



2026 Annual Shareholders Meeting Corporate Update

June 2026

Nasdaq: IONS



Yajaira (with family)
Living with sHTG

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 and our expectations regarding development and regulatory milestones. Any statement describing Ionis' goals, expectations, financial or other projections or guidance, 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, 2025, 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.

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Ionis: Pioneered the Field of Oligonucleotide Therapeutics



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



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

Well Positioned for Accelerating Growth



Fully integrated, commercial-stage biotechnology company



Groundbreaking technology fueling **high-value innovative pipeline**



Consistently delivering breakthrough clinical results enabling **highly successful commercial launches**^{1,2}



Clear path to **accelerating revenue growth, sustained positive cash flow** and **substantial value creation**²



Jared
living with sHTG

1. Assuming approval. 2. Based on current timing assumptions, subject to change.

Strong Track Record of Industry-Leading Success¹⁻⁴

Key Recent Achievements

6

Positive Phase 3
Data Readouts



4

Approved
Medicines

 Tryngolza®
(olezarsen) 80 mg
injection

 DAWNZERA™
(donidalorsen) 80 mg/0.8 mL
injection

 WAINUA®
(eplintersen) 45 mg
injection for subcutaneous use

 QALSODY.
(tofersen) 100 mg/15 mL
injection

2

Independent
Launches

 Tryngolza®
(olezarsen) 80 mg
injection

 DAWNZERA™
(donidalorsen) 80 mg/0.8 mL
injection

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Medicines in
Late-Stage Development



1. TRYNGOLZA is approved in the U.S. for Familial Chylomicronemia Syndrome (FCS) in adults as an adjunct to diet; see [Full Prescribing Information](#); Approved in the EU as an adjunct to diet in adult patients for the treatment of genetically confirmed FCS. 2. DAWNZERA is approved in the U.S. for hereditary angioedema in adults and pediatric patients 12 years of age and older; see [Full Prescribing Information](#). 3. QALSODY.com. 4. WAINUA.com.

DAWNZERA Launch Gaining Significant Momentum¹

Delivering on What HAE Patients Need Most

First and Only RNA-Targeted Treatment to Prevent HAE Attacks



Indicated for prophylaxis to prevent attacks of HAE in adult and pediatric patients ≥12 years old

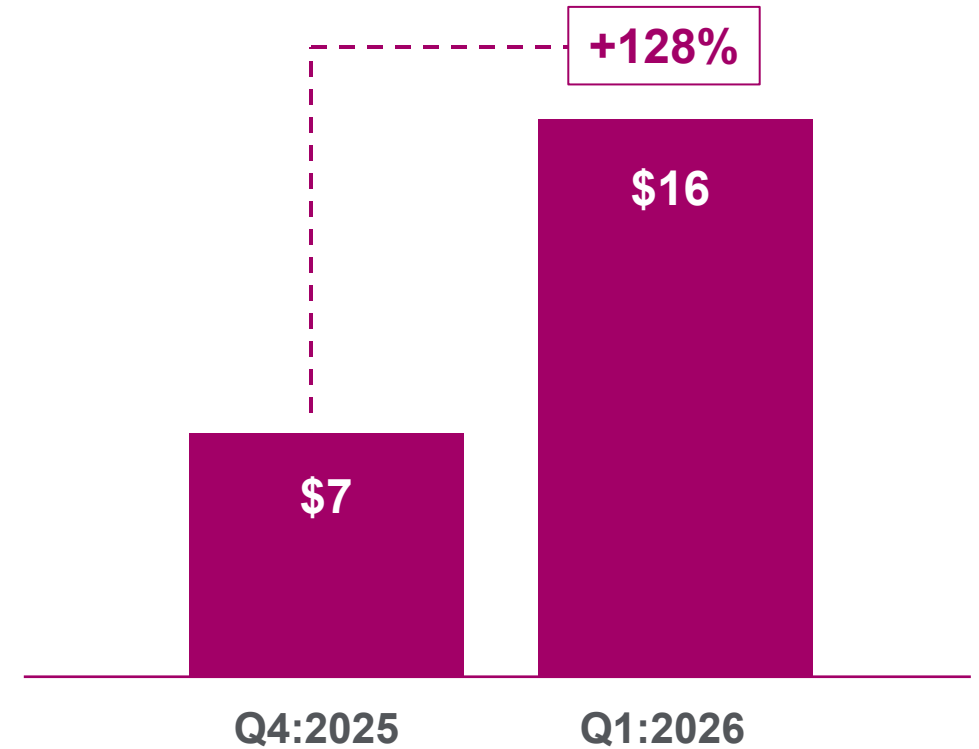
Prescriptions written for all patient segments:

- Switches from other long-term prophylactic treatments
- Previously on-demand treatment only
- Treatment naïve

Growing number of repeat prescribers

Approved in U.S. and EU²

Generated \$16 million in Q1:2026



DAWNZERA, U.S. Product Sales, net (millions)

1. DAWNZERA is approved in the U.S. for hereditary angioedema in adults and pediatric patients 12 years of age and older; see [Full Prescribing Information](#). 2. Otsuka is responsible for commercializing DAWNZERA in the EU.

