IONIS® Innovation Day

Discovering, Developing and Delivering Transformational Medicines

October 4, 2023 | Nasdaq: IONS

Forward-Looking Statements

This presentation includes forward-looking statements regarding our business, financial guidance and the therapeutic and commercial potential of QALSODY™ (tofersen), SPINRAZA® (nusinersen), TEGSEDI® (inotersen), WAYLIVRA® (volanesorsen), eplontersen, olezarsen, donidalorsen, ulefnersen, zilganersen, pelacarsen, bepirovirsen, IONIS-FB-L_{Rx}, Ionis' technologies, and Ionis' other products in development. 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. 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 Form 10-K for the year ended December 31, 2022, and most recent Form 10-Q, which are on file with the SEC. Copies of these and other documents are available at www.ionispharma.com.

In this presentation, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries.

Commitment to Responsibility Supports Value and Resiliency

At Ionis, we work with integrity and purpose to discover, develop and deliver life transforming medicines for the people who depend on us

We believe operating responsibly and sustainably builds value and resiliency for our company and stakeholders

Read our most recent report

Ionis Leadership Here Today

Brett Monia, Ph.D.

Chief Executive Officer

Onaiza Cadoret

Executive Vice President,
Chief Global Product Strategy
& Operations Officer

Eric Swayze, Ph.D.

Executive Vice President,
Research

Beth Hougen

Chief Financial Officer

Wade Walke, Ph.D.

Senior Vice President,
Investor Relations

Sam Tsimikas, M.D.

Senior Vice President, Global
Cardiovascular Development

Kenneth Newman, M.D.

Senior Vice President,
Clinical Development

Holly Kordasiewicz, Ph.D.

Senior Vice President,
Neurology

Rachel Carnes

Senior Vice President,
New Product Strategy

Thought Leaders Here Today

Henry N. Ginsberg, M.D.
Irving Professor of Medicine and Past Director, Irving Institute for Clinical and Translational Research, Columbia University

Raffi Tachdjian, M.D., MPH, FAAAAI, FACAAI
Associate Clinical Professor of Medicine and Pediatrics, UCLA School of Medicine; Chief, Division of Allergy and Immunology, Providence St. John Medical Center

Agenda

Welcome	Wade Walke, Ph.D.
The Ionis Evolution *Fully Integrated and Focused*	Brett Monia, Ph.D.
On the Horizon: Important Medicines for Patients in Need	
Poised to Bring Important Medicines to Patients	Onaiza Cadoret
Eplontersen: A Potential Treatment of Choice for Global ATTR Population	Sam Tsimikas, M.D. Onaiza Cadoret
Olezarsen: A Potential New Standard-of-Care FCS and SHTG	Henry N. Ginsberg, M.D. Sam Tsimikas, M.D. Onaiza Cadoret
Break	
Donidalorsen: A Potential Advance in Prophylactic Treatment for Hereditary Angioedema	Raffi Tachdjian, M.D., MPH, FAAAAI, FACAAI Kenneth Newman, M.D. Onaiza Cadoret
Q&A	
Technology Advances Power Our Future Medicines	Eric Swayze, Ph.D.
Lunch	
Beyond the Horizon: Next Wave of Wholly Owned Medicines	Holly Kordasiewicz, Ph.D. Rachel Carnes
Clear Path to Unlocking Next-Level Value	Beth Hougen
Focused and Ready to Deliver Next-Level Value to Patients and Stakeholders	Brett Monia, Ph.D.
Q&A	

The Ionis Evolution

Fully Integrated and Focused

Brett Monia, Ph.D.

Chief Executive Officer

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

Expand and Diversify Drug Discovery Capabilities

Deliver Medicines to Patients

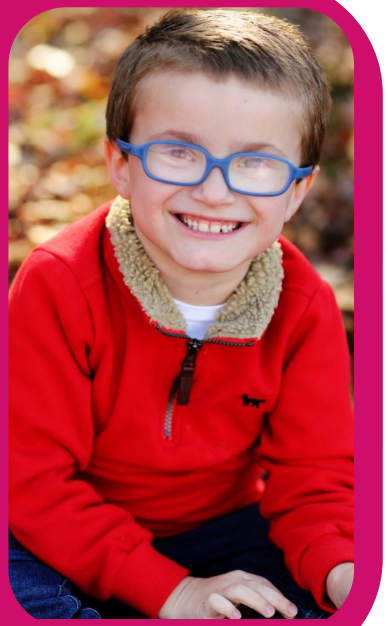
Scientific and Clinical Innovation

—

Financial Responsibility





Maximize Value for Patients

Expand and Diversify Drug Discovery Capabilities

Deliver Medicines to Patients

Scientific and Clinical Innovation

—

Financial Responsibility

Ionis Today: Discovering, Developing and Delivering Transformational Medicines to People in Need

World Class Research & Development Organization

4

Medicines for Serious Diseases

Discovered by Ionis and on the Market

Including 2 Breakthrough Neurological Disease Medicines

Broadened Drug Discovery Capabilities

- Strengthening Existing Franchises
- Creating New Therapeutic Franchises
- Diversifying Chemistries & Mechanisms

Rich Late-Stage Pipeline

9

Medicines in Phase 3

11

Indications

Leading Cardiology & Neurology Franchises

Ready to Bring Medicines to Patients

3

Near-Term Launches

Eplontersen

Co-commercializing with AstraZeneca

Olezarsen

Donidalorsen

Next Wave of Wholly Owned Medicines

Strong Financial Profile

Enables Investments to Drive Increasing Value

Ionis Today: Discovering, Developing and Delivering Transformational Medicines to People in Need

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Next Wave of Wholly Owned Medicines

Strong Financial Profile

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World-Class Research Organization: Advancing Technology for Future Medicines

Reaching New Patients and Optimizing Therapies in Existing Disease Areas

Leading Medicinal Chemistry Platform

World-Class Research Organization: Advancing Technology for Future Medicines

Reaching New Patients and Optimizing Therapies in Existing Disease Areas

Enhancing Product Profile

Mechanism Agnostic

ASO | siRNA | DNA Editing

Optimizing Potency and Durability

Systemic and Local Applications

Leading Medicinal Chemistry Platform

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Optimizing Potency and Durability

Systemic and Local Applications

Optimizing Delivery

- ***Existing Franchises***
- ***New Therapeutic Areas***

Targeted Delivery (e.g., LICA)

Cardiac Muscle

Skeletal Muscle

Blood Brain Barrier

Leading Medicinal Chemistry Platform

World-Class Research Organization: Advancing Technology for Future Medicines

Reaching New Patients and Optimizing Therapies in Existing Disease Areas

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Systemic and Local Applications

Optimizing Delivery

- *Existing Franchises*
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Targeted Delivery (e.g., LICA)

