Targeted HCP Education**

Targeting physicians who treat patients with sHTG to **increase FCS awareness** and **diagnosis**

**Establishing Broad, Durable Access is Key**

Important that formal **policies** support both **clinical and genetic testing pathways**

1. TRYNGOLZA is approved in the U.S. for Familial Chylomicronemia Syndrome in adults as an adjunct to diet; see Full Prescribing Information. 2. Dron JS, et al. *BMC Med Genomics* 2020;13(1):23. 3. Hegele RA. *Nat Rev Genet* 2009;10(2):109-21. 4. Pallazola VA, et al. *Eur J Prev Cardiol* 2020;27(19):2276-8. 5. Tripathi M, et al. *Endocr Pract* 2021;27(1):71-6. 6. Warden BA, et al. *J Clin Lipidol* 2020;14(2):201-6.

# sHTG: A Serious Condition with High Unmet Need[1-7]

## sHTG

Defined by **triglyceride** levels **over 500mg/dL**

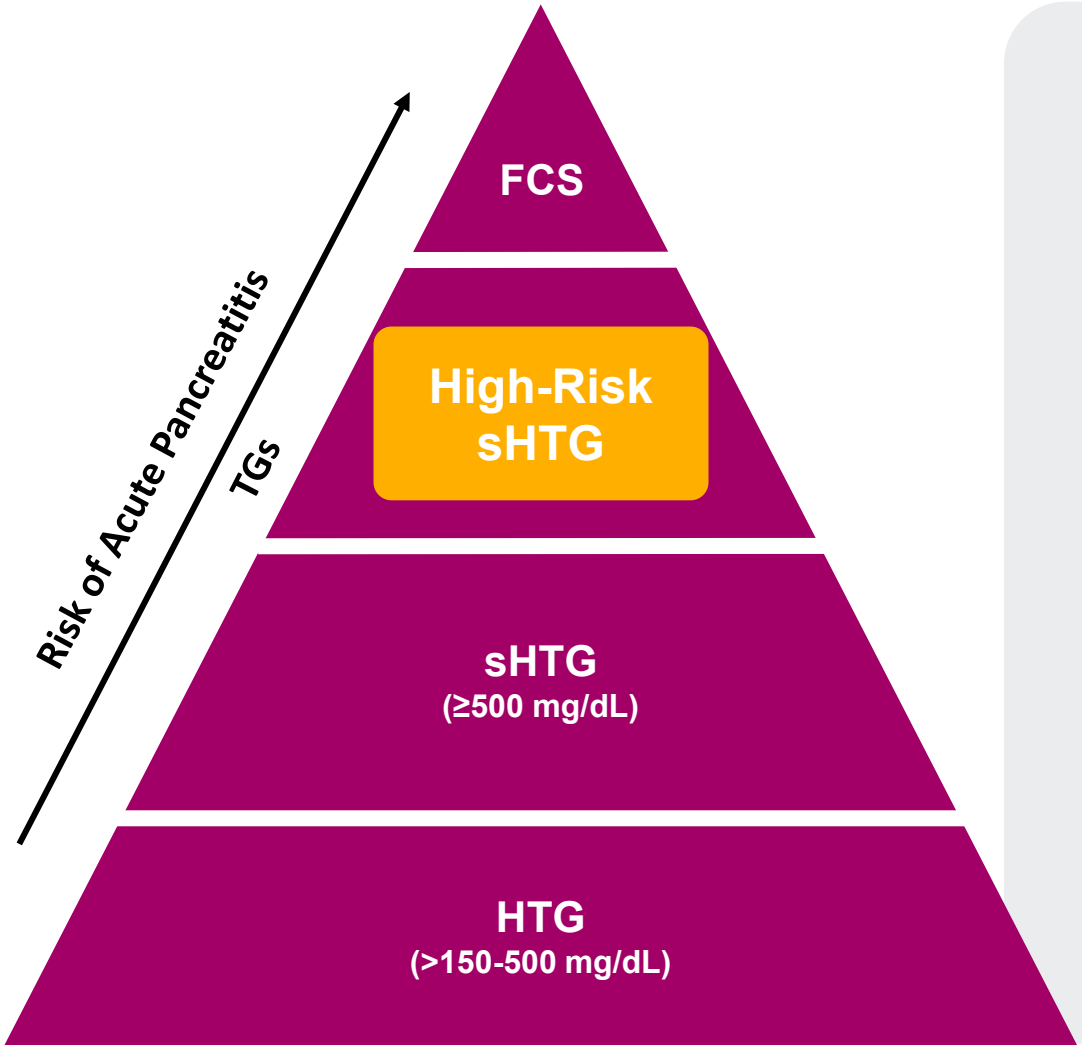
**High unmet need:**

**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. 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.

# Initial Launch to Focus on High-Risk sHTG[1]




## Initial Target Population

**>1M**
**High-Risk sHTG**
**people in the U.S.**[2]

TGs **≥880mg/dl**

- or -

TGs **≥500 mg/dL**
with **acute pancreatitis**
history or
other **comorbidities**

1. Assuming approval 2. Sanchez et al. Lipids in Health and Disease 2021;20:72; Christian et al., Am J Cardiol 2011;107:891-897; Saadatagah S, Pasha AK, Alhalabi L, et al. Coronary Heart Disease Risk Associated with Primary Isolated Hypertriglyceridemia; a Population-Based Study. J Am Heart Assoc. 2021;10(11):e019343.

