# ZANVASTRO™ FDA Approval

ZANVASTRO (zilganersen)

**First and only** disease modifying treatment for Alexander disease in pediatric and adult patients

September 2026
Nasdaq: IONS

IONIS®

# Forward-Looking Statements

This presentation includes forward-looking statements regarding our business, financial guidance and the therapeutic and commercial potential of ZANVASTRO and 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.

# On Today's Call

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

**Holly Kordasiewicz, Ph.D.**
Chief Development Officer

**Kyle Jenne**
Chief Global Product Strategy Officer

# Agenda

| Topic | Speaker |
| --- | --- |
| **ZANVASTRO: The First and Only Disease Modifying Treatment Approved for Alexander Disease** | **Brett Monia, Ph.D.,** Chief Executive Officer |
| **Alexander Disease: An Ultra-Rare, Progressive and Often Fatal Neurological Disorder** | **Holly Kordasiewicz, Ph.D.,** Chief Development Officer |
| **Accelerating Value through Commercial Execution** | **Kyle Jenne,** Chief Global Product Strategy Officer |
| **Delivering a Steady Cadence of Transformational Medicines for Serious Diseases** | **Brett Monia, Ph.D.,** Chief Executive Officer |

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# The First and Only Disease Modifying Treatment Approved for Alexander Disease

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

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## NOW APPROVED

The first and only disease modifying therapy approved by the FDA for the treatment of pediatric and adult patients with Alexander disease

1. ZANVASTRO is now approved in the U.S.; see Full Prescribing Information.

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# ZANVASTRO: Ionis' First Independent Neurology Medicine Launch[1]

## ZANVASTRO for the treatment of Alexander disease

**First** and **only disease modifying treatment approved** for Alexander disease

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**Broad label**, enabling treatment **for children and adults** with Alexander disease

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**Positive pivotal study data:** statistically significant stabilization of motor function, favorable trends across key symptoms and favorable safety

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**Commercializing outside the U.S.** with Recordati[2]

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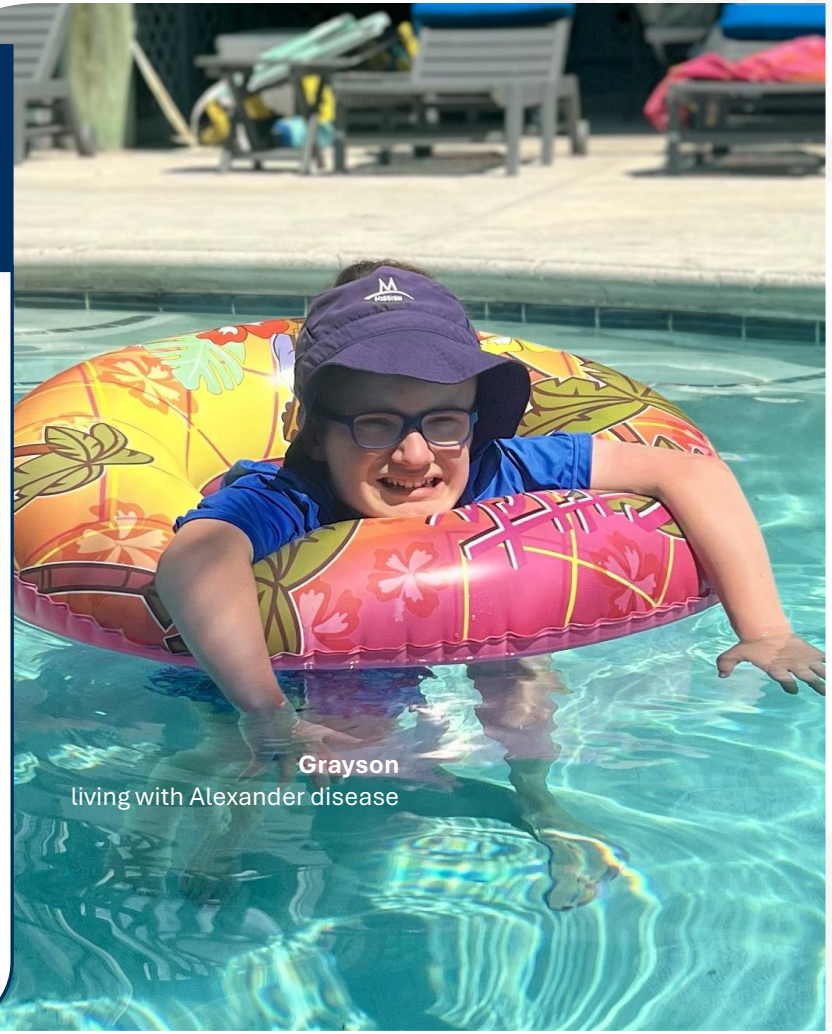
Awarded a **Rare Pediatric Disease Priority Review Voucher** in connection with the ZANVASTRO approval