Cardiac Muscle

Skeletal Muscle

Blood Brain Barrier

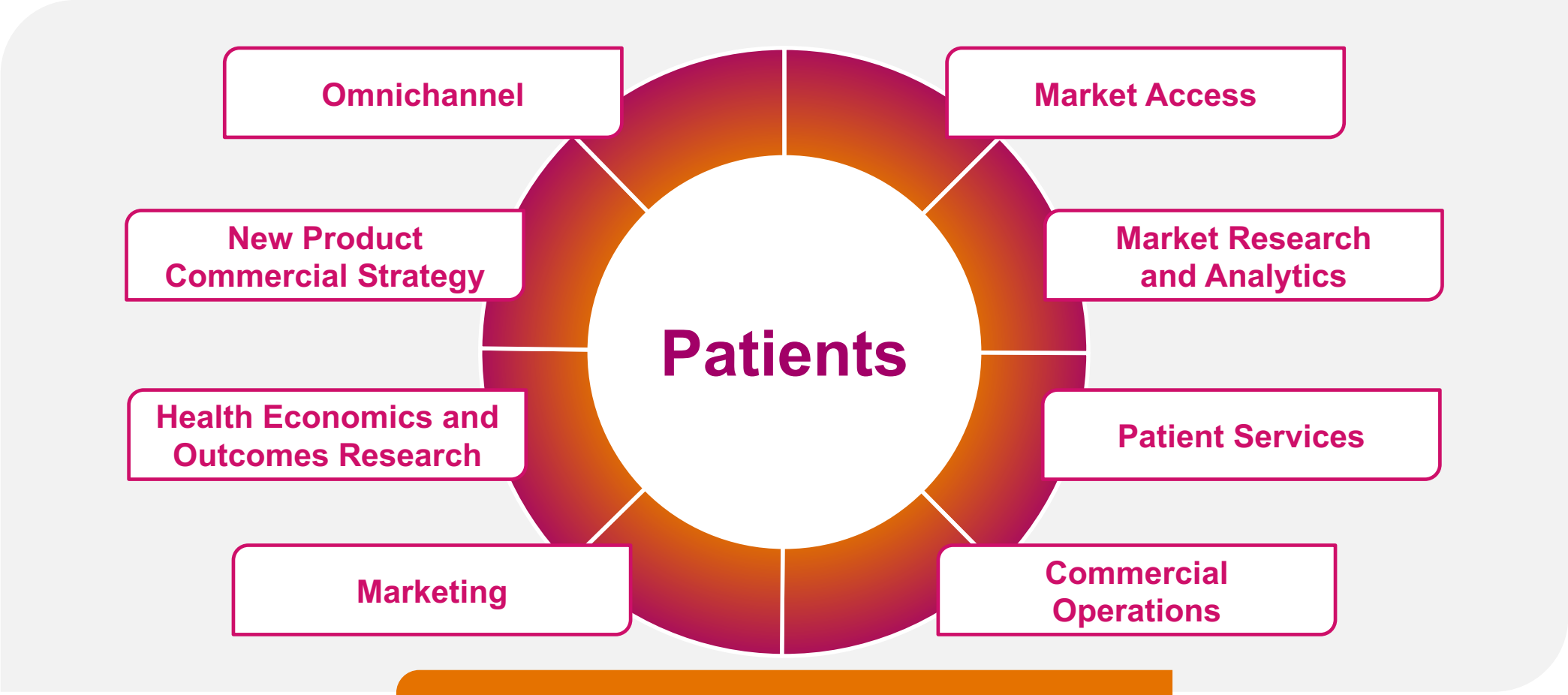
Laying the Groundwork for Expanded & Sustained Delivery of Transformational Medicines

Established Franchises
Cardiovascular | Neurology

New Potential Focus Areas
Pulmonary | Renal

Leading Medicinal Chemistry Platform

Commercial Infrastructure in Place: Ready to Deliver Medicines to People in Need



Realizing the Promise of our Innovative Medicines

Commercial Strategy to Maximize Value

First Ionis-Commercialized Medicine Positioned to Reach Patients[1]

Eplontersen

ATTRv-Polyneuropathy

ATTR Cardiomyopathy[2]

Co-developing and commercializing in the US with AstraZeneca

Accelerated commercial infrastructure build

First Ionis Independent Medicine Launches[1]

Olezarsen

FCS & SHTG

Donidalorsen

HAE

Built an agile commercial operating model

Establishing global access to our medicines

Next Wave of Wholly Owned Medicines

Extensive Neurology Opportunities

Potential breakthrough medicines with transformational profiles

Right-sized resources to grow scalable capabilities

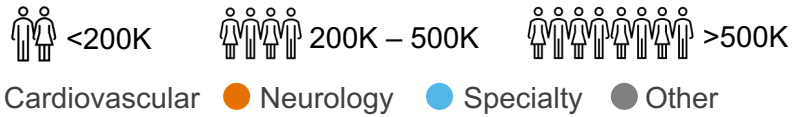
1. Assuming approval. 2. Data planned for ATTR-CM as early as H1:2025

Well Positioned to Deliver Steady Cadence of Potentially Transformational Medicines

Phase 3 Pipeline

	Indication	Prevalence[1]	Next Event[2]
Eplontersen (IONIS / AstraZeneca)	ATTRv-PN		**US approval (2023)** **OUS submissions (2023)**
	ATTR-CM		**Ph3 data (2025)**
Olezarsen (IONIS)	FCS		**NDA filing (2024)**
	SHTG		**Ph3 data (2024)**
Donidalorsen (IONIS)	HAE		**Ph3 data (2024)**
Zilganersen (IONIS)	Alexander disease		**Ph3 data (2025)**
Ulefnersen (IONIS)	FUS-ALS		**Ph3 data (2025)**
Pelacarsen (Novartis)	Lp(a) CVD		**Ph3 data & filing (2025)**
Bepirovirsen (GSK)	HBV		**Ph2b B-Together data (2023)**
IONIS-FB-L$_{Rx}$ (Roche)	IgA nephropathy[3]		**Ph2 data (2023)**
Tofersen (Biogen)	Presymptomatic SOD1-ALS		**Ph3 data (2027)**

1. Market data on file. 2. Timing expectations are based on current assumptions and are subject to change.
3. IONIS-FB-L$_{Rx}$ is also in the Phase 2 GOLDEN study in patients with Geographic Atrophy, with topline data expected in 2024.



Substantial Progress Year to Date

Clinical Data Events

- **Eplontersen:** Phase 3, NEURO-TTRansform 35, 66 & 85-week data, ATTRv-PN
- **Olezarsen:** Phase 3, Balance study data, FCS
- **Donidalorsen:** Phase 2, OLE 1-year data, HAE
- **Donidalorsen:** Phase 2, OLE 2-year data, HAE
- **SPINRAZA:** Phase 4, interim RESPOND data, SMA

Enrollment Achievements

- **Donidalorsen:** Phase 3, OASIS-HAE full enrollment, HAE
- **Eplontersen:** Phase 3, CARDIO-TTRansform full enrollment, ATTR-CM
- **IONIS-FB-L$_{Rx}$:** Phase 2, GOLDEN study full enrollment, GA

Phase 3 Initiations

- **Bepirovirsen:** chronic HBV
- **IONIS-FB-L$_{Rx}$:** IgA nephropathy
- **Zilganersen:** Alexander disease

Regulatory Actions

- **QALSODY:** FDA approval SOD1-ALS
- **Eplontersen:** NDA filing acceptance, ATTRv-PN
  PDUFA: December 22, 2023
- **Eplontersen:** Health Canada filing acceptance, ATTRv-PN
- **Orphan Drug Designations:**
  - Donidalorsen (US)
  - ION356 (US)

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Key Value-Driving Events Today Through 2024[1]

Phase 2 Clinical Data Events

Donidalorsen
OLE 2-year full data, HAE

Bepirovirsen
B-Together data, HBV

IONIS-FB-L$_{Rx}$
Geographic Atrophy

IgA nephropathy

ION582
Angelman syndrome

ION541
ALS

Phase 3 Clinical Data Events

Olezarsen
Balance study full data, FCS

CORE, CORE2, ESSENCE data, SHTG[2]

Donidalorsen
OASIS-HAE data

OASIS-PLUS switch data

Eplontersen
NEURO-TTRansform Week-85 full data, ATTRv-PN

Regulatory Actions

Eplontersen
FDA approval decision, ATTRv-PN

Eplontersen
OUS filings, ATTRv-PN

Olezarsen
FDA approval decision, FCS[3]

EU filing, FCS

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New Product Launches

Eplontersen
ATTRv-PN

Olezarsen
FCS

QALSODY
OUS, SOD1-ALS

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Ionis Innovation Day: Key Takeaways

Drive Next-Level Value for Patients and All Ionis Stakeholders

Jackson,
Angelman Syndrome Patient

Ionis Innovation Day: Key Takeaways

Drive Next-Level Value for Patients and All Ionis Stakeholders

01

Established Wholly Owned Pipeline

Advancing and growing our wholly owned pipeline in focused therapeutic areas, including neurology

Jackson,
Angelman Syndrome Patient

Ionis Innovation Day: Key Takeaways

Drive Next-Level Value for Patients and All Ionis Stakeholders

01

Established Wholly Owned Pipeline

Advancing and growing our wholly owned pipeline in focused therapeutic areas, including neurology

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Integrated Commercial Capabilities in Place