Delivering Transformational Medicines in Focused Therapeutic Areas



Cardiometabolic

First- or best-in-class medicines that target cardiometabolic diseases, the leading causes of death globally



Neurology

First- or best-in-class medicines to address a broad range of diseases with high unmet need

Rare and prevalent
patient populations
in focused disease
areas

Potential for Multiple Blockbusters¹

Olezarsen: A Transformational Medicine for All sHTG Patients with Urgent Unmet Need¹

Familial Chylomicronemia Syndrome (FCS)

- **Up to ~3,000** people in the U.S.²⁻⁶
- **Rare genetic disorder:** Most severe form of sHTG caused by loss of LPL activity^{6,7}
- **Significant risk** for acute, potentially fatal pancreatitis¹

Severe Hypertriglyceridemia (sHTG)

- **>3 million** people with sHTG in the U.S., including **>1 million people with high-risk sHTG⁸**
- Defined by **fasting triglyceride levels ≥ 500 mg/dL⁹**
- Characterized by **increased risk of acute pancreatitis and ASCVD⁹**
- **Limited benefit from currently available treatments¹⁰⁻¹³**

1. TRYNGOLZA is currently approved in the U.S. for Familial Chylomicronemia Syndrome in adults as an adjunct to diet; see [Full Prescribing Information and the EU](#), the sNDA for sHTG has been submitted to the FDA. Approved in the EU as an adjunct to diet in adult patients for the treatment of genetically confirmed familial chylomicronemia syndrome. 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. Moulin P, et al. Atherosclerosis 2018;275:265-72. 7. Brown EE, et al. J Clin Lipidol 2020;14(4):398-413. 8. Hegele, et al, Lancet Diabetes Endocrinol. 2014 Aug 2(8):655-66. 9. Nawaz H, et al. Am J Gastroenterol. 2015;110(10):1497-1503. 10. Patel SB, et al. Endocr Pract. 2025;31(2):236-262. 11. Santos-Baez, LS et al. Front Endocrinol (Lausanne). 2020;11:616. 12. Skulas-Ray AC, et al. Circulation. 2019;140(12):e673-e691. 13. Aldhalei WA, et al. Pharmaceuticals (Basel). 2024;17(2):199.

Focused Commercial Execution Building Sustainable TRYNGOLZA Demand in FCS¹



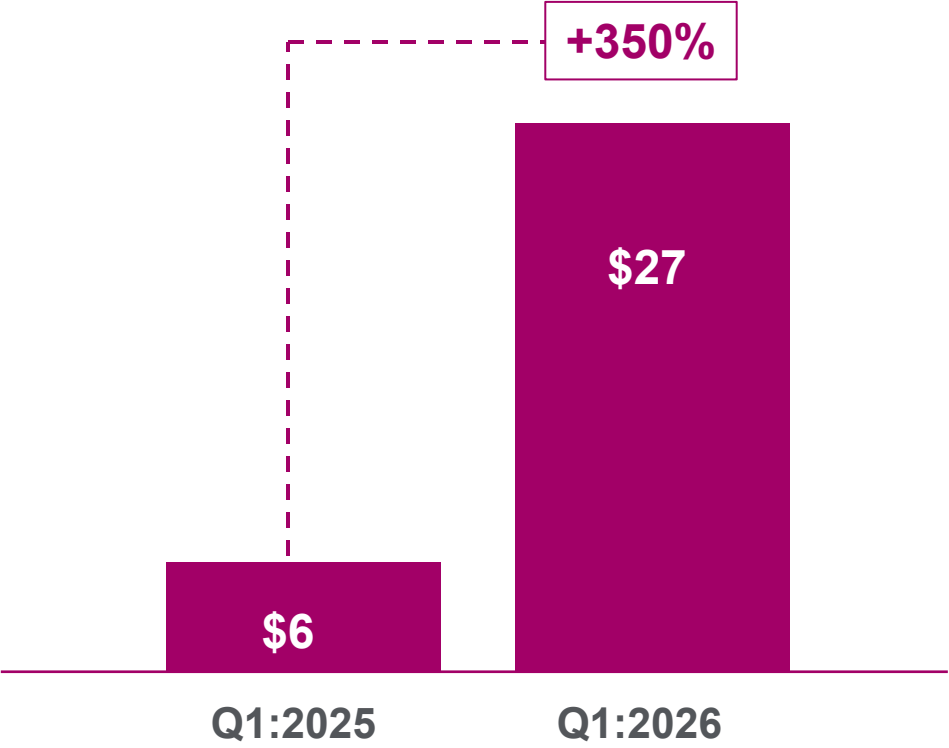
Robust efficacy and safety

- Substantial reductions in triglycerides and in acute pancreatitis events

Convenience of once-monthly self-administration with an autoinjector

EU launch underway²

Generated \$27 million in Q1:2026



TRYNGOLZA, U.S. Product Sales, net (millions)