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

## Blockbuster potential[3]

## First mover advantage[4]

## Positive data in FCS reinforce our confidence to address sHTG

## Phase 3 data coming soon[3]

- ESSENCE safety study data expected Q2:2025
- CORE, CORE2 pivotal study data expected Q3:2025
- Launch planned for 2026

1. Assuming approval. 2. Granted Sobi exclusive rights to commercialize olezarsen in most countries outside of the U.S. 3. Based on current estimates, subject to change. 4. Timing expectations are based on current assumptions and are subject to change.

# Baseline Characteristics from Olezarsen Phase 3 Studies Published in *American Heart Journal*[1]


## CORE and CORE2 Pivotal Studies

- Enrolled 1,063 participants across the two studies
- Nearly all participants were on stable lipid lowering therapies
  - A majority were on two or more lipid lowering therapies[2]
- Median fasting baseline TG levels were 836 mg/dL and 749 mg/dL in CORE and CORE2, respectively
- Nearly half of participants had baseline TG levels ≥880 mg/dL
- 22% and 13% of participants had a history of pancreatitis in CORE and CORE2, respectively[3]
- >90% of eligible participants were enrolled in the CORE/CORE2 open-label extension study[4]

1. Details about the study design and baseline characteristics from the Phase 3 ESSENCE, CORE and CORE2 studies of olezarsen have been published in the *American Heart Journal, here and here*. 2. 60%. 3. In the 10 years prior to enrollment. 4. As of November 2024.

# Our Second Planned Independent Launch: Donidalorsen for HAE

## Robust Clinical Data + HAE Landscape Dynamics Underscore Donidalorsen's Potential[1-3]

**Robust Clinical Data Set** including **Switch Data**[3]

**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**

**Building on WAINUA and TRYNGOLZA launches**

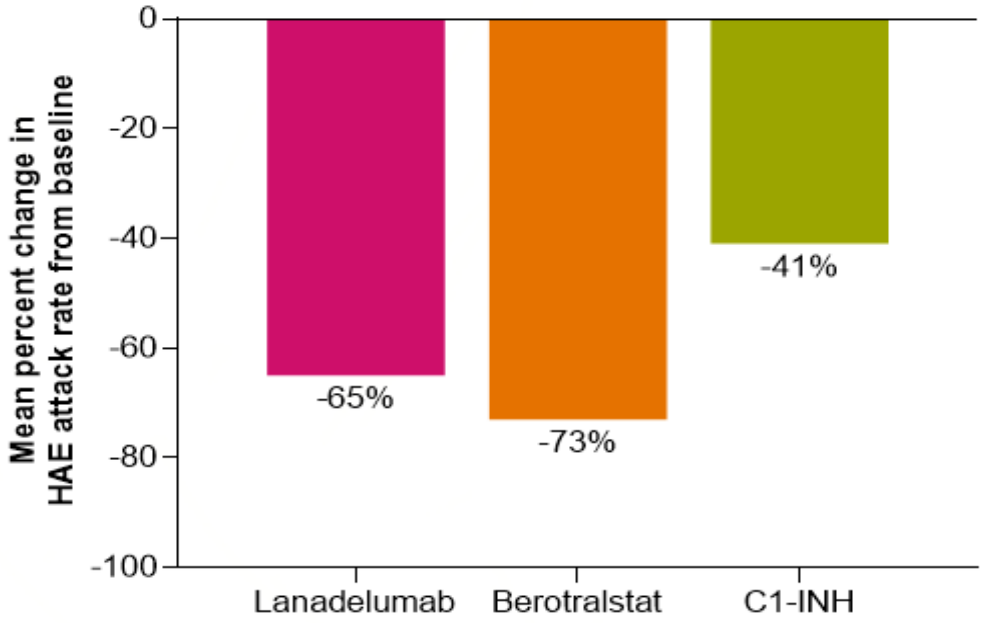
1. Market data on file. 2. Lumry et al. "Hereditary Angioedema: The Economics of Treatment of an Orphan Disease. Front. Med. 16 February 2018 Sec. Hematology Volume 5 – 2018. 3. Based on data generated to date including Phase 2, Phase 2 OLE, Phase 3 and Phase 3 OLE + Switch data. 3. Granted Otsuka exclusive rights to commercialize donidalorsen in Europe and Asia Pacific regions.

