Q2:2025 Business Update and Financial Results

July 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

Richard Geary, Ph.D.
Chief Development Officer

Beth Hougen
Chief Financial Officer

Eugene Schneider, M.D.
Chief Clinical Development Officer

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

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

Q2:2025: Strong Momentum Across the Business

Providing multi-billion revenue potential for Ionis[1]

First Independent Launch Exceeding Expectations

Tryngolza™ (olezarsen) 80 mg injection

First and only FDA-approved treatment for FCS

Q2'25 net sales of **$19M** in its second full quarter on the market[2]

On Track for Second Independent Launch

Donidalorsen

Positioned to transform the HAE Treatment Paradigm

August 21st **PDUFA date on track**[2]

Ready to launch[3]

2025 Phase 3 Readouts

Olezarsen

Potential to transform the treatment paradigm for people with sHTG[3]

Zilganersen

Potential first disease-modifying treatment for people with Alexander disease[3]

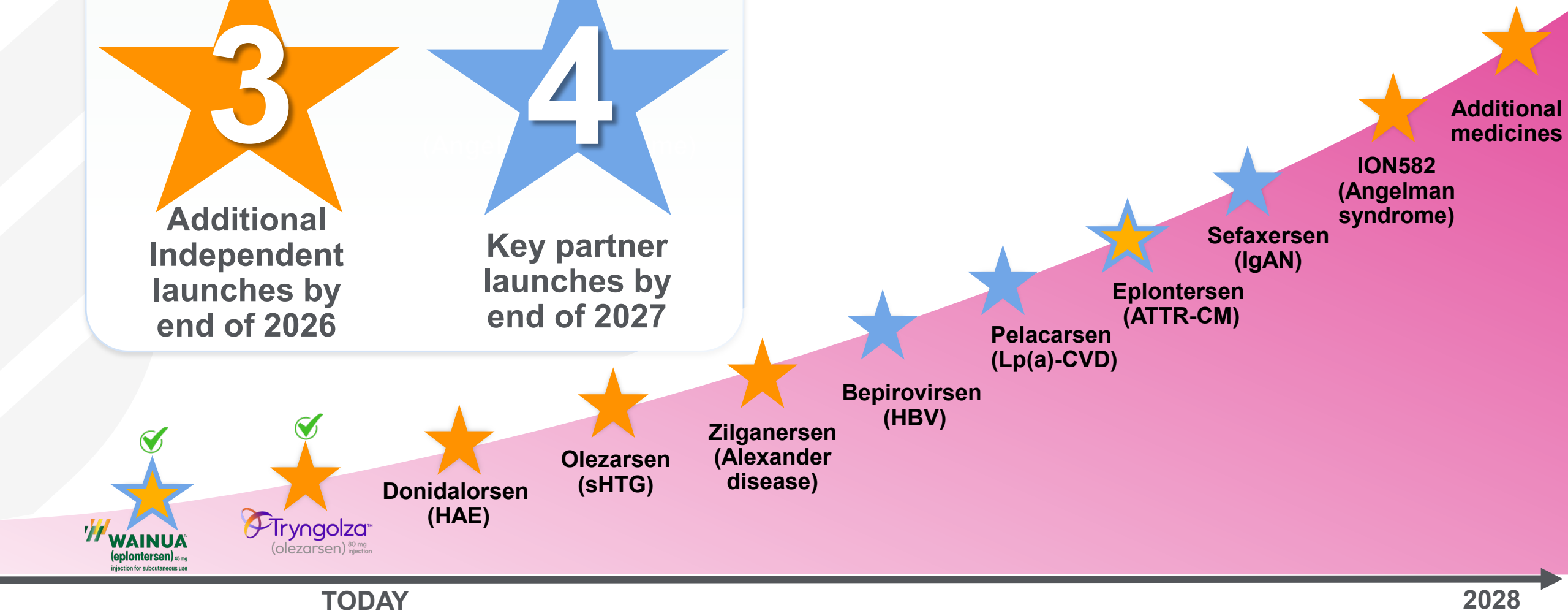
1. Timing expectations and peak sales estimates based on current assumptions and subject to change 2. For the quarter ended June 30, 2025. 3. Assuming approval.