Steady cadence of new potentially **transformational medicines** to the **market**

Jackson,
Angelman Syndrome Patient

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03

Leading Technology

Advancing technology to:

- **Expand existing franchises**
- **Address new therapeutic areas**

Jackson,
Angelman Syndrome Patient

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Drive Next-Level Value for Patients and All Ionis Stakeholders

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Established Wholly Owned Pipeline

Advancing and growing our wholly owned pipeline in focused therapeutic areas, including neurology

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Integrated Commercial Capabilities in Place

Steady cadence of new potentially **transformational medicines** to the **market**

03

Leading Technology

Advancing technology to:

- **Expand existing franchises**
- **Address new therapeutic areas**

04

Strong Financial Foundation Poised for Growth

Multi-billion-dollar revenue opportunity will enable **positive cash flow**

Jackson,
Angelman Syndrome Patient

On the Horizon: Important Medicines for Patients in Need

Poised to Bring Important Medicines to Patients

Onaiza Cadoret

Executive Vice President, Chief Global
Product Strategy & Operations Officer

Realizing the Promise of our Innovative Medicines[1]

Significant Progress Made Toward Realizing our Commercial Vision

Maximize
the Value of our Innovation

- Focus remains on near-term late-stage **commercial opportunities**
- Executing our strategic plans to meet underserved **patients**, drive commercial **success**
- Robust portfolio prioritization creating a **focused**, **high value evergreen portfolio**

Focus
on 2 Core Franchises
Cardiovascular and Neurology

- Exceptional and experienced **talent on board** and focused on **go-to-market execution** in the US
- Opportunistic with **specialty medicines** that have an **attractive** product **profile** for underserved patients

Invest
in Commercial Capabilities
for Wholly Owned Medicines

- Core **capabilities established**
- **Right-sized** resources to grow **scalable capabilities** that enable near and longer-term commercial success

1. Assuming approval.

Key Commercial and Medical Affairs Leadership in Place

Jonathan Birchall
Chief Commercial Officer

Rachel Carnes
Senior Vice President, Global Product Strategy

Chris Kramer
Vice President, Portfolio Planning and Market Insights

Shay Bujanover
Vice President, Medical Affairs

Sheetal Patel
Vice President, US Market Access and Reimbursement

Jason Zwerner
Vice President, Marketing (Olezarsen)

Dawn Henson
Vice President, Marketing (Eplontersen and Donidalorsen)

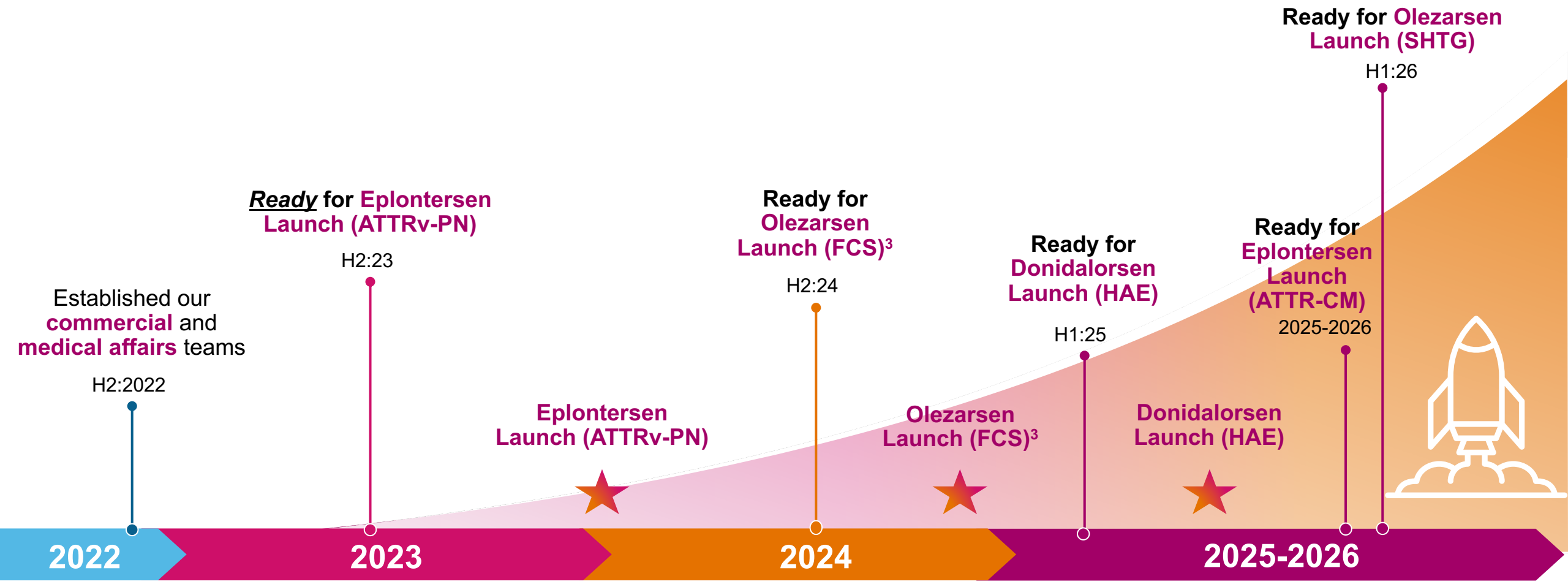
Kara Malewicz
Vice President, New Product Commercialization (Neurology)

Eric Schupp
Executive Director, Patient Services

Cory Varney
Executive Director, Commercial Operations

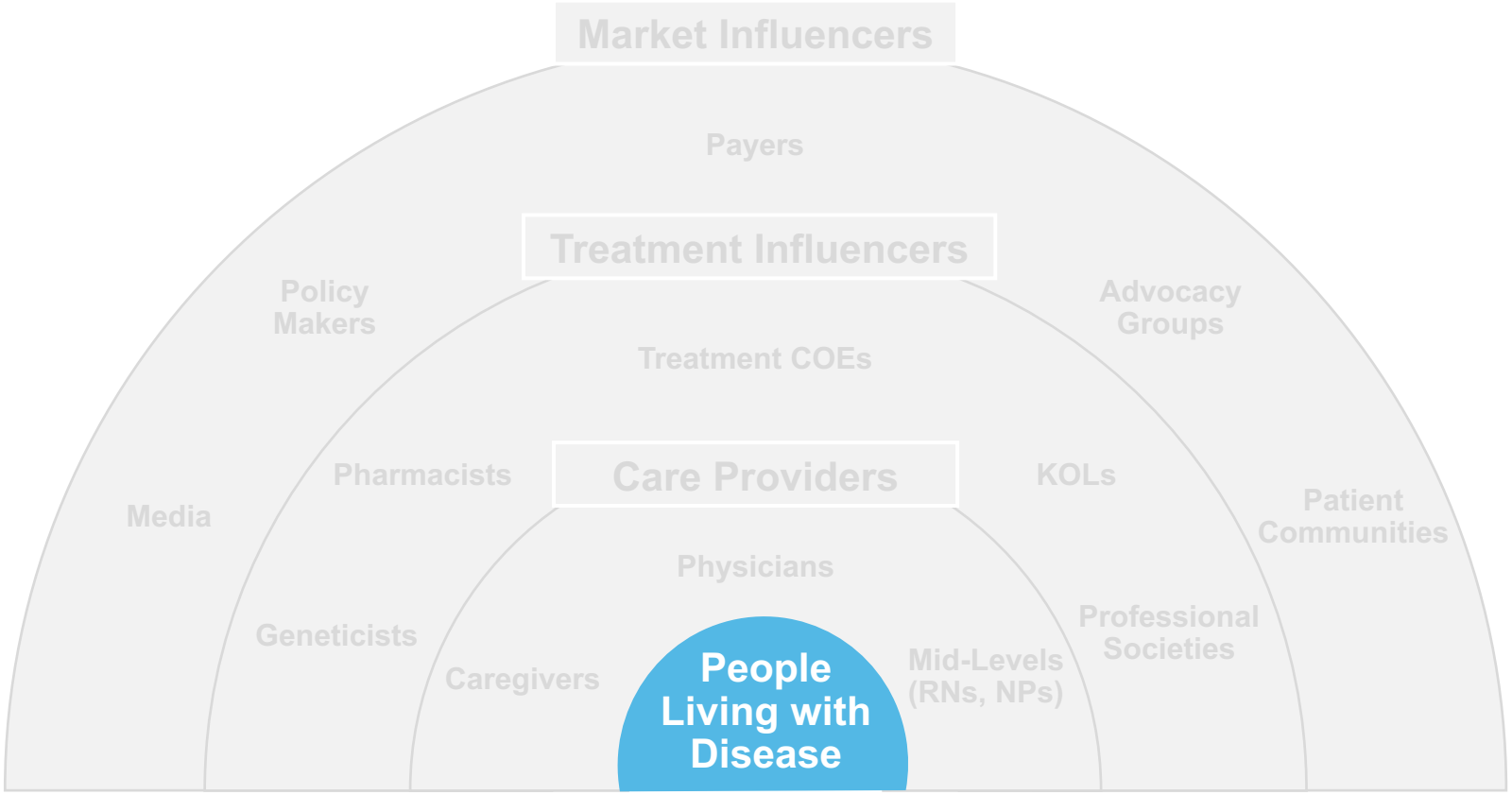
Leo Londono
Executive Director, Omnichannel Customer Engagement