1. TRYNGOLZA is approved in the U.S. for Familial Chylomicronemia Syndrome in adults as an adjunct to diet; see [Full Prescribing Information](#). 2. Approved in the EU as an adjunct to diet in adult patients for the treatment of genetically confirmed familial chylomicronemia syndrome (FCS).

Olezarsen: Poised to Become Ionis' First Multi-Billion Dollar Medicine



>3 million people with sHTG in the U.S.¹

- Includes >1 million people with high-risk sHTG¹
- Early launch focus on high-risk sHTG with >880 mg/dL or ≥500 mg/dL + AP history and/or comorbidities



- **Substantial, highly statistically significant** and **clinically meaningful** reductions in fasting **triglycerides**²
- **First and only** investigational treatment to **significantly reduce acute pancreatitis** events in **people with sHTG**²



Simplicity of **monthly self-administration** with a patient-friendly **autoinjector**



- **First mover** advantage
- Full field team **deployed**
- **Granted Priority Review**; PDUFA June 30, 2026

Annual Peak Product Revenue Opportunity³

Increased to

>\$3B

—
(Previous: >\$2B)

Building a Leading Cardiometabolic Pipeline^{1,2}

2

Wholly Owned Medicines in Clinical Development



4

Partnered Medicines in Clinical Development

6

Medicines in Clinical Development

Wholly Owned Medicines

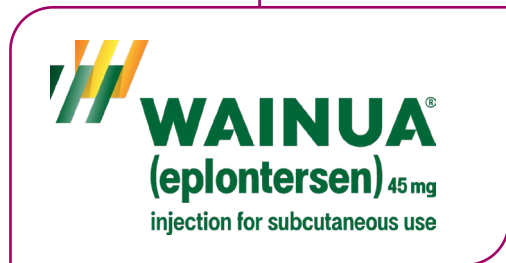
	Indication	Preclinical	Ph1	Ph2	Ph3
Olezarsen (ApoC-III)	sHTG	PDUFA: June 30, 2026			
ION775 (ApoC-III)	sHTG				
ION501 (undisclosed)	Myocardial disease	(TfR1-Targeting)			
ION924 (Apo(a))	Cardiovascular disease				
ION573 (undisclosed)	Cardiovascular disease				

Partnered Medicines

Eplontersen (TTR) ³	ATTR-CM				
Pelacarsen (Apo(a))	Cardiovascular disease				
Tonlamarsen (Angiotensinogen)	Acute severe hypertension				
ION826/AZD4063 (PLN) ⁴	Myocardial disease	(TfR1-Targeting)			

1. Timing and expectations based on current assumptions and subject to change. 2. Assuming approval. 3. Co-developing and commercializing WAINUA for ATTRv-PN and ATTR-CM in U.S. with AstraZeneca. 4. In-licensed by AstraZeneca in 2023.

3 Approved Medicines¹



Leading Neurology Portfolio Positioned to Deliver Accelerating Value



Strong track record in delivering **first-in-class** neurology medicines



Well-positioned to deliver a **steady cadence of medicines²**

- **Strong pipeline** of wholly owned and partnered medicines in clinical development
- **First independent neurology launch** expected in **2026** with **zilganersen** for Alexander disease