# Positive Results from Donidalorsen Switch Study[1]

**84%**

of
**Switch Patients**
Surveyed
**Preferred**
**Donidalorsen**

## % Reduction in HAE Attack Rate[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).

# Ongoing and Upcoming Independent Launches to Power Growth[1,2]


**3 More Launches Planned Over Next 2 Years with More to Follow[2]**

TODAY

2028

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

# Q1 2025 Financial Performance

Beth Hougen

Chief Financial Officer

# Q1:2025 Financial Highlights[1]

Increased 2025 Financial Guidance by >20%

**$132M**

## Revenue

### Commercial Revenue: $76M

- SPINRAZA comprised largest component
- Over $6M in TRYNGOLZA product sales

### R&D Revenue: $56M

- Reflects the value Ionis' technology creates as partnered programs advance

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**$249M**

## Operating Expenses[2]

### R&D Expenses[2]: $181M

- Decreased YoY, while appropriately funding growth opportunities
- Large majority funding late-stage programs

### SG&A Expenses[2]: $67M

- Increased YoY in support of ongoing and planned launches

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**$2.1B[3]**

## Cash & Short-term Investments

- Enables investments in launches and Ionis-owned pipeline
- Recent licensing transactions drive increased 2025 financial guidance

1. For the quarter ended March 31, 2025. 2. Non-GAAP – please see reconciliation to GAAP in Q1:2025 press release.3. Upfront payments from recent licensing transactions not included in cash balance at March 31, 2025.

# Increased 2025 Financial Guidance Highlights Pipeline Value[1]

**Revenue**

**$725-$750** million

***Prior >$600 million***

**Operating Loss**

**<$375** million[2]

***Prior <$495 million***

**Cash**

**~$1.9** billion

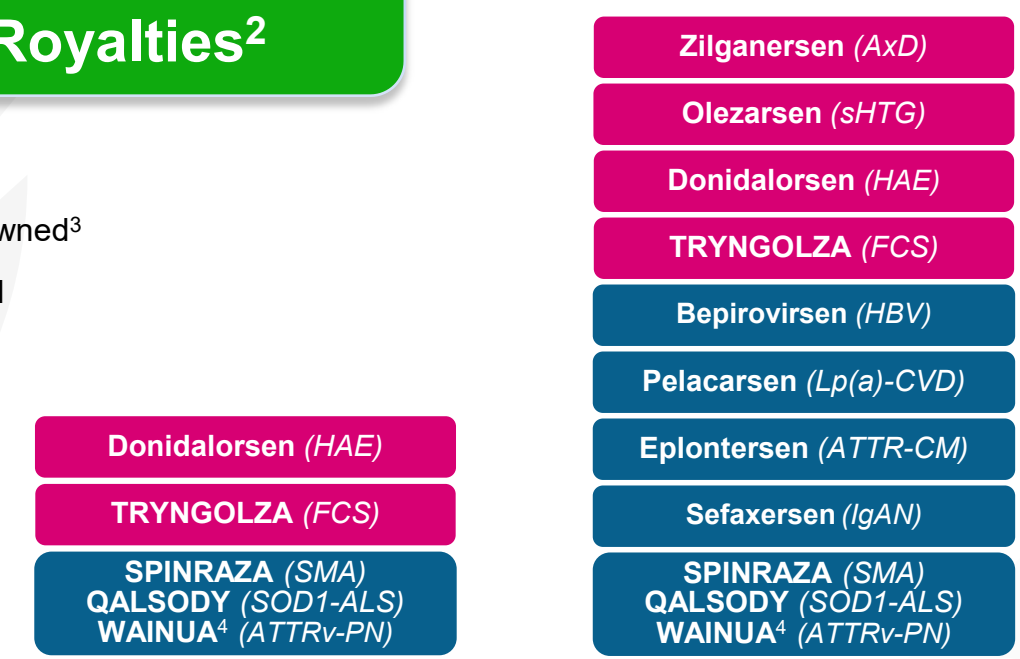
***Prior $1.7 billion***

1. Based on current assumptions, subject to change. 2. Non-GAAP – please see reconciliation to GAAP in Q1:2025 press release.

# Steady Cadence of Expected Launches to Power Revenue Growth and Anticipated 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.

# Conclusion

Brett Monia, Ph.D.

Chief Executive Officer

# 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


IONIS®
HOPE
HOPE
HOPE
Hope
Hope
Delivering Accelerated Value

# Appendix

# 2025 and 2026 Key Value-Driving Events[1]

## Phase 3 **Clinical Events**

### 2025

**Olezarsen**
Data
(sHTG)

**Zilganersen**
Data
(Alexander disease)

**ION582**
Study start
(Angelman syndrome)

### 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**
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.