Established Foundational Commercial and Medical Affairs Capabilities as we Begin our Near-Term Launch Ramp Up[1,2]

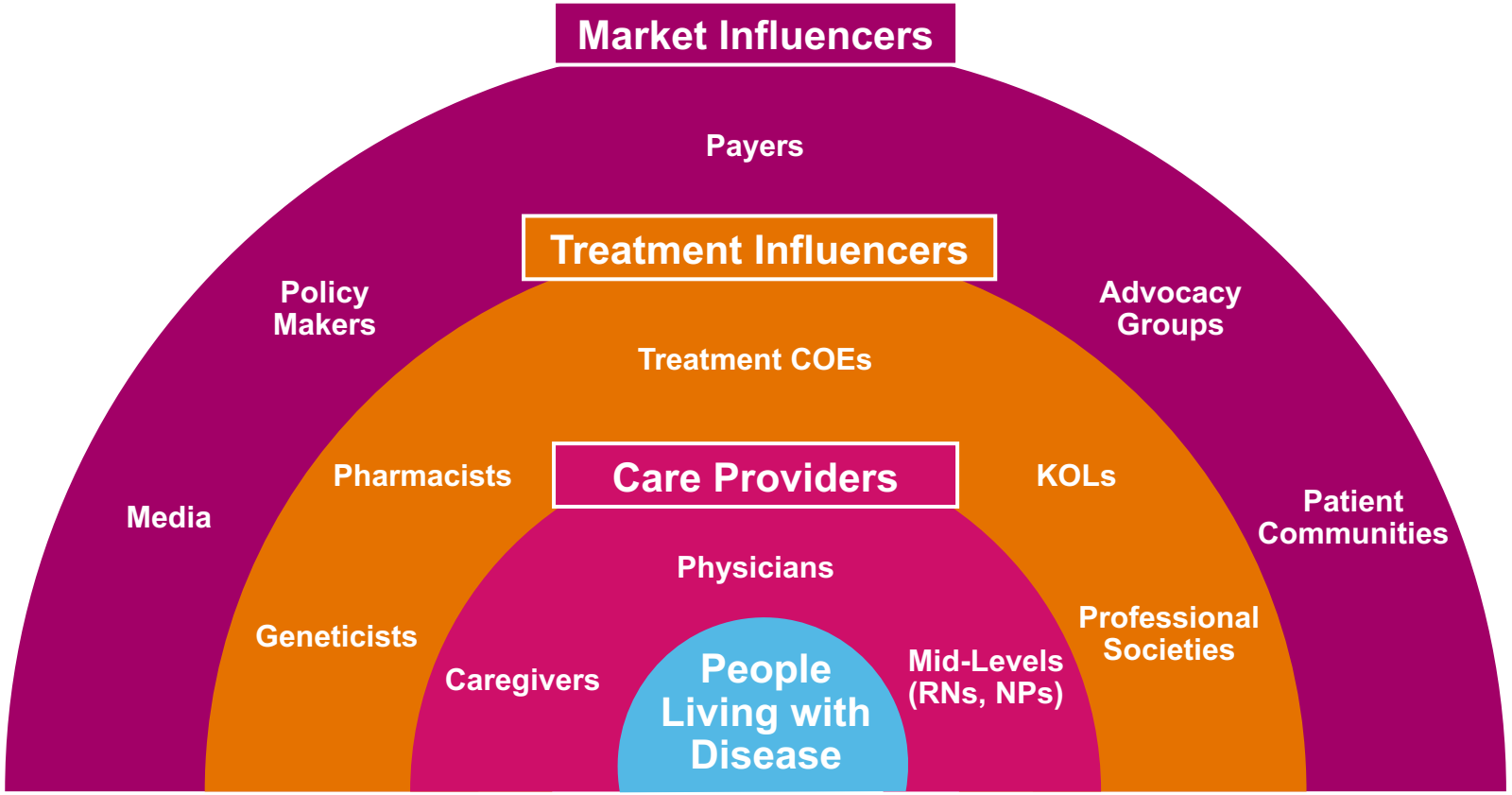


1. Timing expectations based on current assumptions and subject to change 2. Assuming approval. 3. Assuming priority review.

Positioned to Maximize Success Through Innovative Customer Experience



Positioned to Maximize Success Through Innovative Customer Experience



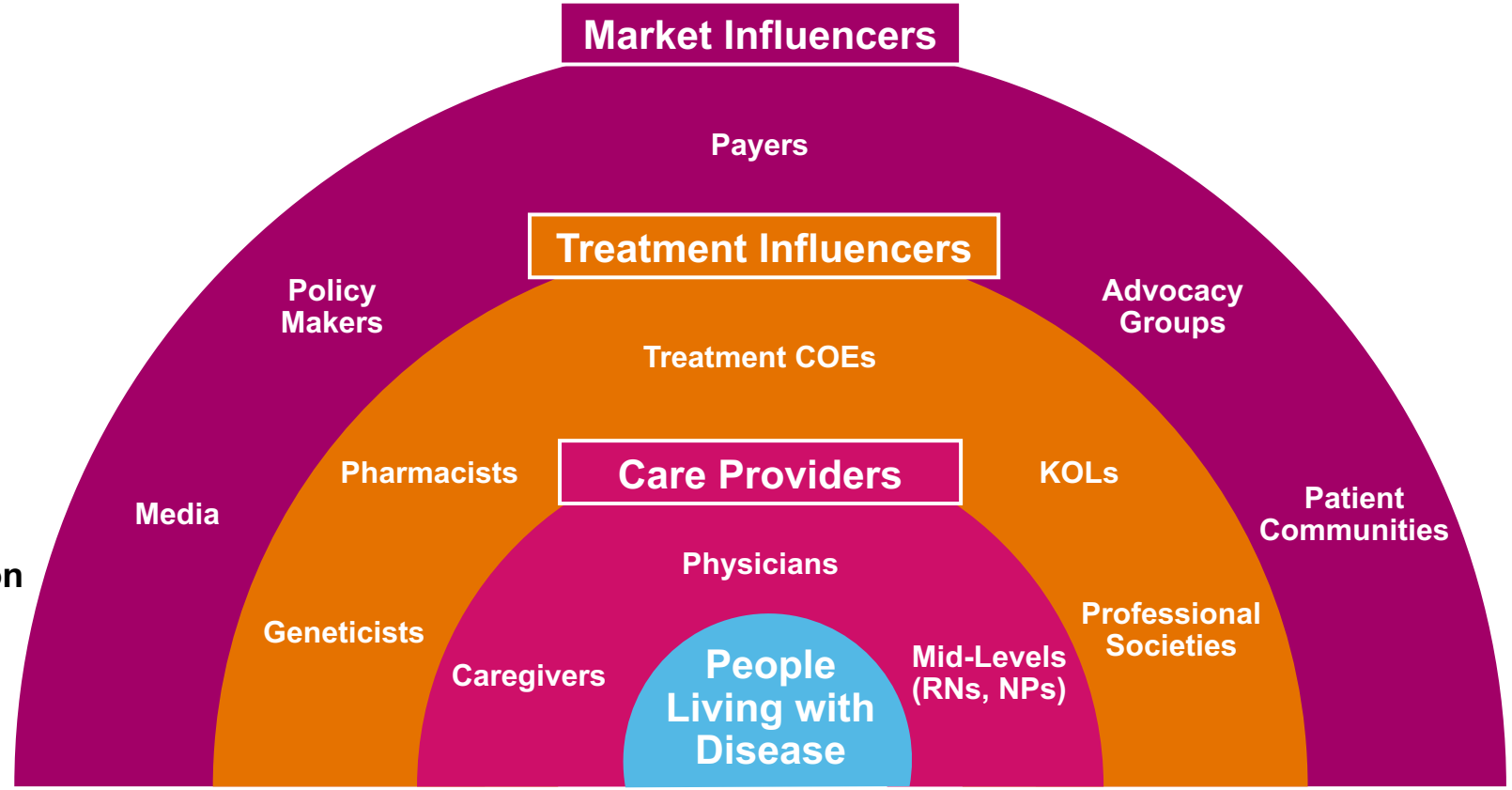
Positioned to Maximize Success Through Innovative Customer Experience