Focused strategy for expanding our wholly owned neurology portfolio



Focused on continuous **innovation** and **advancing proven technology**

Zilganersen: Preparations on Track for First Independent Neurology Launch¹

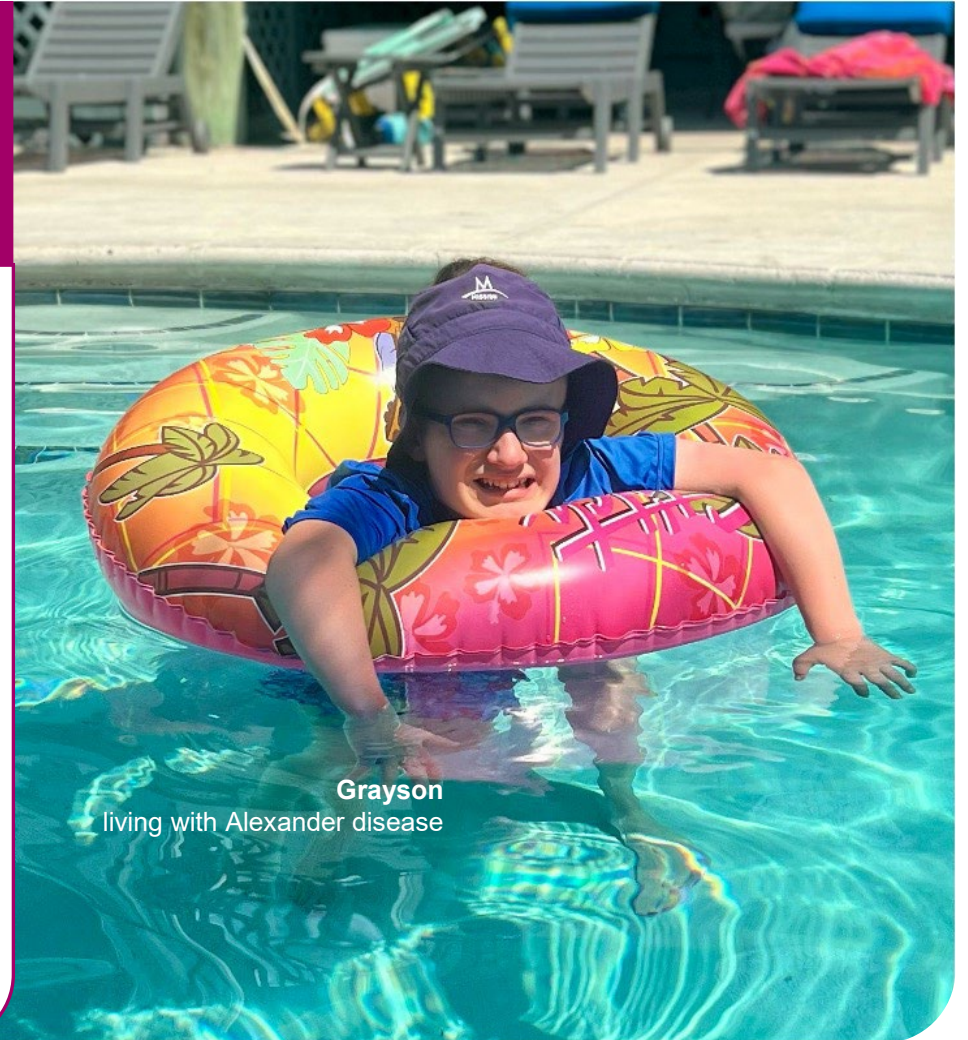
Zilganersen for the Treatment of Alexander Disease

First and only investigational medicine to demonstrate clinically meaningful disease-modifying impact

Prevalence: ~1 in 1-3 million; accounts for ~2-8% of leukodystrophies, potentially underestimated²

U.S. and EU Orphan designation; U.S. Fast Track designation

Granted Priority Review; PDUFA September 22, 2026



Grayson
living with Alexander disease

1. Based on current timing assumptions, subject to change. 2. 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. *Med Genet.* 2016;59:315-319.

Obudanersen: A Promising Investigational Medicine for Angelman Syndrome



The Opportunity

- **>100k people** in major geographies with **Angelman syndrome**, a severe, rare neurodevelopmental disorder¹
- **Significant unmet need** with **no approved disease-modifying treatments**