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

Numerous Near-Term Growth Drivers[1,2]

3 Additional Independent launches by end of 2026

4 Key partner launches by end of 2027



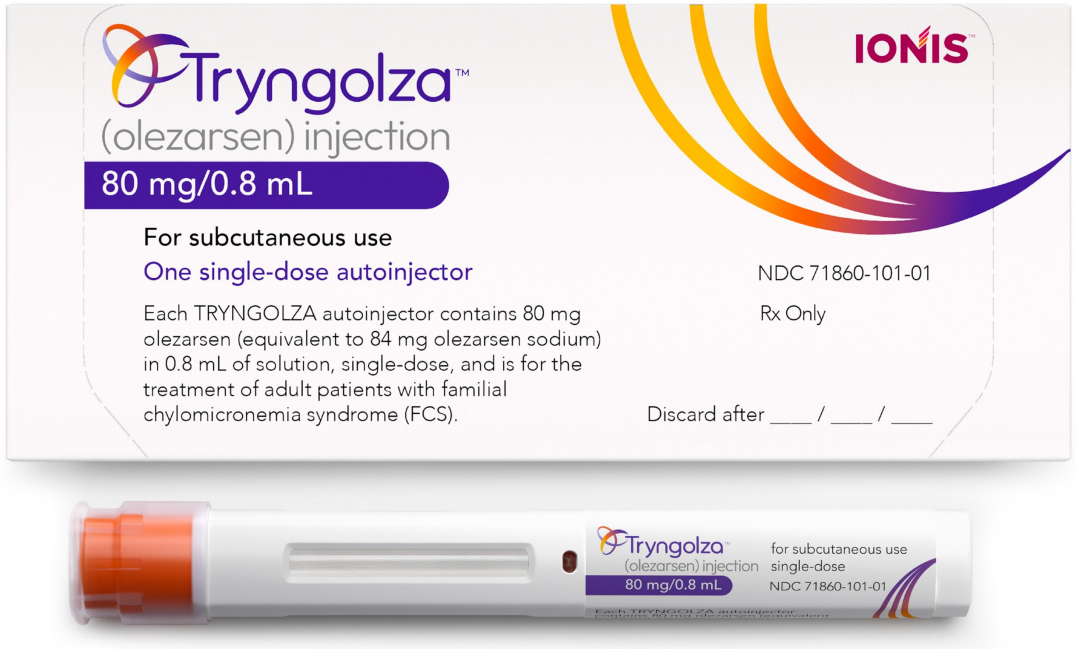
1. Assuming approval. 2. Timing expectations are based on current assumptions and are subject to change.