+ Early Payer Engagement Around Value

+ Fully Integrated Access Hub

+ Direct to Patient Education & Activation

+ Dedicated Patient Finding & Identification



+ Optimized Insights, Data Integration & Advanced Analytics

+ Rich Omnichannel & Digital Delivery

+ Industry-Leading Patient Hub Services & Support

+ Optimized Distribution & Delivery

Substantial Opportunity from our Three Near-Term Commercial Medicines[1,2,3]

Eplontersen

Strong efficacy and **safety** data with **self-administration** profile for the global ATTR market

On track for ATTRv-PN **launch** & go-to-market plans for ATTR-CM

Well positioned with Ionis' **ATTR market knowledge &** AstraZeneca's **global scale**

Estimated peak sales: **Multibillion**[4]

Olezarsen

Expected to be a **first-in-class** US treatment for patients with **severely elevated triglycerides**

On track for first independent **launch** in FCS

Independent launch in **larger** SHTG indication **to follow**

Estimated peak sales: **>$1 Billion**

Donidalorsen

Potential **advance in prophylactic treatment** for patients with HAE

On track for independent **launch** in HAE

Attractive **market** with **concentrated prescriber** base

Estimated peak sales: **>$500 Million**

Preparing for Next Wave of Wholly Owned Medicines

1. Global peak sales estimates are based on current assumptions and are subject to change. 2. Profile based on data generated to date. 3. Assuming approval. 4. Estimated global peak sales includes ATTRv-PN and ATTR-CM.

Key Takeaways:

Poised to Bring Important Medicines to Patients

Top Talent in Place

Multiple Upcoming Launches

Unique and Innovative Approach to Bring our Medicines to Patients

Eplontersen

A Potential Treatment of Choice for
Global ATTR Population

ATTR & Eplontersen Program Overview

Sam Tsimikas, M.D.

Senior Vice President,
Global Cardiovascular Development

TTR Amyloidosis (ATTR) Remains an Area of High Need[1,2,3,4]

ATTR

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

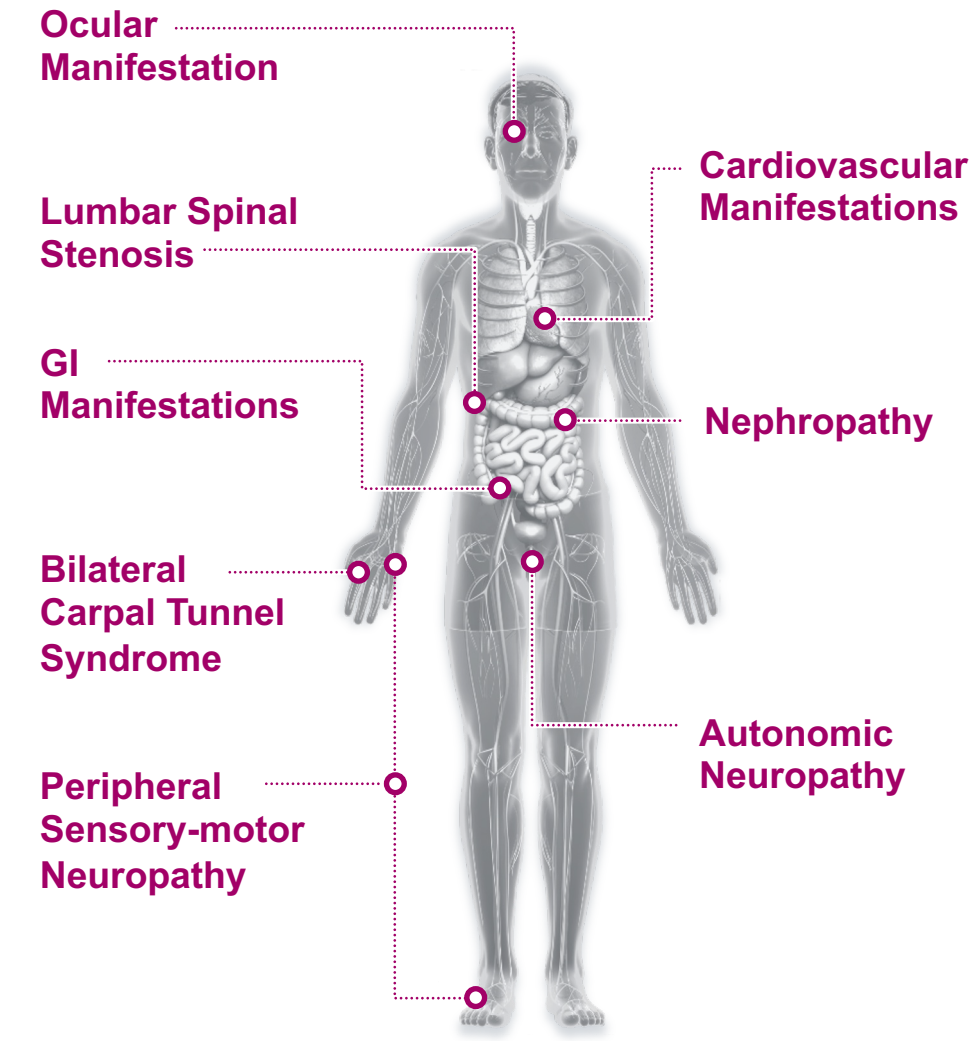
ATTR is caused by **accumulation of misfolded protein that can occur in multiple tissues**, including heart, nerves and GI tract

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.

Eplontersen's Development Program is Designed to Deliver Robust Dataset Supporting Treatment for ATTR[1]

ATTRv Polyneuropathy

neuro TTRansform

Met co-primary + secondary endpoints in Phase 3 with favorable safety and tolerability

NDA accepted, PDUFA date of December 22, 2023

Health Canada accepted New Drug Submission for review

On track for additional **OUS submissions,** including **EU** in **2023**

ATTR Cardiomyopathy

cardio TTRansform

Largest study conducted in ATTR-CM now fully enrolled with >1,400 patients

Positioned to deliver **robust data** in broad patient population

On track for data as early as H1:2025

ATTR

TTRansform beyond

Open-label extension studies in patients with ATTRv-PN and ATTR-CM enrolling

Imaging sub-studies in ATTR-CM to assess the effects on cardiac structure and function underway