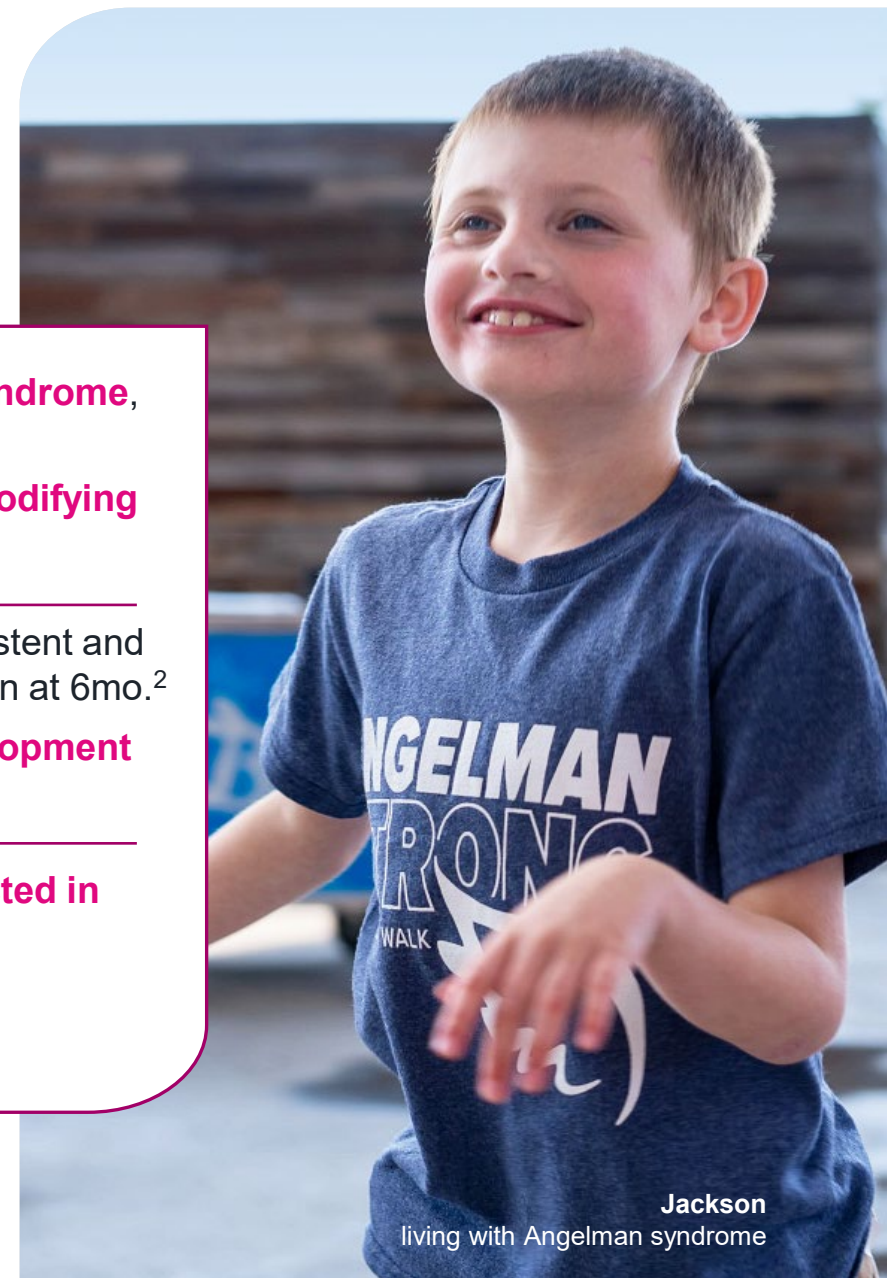
Key Clinical Highlights

- **Positive results seen in the HALOS study**, with consistent and meaningful improvements in key areas of clinical function at 6mo.²
- **Long-term extension data** continues to **support development**
- **Granted Breakthrough Therapy designation**



Next Steps

- Full enrollment of pivotal Phase 3 REVEAL study **expected in 2026³**
- Phase 3 **data expected in 2027³**
- UPD/ID CHAMPION **study initiation expected in 2026**



Jackson
living with Angelman syndrome

Leading the Way in the Treatment of Neurological Diseases

7

Wholly Owned Medicines in Clinical Development



6

Partnered Medicines in Clinical Development

13

Medicines in Clinical Development

Approved Medicines¹⁻³



Wholly Owned Medicines

	Indication	Preclinical	Ph1	Ph2	Ph3
Zilganersen (GFAP)	Alexander disease	PDUFA: September 22, 2026			
Obudanersen (UBE3A-ATS)	Angelman syndrome				
ION464 (SNCA)	Multiple System Atrophy				
ION717 (PRNP)	Prion disease				
ION356 (PLP1)	Pelizaeus-Merzbacher disease				
ION440 (MECP2)	MECP2 Duplication syndrome				
ION337 (SCN1A)	Dravet syndrome				

Partnered Medicines

Ulefnersen (FUS)	Amyotrophic Lateral Sclerosis (ALS)				
Tofersen (SOD1)	ALS (Presymptomatic SOD1)				
Salanersen (SMN2)	Spinal Muscular Atrophy				
Diranersen ⁴ (TAU)	Alzheimer's disease	Data to be presented at AAIC			
Tominersen (HTT)	Huntington's disease				
RG6496 (HTT SNP)	Huntington's disease				

1. SPINRAZA.com 2. QALSODY.com. 3. WAINUA.com. 4. Biogen plans to advance to Phase 3 development in 2026. Formally called IONIS-MAPT_{Rx}

2026 Key Value-Driving Events¹

Clinical Events

Phase 3

✓ **Bepirovirsen**
B-Well data
(CHB)

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

Eplontersen
CARDIO-TTRansform data
(ATTR-CM)

Ulefnersen
FUSION data
(FUS-ALS)

Sefaxersen
IMAGINATION data
(IgAN)