Building on the Early Commercial Success of TRYNGOLZA

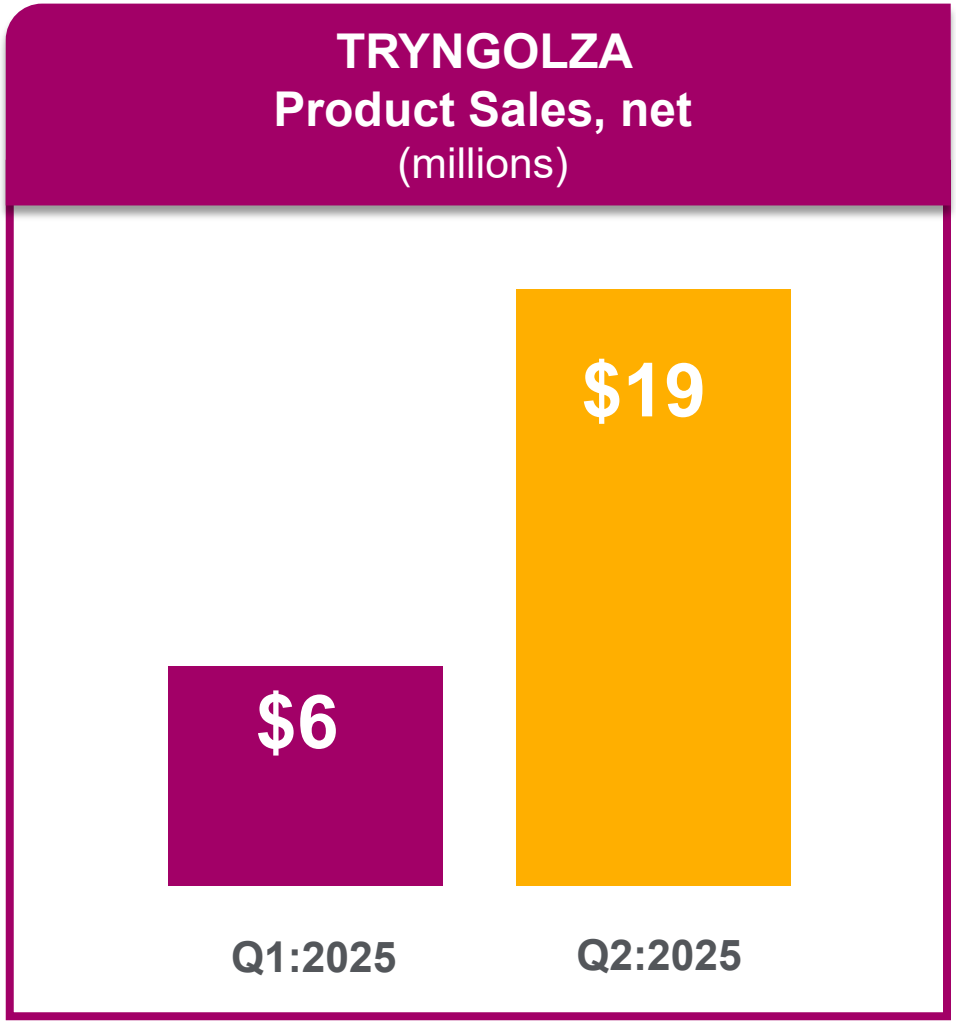
Kyle Jenne

Chief Global Product Strategy Officer

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**



1. TRYNGOLZA is approved in the U.S. for Familial Chylomicronemia Syndrome in adults as an adjunct to diet; see Full Prescribing Information.

TRYNGOLZA Continued to Surpass Expectations[1,2]

Strong Patient Uptake

- ✓ Effective patient identification efforts
- ✓ Breadth and depth of unique physicians prescribing TRYNGOLZA continues to grow with many having prescribed to two or more patients
- ✓ Highly favorable feedback

Favorable Physician Engagement

- ✓ Targeting over 3,000 physicians
- ✓ Leveraging omnichannel capabilities
- ✓ 50% cardiologists, 30% endocrinologists, 20% from lipidologists and internal medicine
- ✓ Awareness of TRYNGOLZA continues to gain traction

Positive Access Dynamics

- ✓ Coverage split: ~60% commercial, ~40% government
- ✓ Clinically diagnosed and genetically confirmed patients gaining access
- ✓ >90% of patients had $0 out-of-pocket costs in commercial setting

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 June 30, 2025.

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

Tryngolza™ (olezarsen) 80mg injection

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

Nearly all patients have opted-into Ionis Every Step[1]

1. As of June 30, 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 is Essential

Targeting over 3,000 physicians to **increase FCS awareness** and **diagnosis** with customer facing field team

Further leveraging reach with omnichannel and targeted marketing

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.

Olezarsen: Advancing Toward a Potential Blockbuster Opportunity in Severe Hypertriglyceridemia[1,2]

Blockbuster potential[3]

- >1 million high-risk sHTG people in the U.S.[4]

First mover advantage[5]

Positive data in FCS reinforce our confidence to address sHTG

Phase 3 data coming soon[5]

- Reported positive ESSENCE safety study data
- CORE, CORE2 pivotal study data expected September
- 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. 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. 5. Timing expectations are based on current assumptions and are subject to change.

Donidalorsen for HAE: Our Second Planned Independent Launch

Compelling Product Profile + HAE Landscape Dynamics Underscore Donidalorsen's Potential[1-3]

Robust Clinical Data Set including **Switch Data**[4]

Well Defined Opportunity

~7K in U.S.[5]