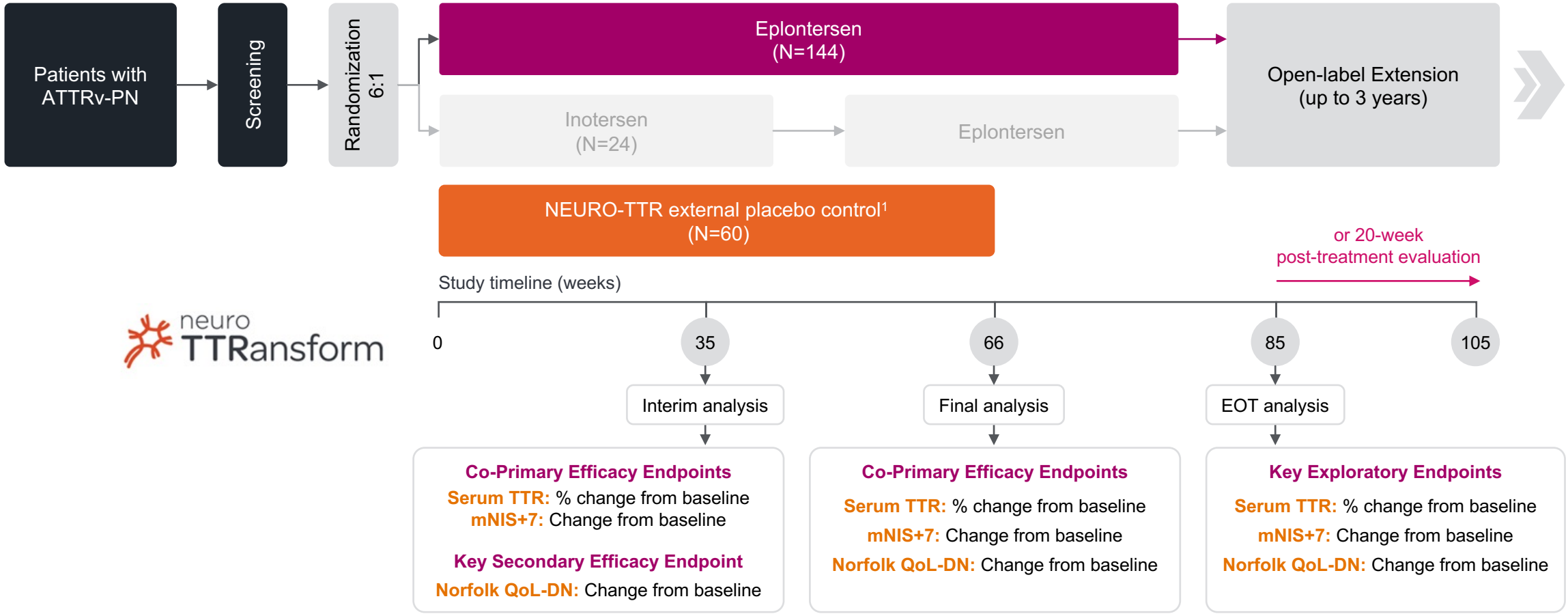
Additional profile-enhancing studies underway

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

ATTRv Polyneuropathy & NEURO-TTRansform

NEURO-TTRansform Study Designed to Demonstrate Benefit in Patients with ATTRv-PN

A Multicenter, Open-label Study in 168 Patients with ATTRv-PN



1. Benson et al, N Engl J Med (2018) 379:22-3 1. Figure adapted from Coelho et al, Neurol Ther (2021) 10:375-89.

Co-Primary Endpoints of NEURO-TTRansform

Serum TTR

TTR Concentration

% change from baseline

— Conservative measure of TTR at just prior to next dose

Composite Neuropathy Impairment Score

mNIS+7[1]

Measures:

— Motor neuropathy

— Sensory neuropathy

— Autonomic neuropathy

Includes:

— Motor, reflex, and sensation deficits scored by neurologist

— Nerve conduction tests

— Full body quantitative sensation testing of small and large fibers

— Autonomic deficit by HRdb[2]

Neuropathy QoL Instrument[3]

Norfolk QoL-DN[3,4]

Sum of 5 Domains:

— Physical functioning/large fiber neuropathy

— Activities of daily living

— Symptoms

— Small fiber neuropathy

— Autonomic neuropathy

1. Total Score, change from baseline at Week-35 and Week-66. 2. HRdb, heart rate response to deep breathing. 3. Secondary endpoint at Week-35 interim analysis. 4. Norfolk Quality of Life-Diabetic Neuropathy questionnaire.

Baseline Characteristics[1,2]

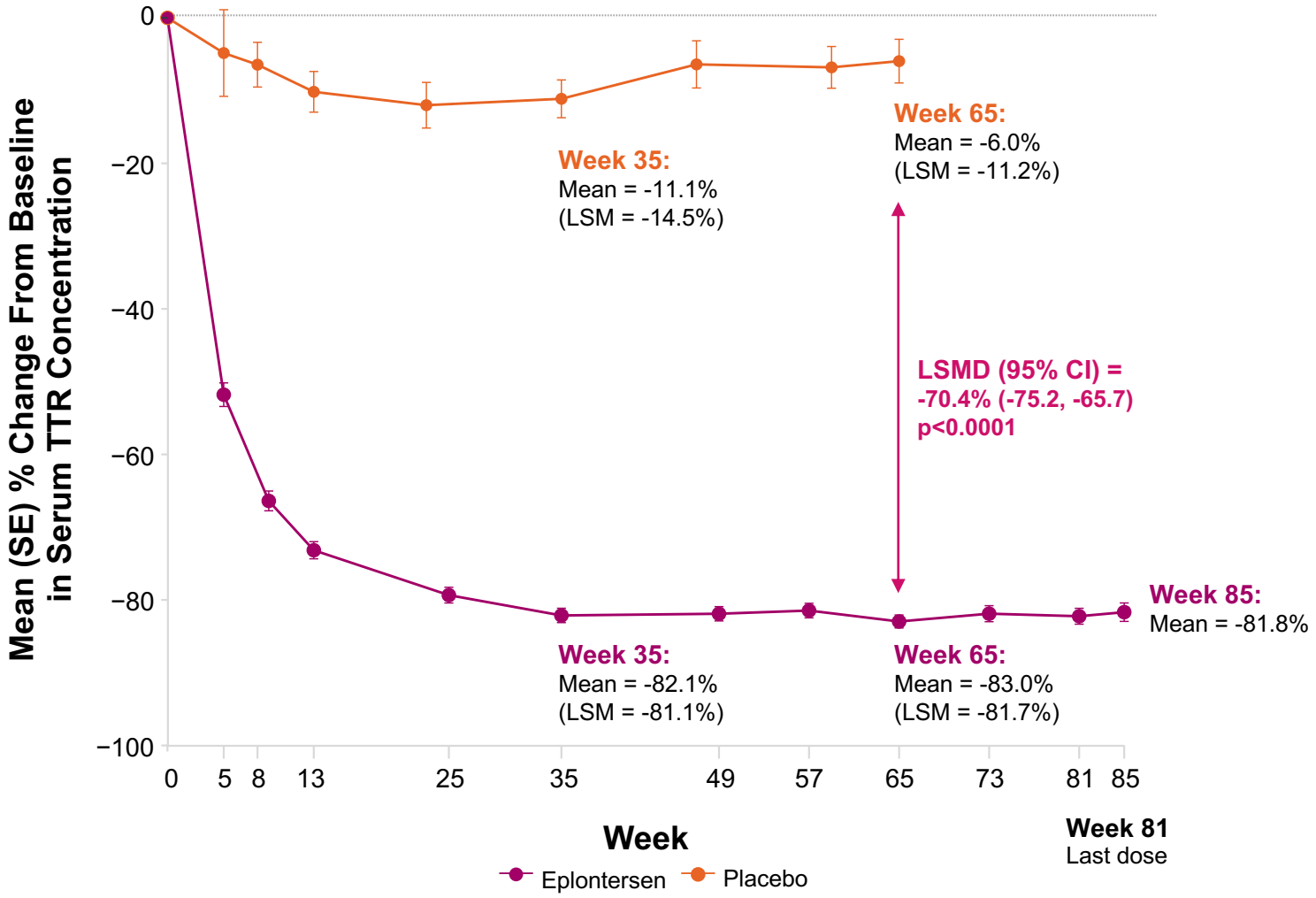
Baseline Characteristics	Placebo	Eplontersen
N	60	144
Age, mean years (SD)	59.5 (14.0)	53.0 (15.0)
Male, n (%)	41 (68.3)	100 (69.4)
Race, n (%)		
White	53 (88.3)	112 (78.3)
Asian	3 (5.0)	22 (15.4)
Black or African American	1 (1.7)	5 (3.5)
Other/Multiple	3 (5.0)	4 (2.8)
Region, n (%)		
Europe	23 (38.3)	54 (37.5)
North America	26 (43.3)	21 (14.6)
So. America/Australasia	11 (18.3)	69 (47.9)
Previous treatment, n (%)		
Tafamidis or Diflunisal	36 (60.0)	100 (69.4)