Sapablursen
Phase 3 initiation
(PV)

Obudanersen
Enrollment completion
(Angelman syndrome)

✓ **Salanersen**
Phase 3 initiation
(SMA)

Phase 2

✓ **Diranersen**
CELIA data
(Alzheimer's disease)

Tominersen
GENERATION HD2 data
(Huntington's disease)

✓ **Tonlamarsen**
Phase 2 data
(Uncontrolled hypertension)

Regulatory Actions

Donidalorsen
✓ EU approval
(HAE)

Olezarsen
U.S. approval
✓ EU submission
(sHTG)

✓ **Zilganersen**
U.S. submission
U.S. approval
(AxD)

High Dose Nusinersen

✓ U.S. approval
✓ EU approval
(SMA)

Bepirovirsen
✓ Submission
Approval
(CHB)

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

Eplontersen
U.S. submission
(ATTR-CM)

Product Launches

✓ **DAWNZERA**
EU
(HAE)

Olezarsen
U.S.
(sHTG)

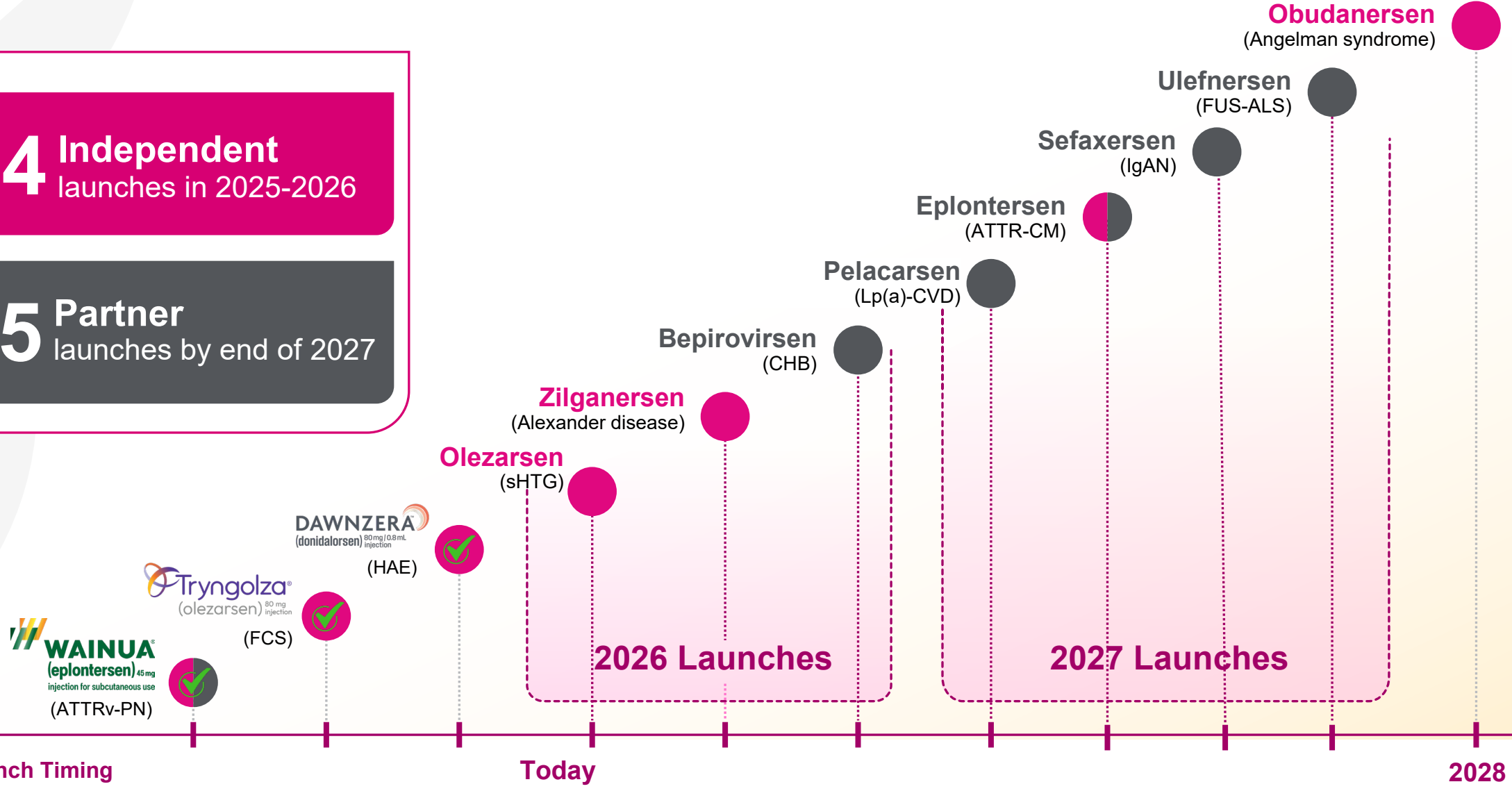
Zilganersen
U.S.
(Alexander disease)

Bepirovirsen
U.S. & Japan
(CHB)

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.