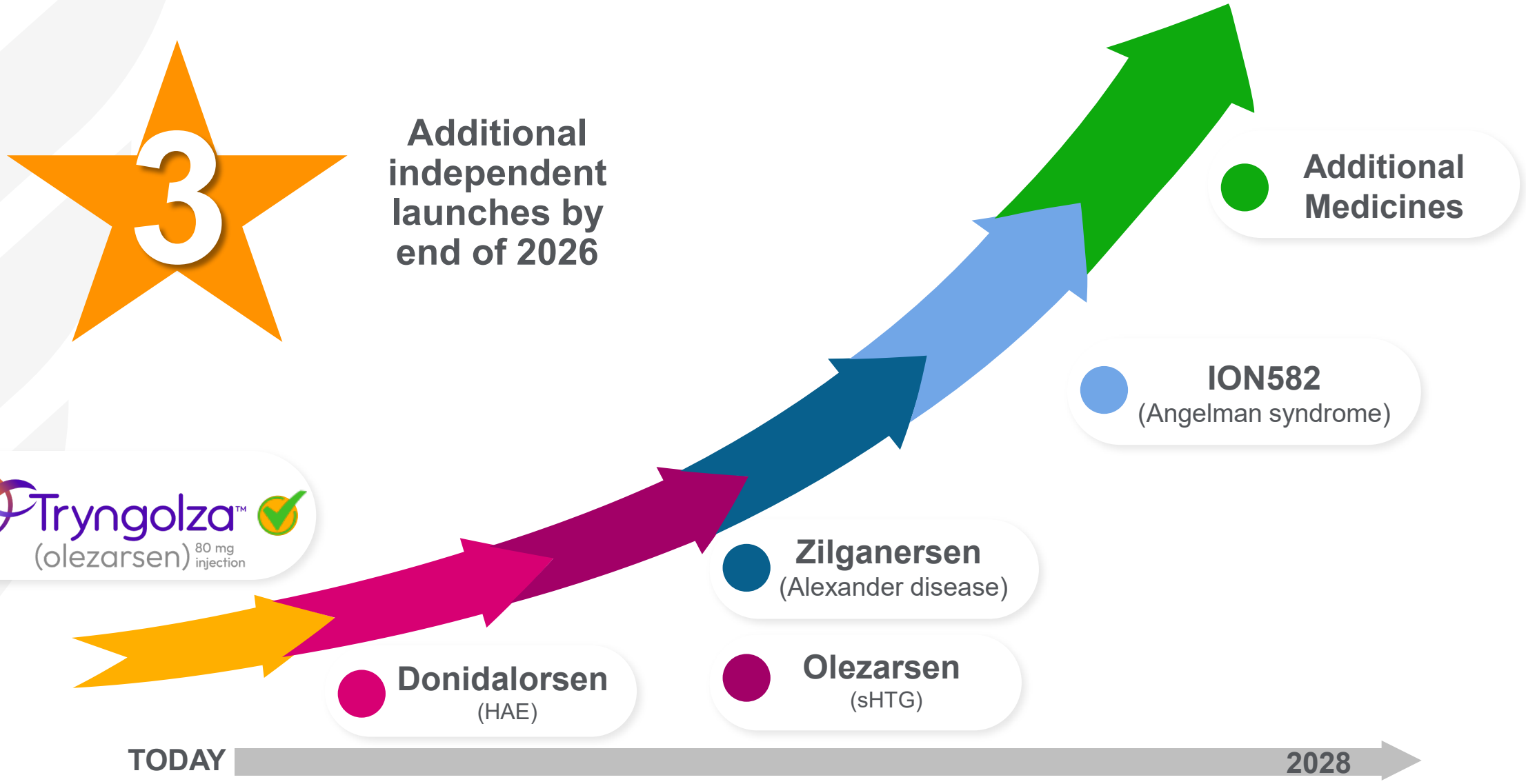
New Treatment Options Needed

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

Building on the TRYNGOLZA launch

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. Granted Otsuka exclusive rights to commercialize donidalorsen in Europe and Asia Pacific regions. 4. Based on data generated to date including Phase 2, Phase 2 OLE, Phase 3 and Phase 3 OLE + Switch data. 5. Riedl et al. 2023 J ALLERGY CLIN IMMUNOL PRACT VOLUME 11, NUMBER 8; Sylvestre et al 2021 J ALLERGY CLIN IMMUNOL PRACT VOLUME 9, NUMBER 12; Nieto et al 2023 World Allergy Organization Journal 16:100812.

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



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

Bringing a Steady Cadence of Transformational Medicines to People with Serious Diseases

Richard Geary, Ph.D.