Baseline Characteristics	Placebo	Eplontersen
N	60	144
Disease stage, n (%)		
Stage 1 – mild	42 (70.0)	115 (79.9)
Stage 2 – moderate (use aids)	18 (30.0)	29 (20.1)
PND score, n (%)		
I (sensory, but can walk)	23 (38.3)	56 (39.2)
II (difficulty walking, no aids)	19 (31.7)	61 (42.7)
IIIA (1 walk stick or crutch)	15 (25.0)	16 (11.2)
IIIB (2 walk sticks or crutches)	3 (5.0)	10 (7.0)
***TTR* variant**, n (%)		
V30M	33 (55.0)	85 (59.0)
Non-V30M	27 (45.0)	59 (41.0)
mNIS+7[2], mean (SD)	74.8 (39.0)	81.3 (43.4)
Norfolk QoL-DN[2], mean (SD)	48.7 (26.7)	44.1 (26.6)

Baseline demographics and clinical characteristics were generally well balanced between groups

1. Published in *JAMA*. 2. mNIS+7 maximum 346 points; Norfolk QoL-DN maximum 136 points.

Eplontersen Treatment Resulted in Substantial and Sustained Reductions in Serum TTR Concentration Compared to Baseline Through Week-85[1,2,3]



1. Results from NEURO-TTRansform study, Primary endpoint at Week-66 compared to external placebo. Data reported at Week-85 are exploratory; 2. The statistical analysis of LSM percent change from baseline is based on a mixed effects model with repeated measures (MMRM) adjusted by propensity score weights with fixed categorical effects for treatment, time, treatment-by-time interaction, disease stage, V30M variant, previous treatment, and fixed covariates for the baseline value and the baseline-by-time interaction. LSM: Least Square Mean; LSMD: Least Square Mean Difference; SE: Standard Error. 3. Published in *JAMA*.

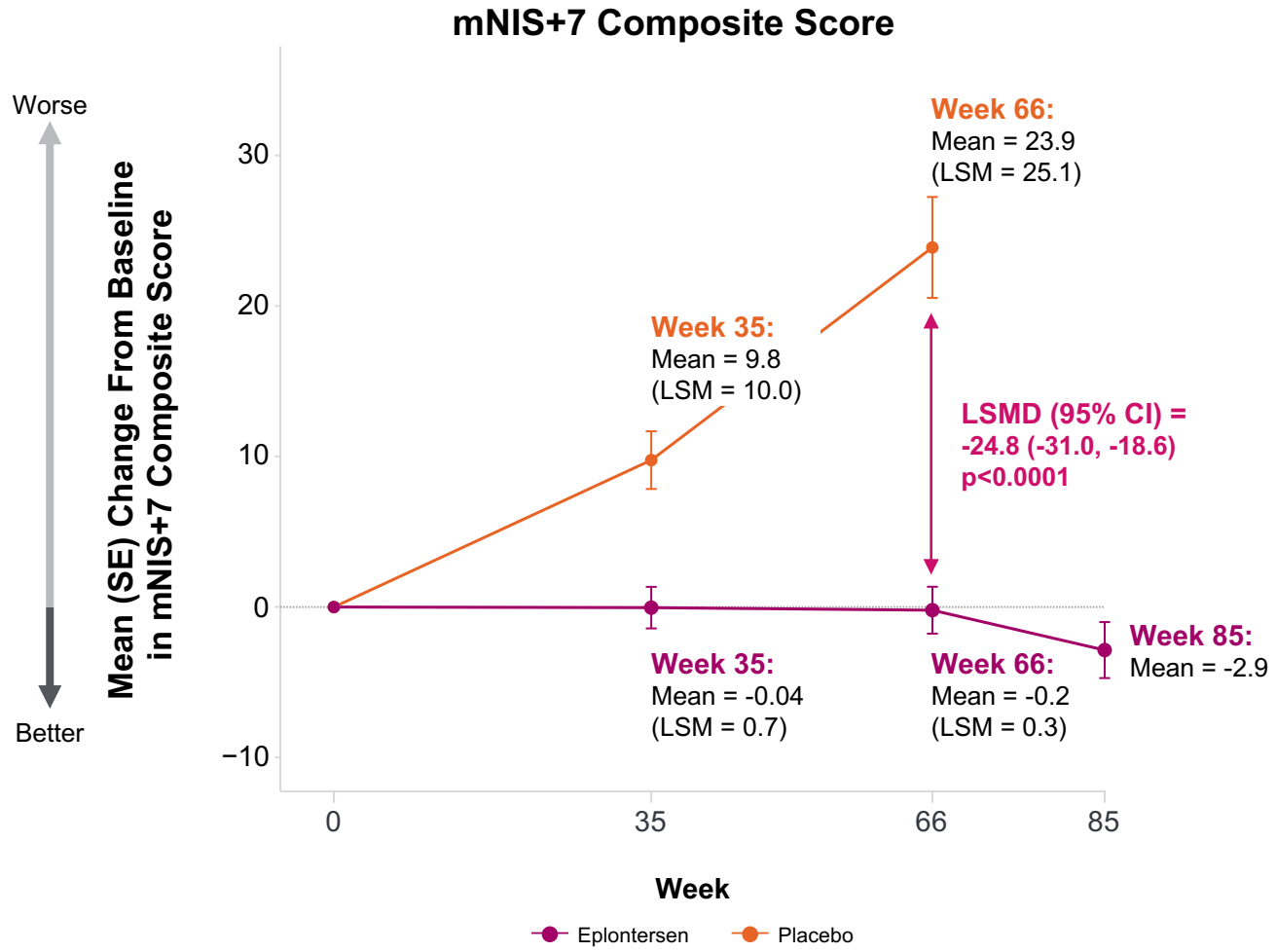
Eplontersen Continued to Halt Neuropathy Progression Through 85 Weeks[1,2,3]

53% of treated patients showed **improvement** in neuropathy at Week-66 compared to baseline[3]

- Greater proportion of patients continued to show **improvement in neuropathy** impairment through Week-85

Eplontersen treatment effect was **consistent** across:

- Prespecified **subgroups**; and
- mNIS+7 **components**



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Eplontersen Continued to Improve Quality of Life Through 85 Weeks[1,2,3]