Delivering a Steady Cadence of New Medicines^{1,2}

- 4 Independent launches in 2025-2026
- 5 Partner launches by end of 2027



1. Assuming approval. 2. Based on current timing assumptions, subject to change.

Marketed Products and Planned Launches Provide Substantial Revenue Growth Opportunity¹

Ionis-Owned Medicines

>\$5B

in Potential Annual Peak Product Revenue²



>\$7B

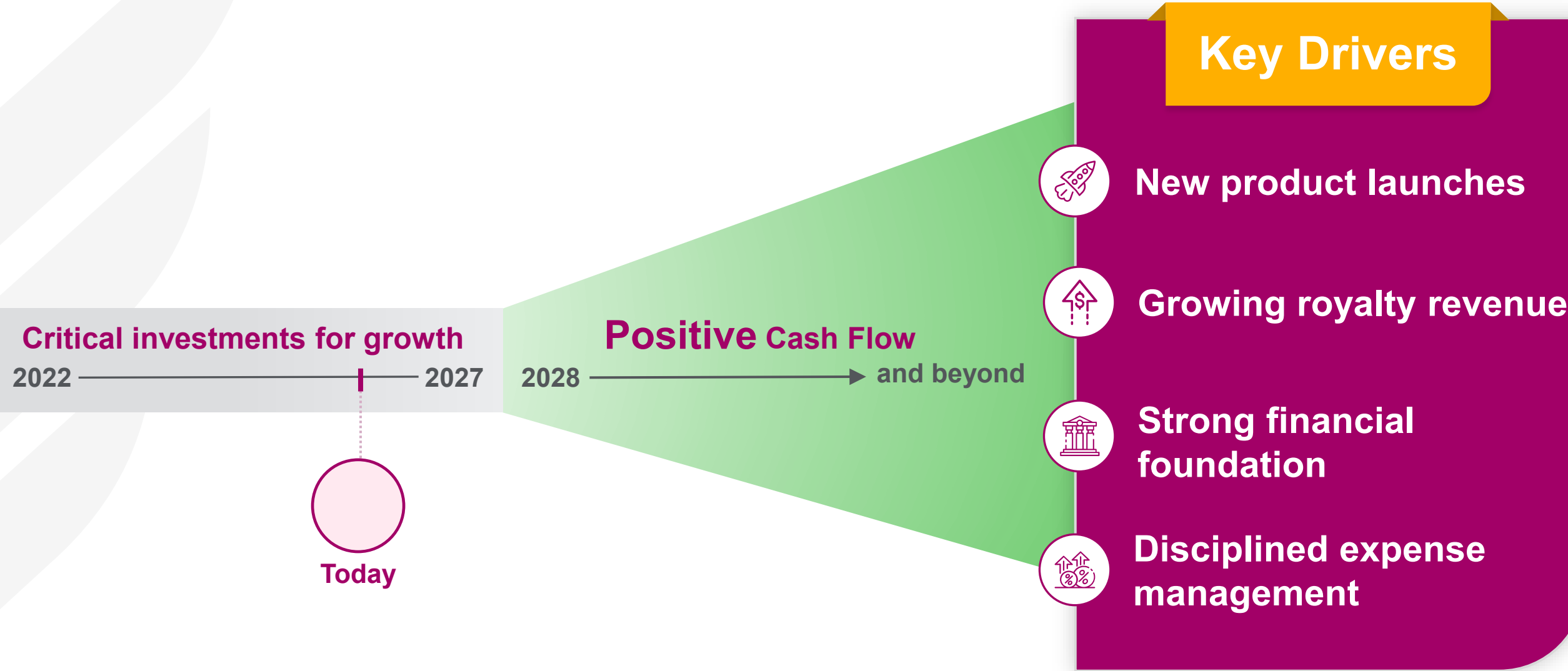
Partner Medicines

>\$2B

in Potential Annual Peak Royalties²

1. Assumes additional approvals through 2028. 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.

Clear Path to Sustained Positive Cash Flow¹



1. Based on current assumptions, subject to change.

Driving Accelerating Growth^{1,2}

2028 Cash Flow Breakeven

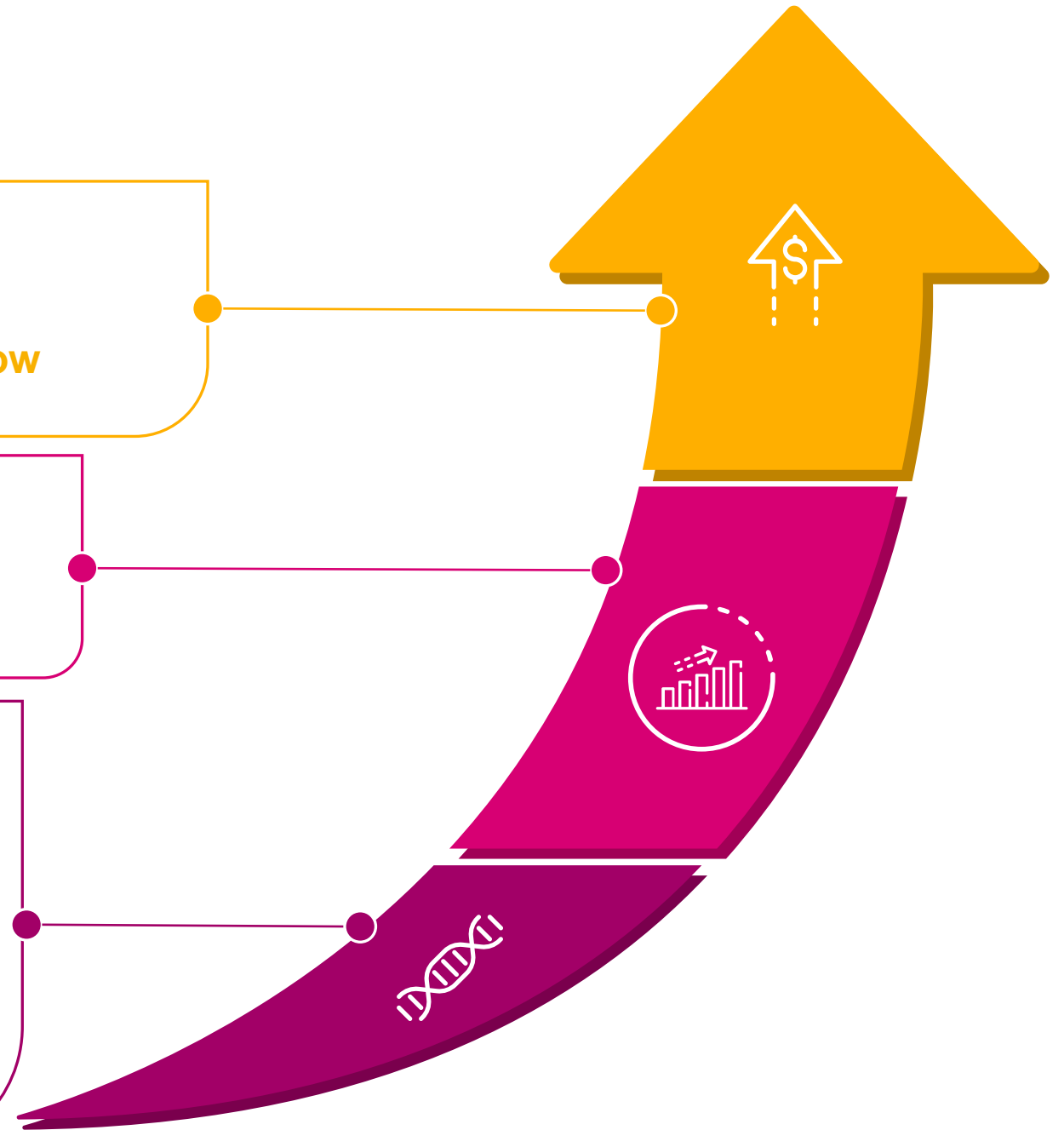
Clear Path to Sustained Positive Cash Flow

Accelerating Revenue Growth

Fully-integrated commercial stage
biotechnology company

Steady cadence of **positive clinical trial
results, successful product approvals and
launches**

Established **leadership in cardiometabolic and
neurology drug discovery and development**



1. Based on current estimates, subject to change. 2. Assuming approvals.

Q&A Session



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

The IONIS logo is centered at the top of the image. It features the word "IONIS" in a bold, magenta, sans-serif font. A stylized graphic element, consisting of three parallel diagonal lines in shades of orange and red, is positioned above the letter "N". A registered trademark symbol (®) is located to the upper right of the "S".

IONIS[®]

The background of the image is a black and white photograph of several hands stacked together in a circle. Each hand is holding a small, light-colored stone or pebble. The word "HOPE" is engraved on several of these stones, while one stone is heart-shaped and also bears the word "Hope". The overall composition is centered and conveys a sense of unity and shared purpose.

Delivering Accelerated Value