**Grayson**
living with Alexander disease

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1. ZANVASTRO is now approved in the U.S.; see Full Prescribing Information. 2. Assuming approval.

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# Alexander Disease: An Ultra-Rare, Progressive and Often Fatal Neurological Disorder

**Holly Kordasiewicz, Ph.D.**
Chief Development Officer

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# Alexander Disease:
# An Ultra-Rare, Progressive and Often Fatal Neurological Disorder

**Max with his mother**
living with Alexander disease

## Alexander Disease (AxD)[1-5]

Characterized by progressive gross/fine motor and cognitive decline, speech difficulties, ataxia and bulbar dysfunction

Caused by mutations in *GFAP* gene

~65% of cases occur in childhood

Prevalence: ~1 in 1-3 million (~300 people in the U.S.); accounts for ~2-8% of leukodystrophies

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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. L. Bonkowsky, X. Ma, K. Householder, M. Vera-Llonch, M.R. McClain, A. Thomas, F. Pathan, X. Wu, S.M. Kymes. HealthCare Cost and Service Utilization by People Living with Alexander Disease. Neurology Clinical Practice (Manuscript in submission). 3. 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.

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# Innovative Pivotal Study Designed to Assess ZANVASTRO in People with Alexander Disease[1,2]

**DESIGN**

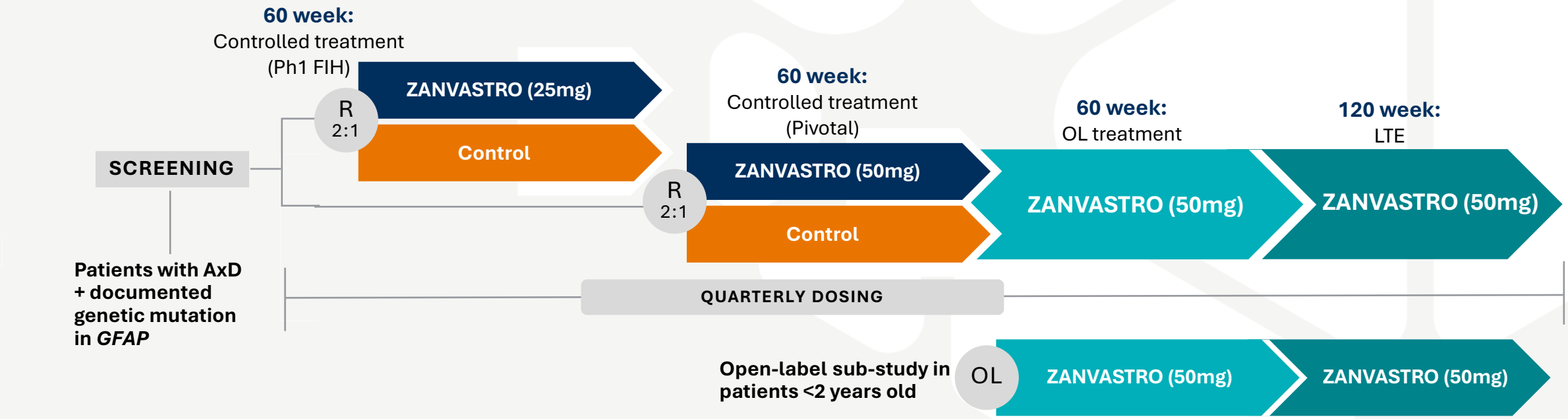
**A global, randomized, double-blind, placebo-controlled study in ~50 patients** with Alexander disease (AxD) 2-65 years old