Chief Development Officer

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

Hereditary Angioedema

Phase 2

- Positive Phase 2 OLE data in up to 4 years of treatment + improved QoL measures
- Positive Phase 2 data published in *NEJM*[3]

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 published in *NEJM*[3]

OASIS plus

- OLE cohort: long-term treatment continued to improve attack rates and QoL measures
- Switch cohort demonstrated:
  - Improved attack rates, QoL measures and disease control
  - Strong preference for donidalorsen
  - Useful data to inform potential switching
  - Positive results published in *JACI: In Practice*[5]

August 21, 2025 PDUFA; MAA Under Review; Ready to launch following approval[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 MA et al. N Engl J Med2024;391:21-31 (Phase 3 study); Fijen LM et al. N Engl J Med 2022;386:1026-10332. (Phase 2 study). 4. Timing expectations based on current assumptions and subject to change. 5. Riedl, M et al. *JACI: In Practice. 2025.*

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

Largest Pivotal Program Ever Conducted in sHTG

On Track for Data from CORE + CORE2 Studies in September[1]

Essence TIMI-73b

- Reported positive topline efficacy and safety data
- Supportive Ph3 safety study in patients w/ TG ≥150 mg/dL (HTG)[2]
- Placebo-adjusted mean reductions in triglyceride levels of 61% and 58% at six months with the 80 and 50 mg monthly doses, respectively
- Results to be used to support olezarsen exposure database
- Nearly 1,500 patients

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 achieved normalized TG levels
- Favorable safety and tolerability[3]

Looking Ahead

- Additional Essence data to be presented at ESC Congress 2025
- Data from CORE and CORE2 studies in patients with sHTG expected in September[4]

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. 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. 3. 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. 4. Timing expectations are based on current assumptions and are subject to change.

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**

>1 million high-risk sHTG 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.

Zilganersen for the Treatment of Alexander Disease

Devastating Neurological Disease with No Approved Disease-Modifying 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.

ION582: A Promising New Investigational Medicine for Angelman Syndrome

Jackson
Living with Angelman Syndrome

Robust Pivotal Phase 3 Study Now Underway[1]

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

Positive Early Results Seen in the HALOS Study[3]

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

1. REVEAL Trial, clinicaltrials.gov/NCT06914609. 2. Timing expectations based on current assumptions and subject to change. 3. Based on data generated to date from the Phase 1/2a HALOS study of ION582.

Extending the SMA Franchise

Nusinersen High Dose

- High dose nusinersen regulatory submissions under review globally
- September 2025 PDUFA[1]

Salanersen

- Designed with a novel Ionis chemistry to achieve strong efficacy & once-yearly dosing
- Interim Phase 1 data showed that once-yearly dosing with both doses tested was well tolerated and led to substantial slowing of neurodegeneration
- Biogen advancing into Phase 3
- Improved economics over SPINRAZA[2]

SPINRAZA® (nusinersen) injection 12 mg/5 mL

1. Timing expectations based on current assumptions and subject to change. 2. SPINRAZA is approved in the U.S. for or the treatment of spinal muscular atrophy in pediatric and adult patients; see Full Prescribing Information.

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

TRYNGOLZA
✓ U.S.
(FCS)

TRYNGOLZA
EU
(FCS)

Donidalorsen
U.S.
(HAE)

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.

Q2 2025 Financial Performance

Beth Hougen

Chief Financial Officer

Q2:2025 Financial Highlights[1]

Increased 2025 Financial Guidance Supported by the Early Launch Excellence of TRYNGOLZA

$452M

Revenue

Commercial Revenue: $103M

- Over $19M in TRYNGOLZA product sales
- Royalty revenues increased ~10% YoY

R&D Revenue: $349M

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

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$282M

Operating Expenses[2]

R&D Expenses[2]: $197M

- Decreased slightly YoY, while strategically funding our advancing pipeline
- Large majority funding late-stage programs

SG&A Expenses[2]: $81M

- Increased YoY to fuel ongoing and planned launches

$154M

Net Income[2]

- Strong revenue enabled Ionis to generate a profit in the second quarter

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$2.3B[3]

Cash & Short-term Investments

- Enables investments in launches and Ionis-owned pipeline

1. For the quarter ended June 30, 2025. 2. Non-GAAP – please see reconciliation to GAAP in Q2:2025 press release.

Increased 2025 Financial Guidance[1]

Driven by Strong YTD Financial Results & Improved Full Year Outlook

Revenue

$825-$850 million

Includes: $75-80 million of TRYNGOLZA net revenues

Prior $725-750 million

Operating Loss

$300-325 million[2]

Prior <$375 million

Cash

~$2.0 billion

Prior $1.9 billion

1. Based on current assumptions, subject to change. 2. Non-GAAP – please see reconciliation to GAAP in Q2:2025 press release.