An open-label sub-study in patients <2 years old conducted at certain sites

**PRIMARY OBJECTIVE**

Assessing **motor function** with **age-appropriate measures**

**Primary endpoint: Percentage change in gait speed** as assessed by the **10-Meter Walk Test** (10MWT) at Week 61

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R, randomized; OL, open-label; LTE, long-term extension. 1. Clinicaltrials.gov/NCT04849741. 2. An extended LTE of up to 240 weeks added for patients outside the U.S.

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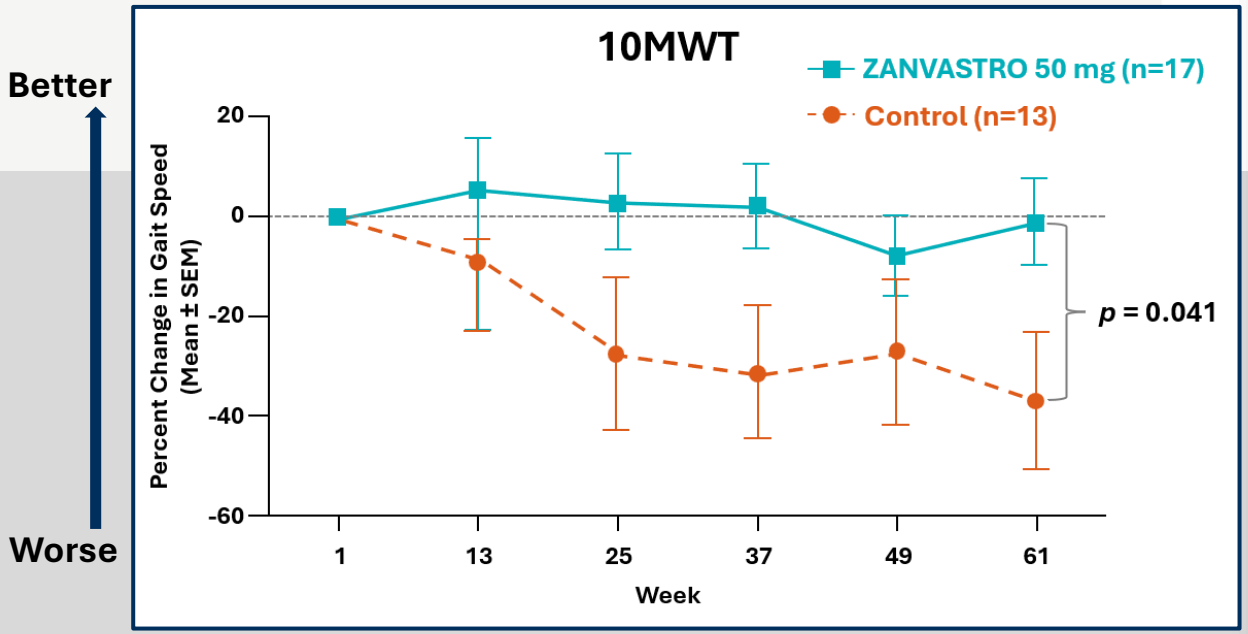
# ZANVASTRO: Primary Endpoint Assessing Gross Motor Function Statistically Significant in Pivotal Study[1]




| Primary Endpoint (10MWT) | | ZANVASTRO (50mg) n=17 | Pooled Control n=13 |
|---|---|---|---|
| Baseline | | | |
| (m/s) | Mean | 1.2 | 1.1 |
| % Change at Week 61 | | | |
| | Mean | -1.0 | -36.9 |
| | Least Squares Mean (LSM) (95% CI) | -2.1 (-23.0, 18.8) | -35.4 (-59.3, -11.5) |
| | LSM Difference (95% CI) | **33.3** (1.4, 65.3) | |
| **P-value**[3] | | ***p* = 0.041** | |

**ZANVASTRO showed a statistically significant and clinically meaningful stabilization in gait speed as measured by the 10-Meter Walk Test (10MWT) in patients ≥ 5 years old**

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1. ZANVASTRO is now approved in the U.S.; see Full Prescribing Information. 2. Meters per second. 3. ANCOVA model.

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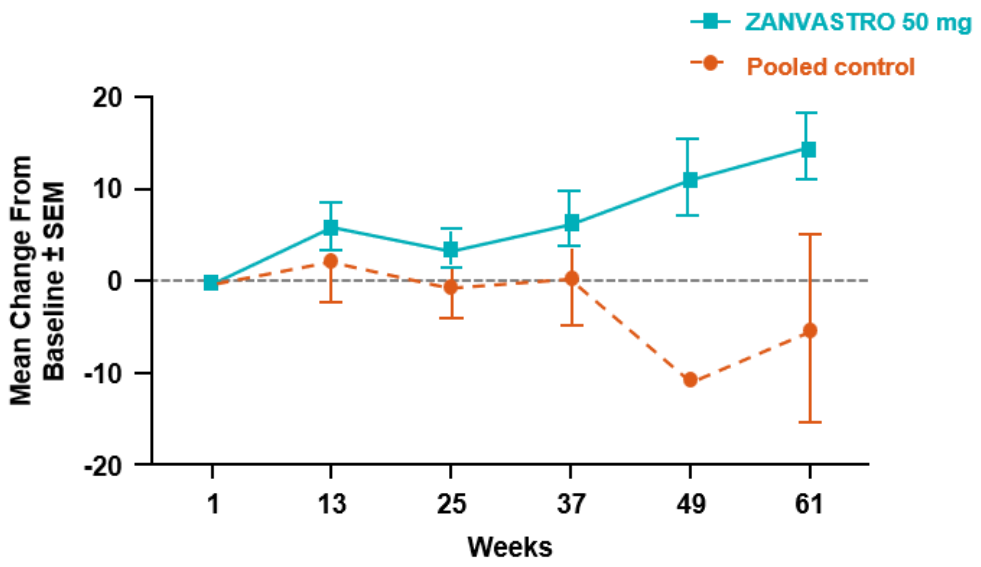
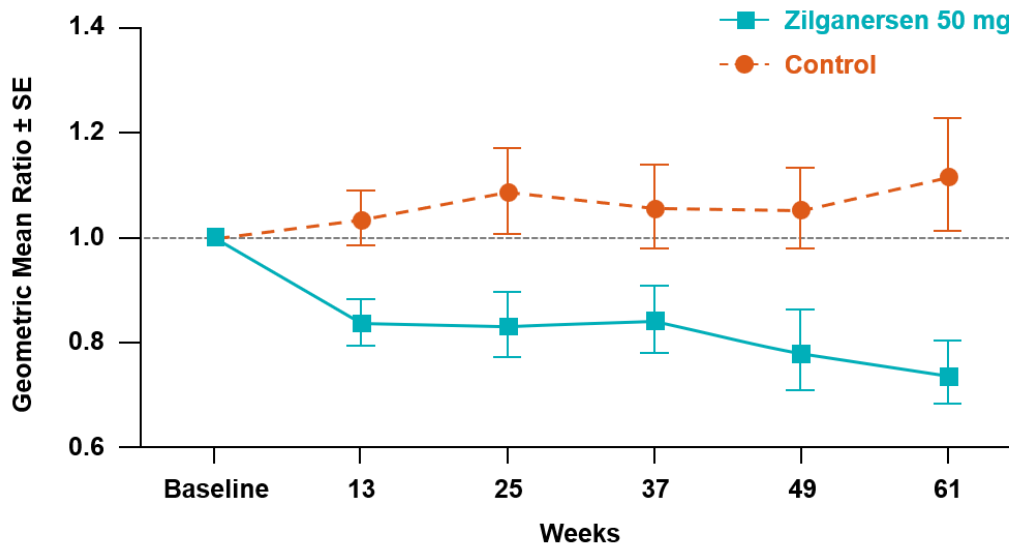
# Secondary and Exploratory Endpoints Consistently Supported ZANVASTRO for the Treatment of Alexander Disease[1]