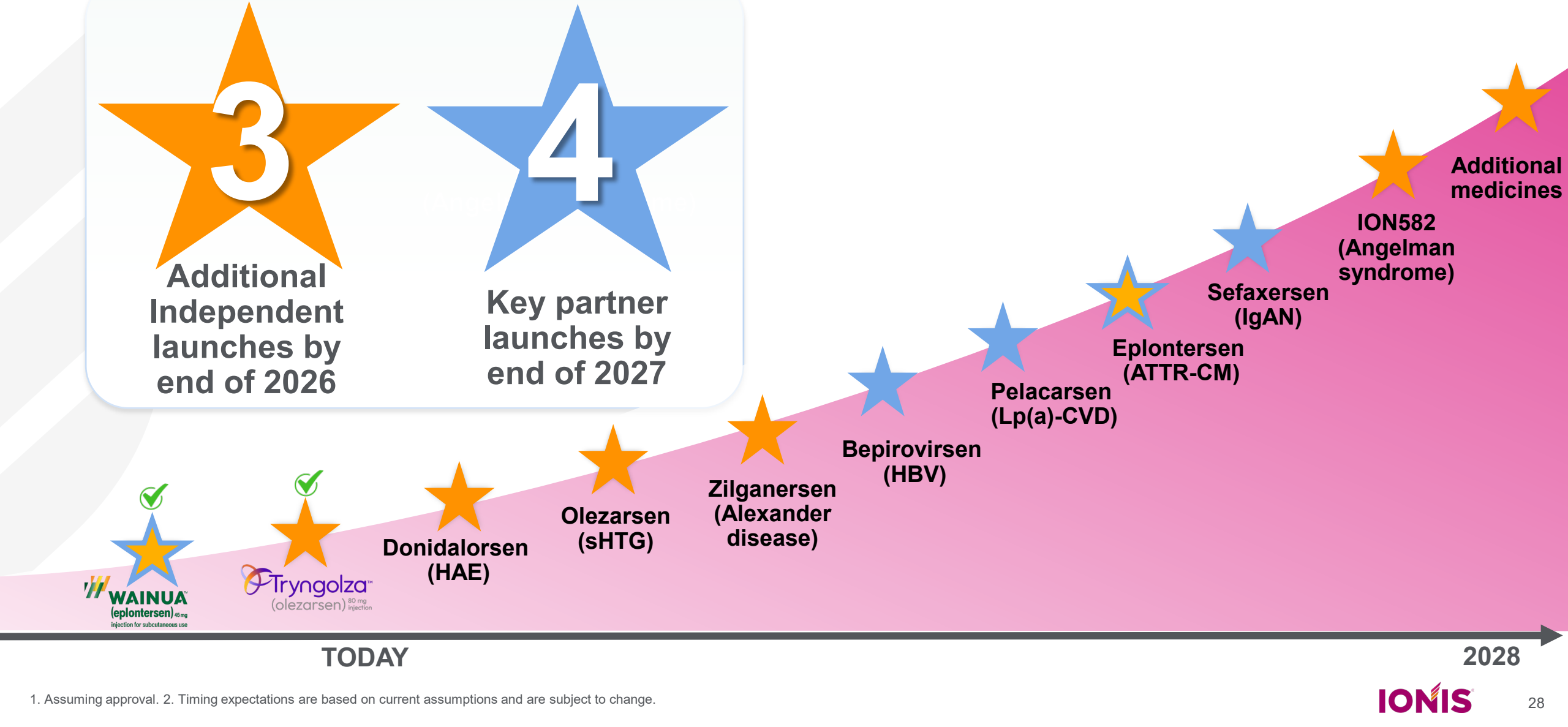
Conclusion

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]



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Q&A

Innovation Day 2025

October 7, 2025 | Nasdaq: IONS