## Gross Motor Function Measure-88 (GMFM-88)




- **GMFM-88:** Age-appropriate measure of motor function in patients 2-4 years old
- **22.9 least square mean difference** at week 61 between ZANVASTRO 50 mg and control (nominal $p = 0.034$)

## Change in Plasma GFAP from Baseline




- **Plasma GFAP:** evidence of target engagement and modulation of the underlying cause of disease in ZANVASTRO treated patients
- **33.6% least square geometric mean ratio lower** at week 61 from baseline compared to control (nominal $p = 0.003$)

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# Favorable Safety and Tolerability Observed in the ZANVASTRO Pivotal Trial[1]

## ZANVASTRO: Favorable Safety and Tolerability Profile

- Most adverse reactions were mild or moderate
- Most common adverse reactions were vomiting, back pain, cough, headache, and post-lumbar puncture syndrome
- Serious adverse reactions occurred less frequently with ZANVASTRO vs. control
- One serious adverse reaction of aseptic meningitis occurred in a ZANVASTRO-treated patient
  - Not associated with clinical signs or symptoms
  - Resolved with treatment
  - Did not lead to treatment discontinuation

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# Accelerating Value through Commercial Execution

**Kyle Jenne**
Chief Global Product Strategy Officer

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# ZANVASTRO: Ionis' First Independent Neurology Launch[1]

## Substantial Unmet Need

**Alexander disease:** An **ultra-rare**, **progressive** and **often fatal** neurological disorder

**First approved disease modifying treatment**

## Broad Label

**ZANVASTRO indication** enables **treatment for children and adults** with Alexander disease

## Well-Established Patient Community

**Strong partnership** with the Alexander disease **patient community**

## Strategy to Reach Patients

**Identification, diagnosis** and **treatment management**

**Education, access** and **support**

Expanding **global access** through **Recordati**[2]

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# Initial ZANVASTRO Launch Strategy[1]

Transition patients to commercial drug from clinical study and EAP

Initiate treatment with ZANVASTRO in patients already diagnosed with AxD

Broaden disease awareness to drive new patient identification

Work with payers to ensure access to ZANVASTRO for patients diagnosed with Alexander disease

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# IONIS EVERY STEP: Designed Specifically to Meet the Unique Needs of the Alexander Disease Community

IONIS EVERY STEP™ SUPPORT SERVICES

- Dedicated patient support from Patient Education Managers
- Access and reimbursement support
- Disease education, treatment support and connection to key resources
- Financial assistance and reimbursement support programs[1]

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1. For commercially covered patients only. Medicare, Medicaid, TRICARE, Department of Defense, or Veterans Administration, or any other state or federal government-funded patients are not eligible.

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# Advancing our Goal of Delivering a Steady Cadence of New Transformational Medicines[1]




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# Delivering a Steady Cadence of Transformational Medicines for Serious Diseases

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

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# Q&A

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# Breakthrough Therapies Driving Accelerating Growth