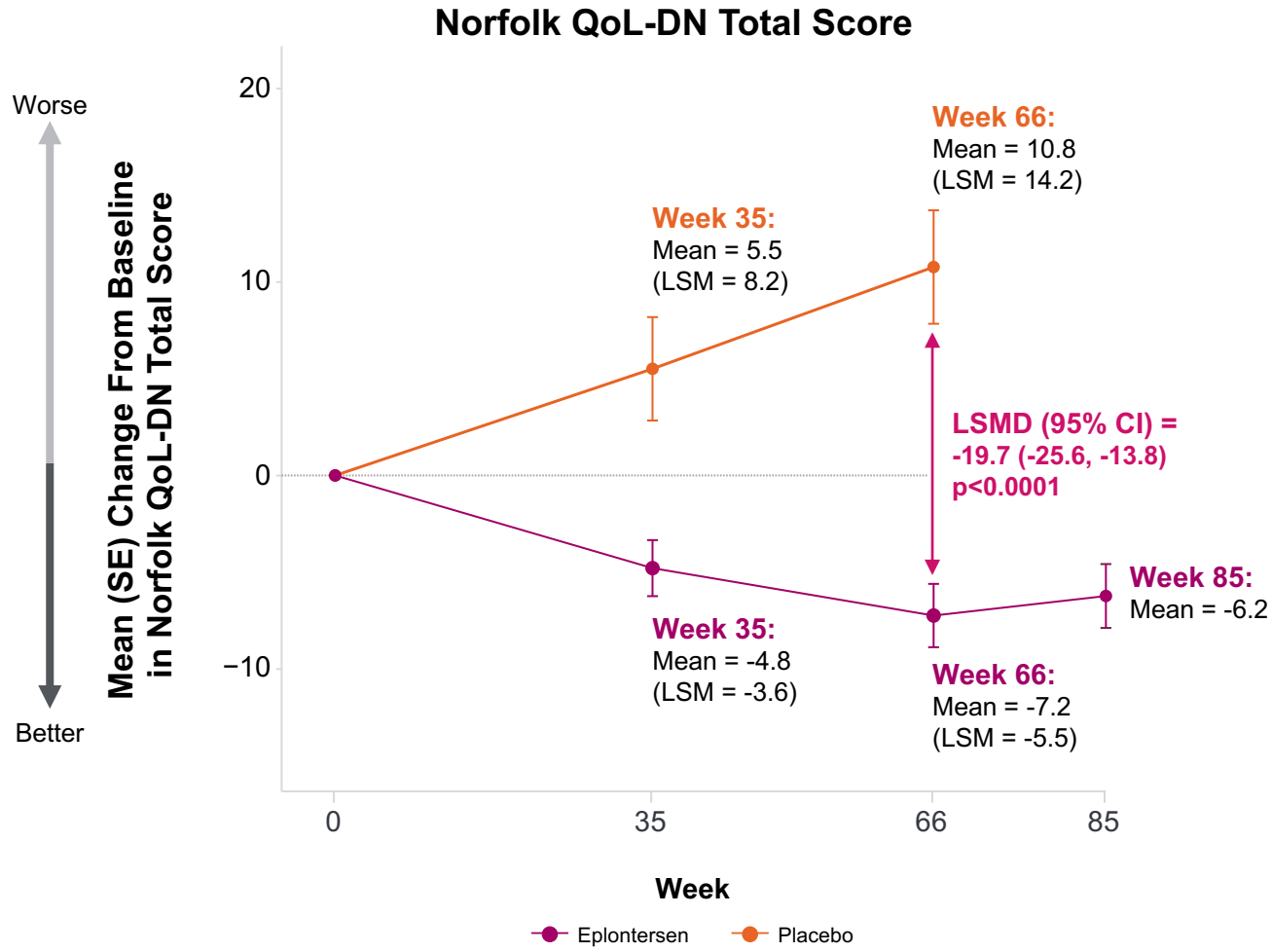
65% of treated patients showed **improvement** in QoL at Week-66 compared to baseline[3]

— Substantial number of patients continued to show **improvement in QoL** through Week-85

Eplontersen treatment effect was **consistent** across:

— Prespecified **subgroups**; and

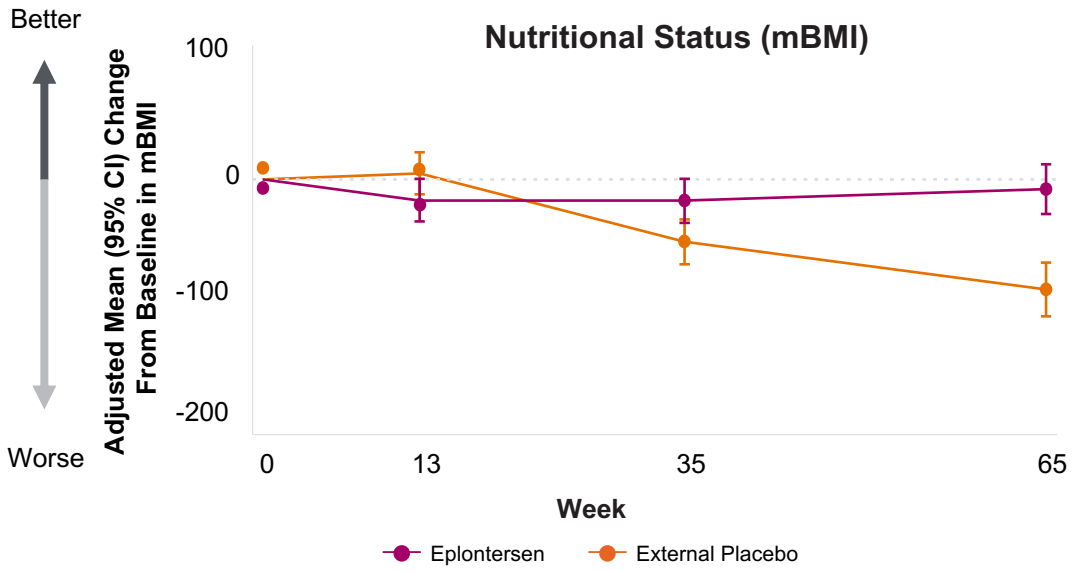
— Norfolk QoL **domains**



1. Results from NEURO-TTRansform study, Primary endpoint at Week-66 compared to external placebo. Data reported at Week-85 are exploratory; 2. The statistical analysis of LSM change from baseline is based on a mixed effects model with repeated measures (MMRM) adjusted by propensity score weights with fixed categorical effects for treatment, time, treatment-by-time interaction, disease stage, V30M variant, previous treatment, and fixed covariates for the baseline value and the baseline-by-time interaction. 3. Responder rates, defined as study completers, were 64.8% for Norfolk QoL-DN in the eplontersen group and 23.1% in the external placebo group. Overall, 57.6% of patients treated with eplontersen improved from baseline in Norfolk QoL-DN; in the external placebo group, 20.0% improved. LSM: Least Square Mean; LSMD: Least Square Mean Difference. SE: Standard Error.3. Published in *JAMA*

Eplontersen Achieved Statistical and Clinical Significance for All Secondary Endpoints at Week-66 Compared to Placebo[1]

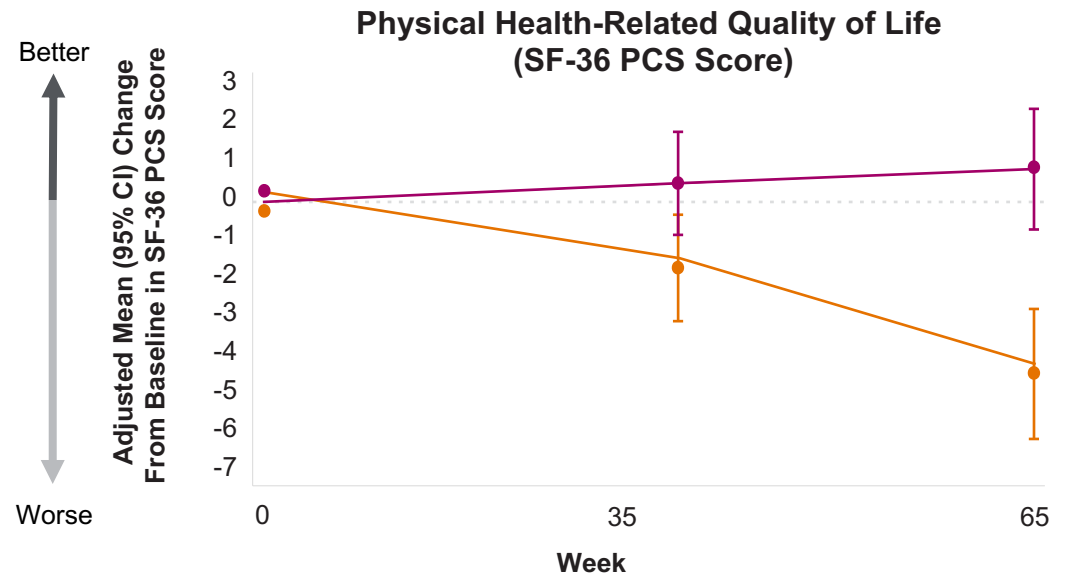
Nutritional status measured by mBMI remained relatively stable with eplontersen and decreased with placebo



Additionally:

- Symptom severity measured by NSC score remained stable with eplontersen and increased with placebo
- Disability/mobility measured by PND score improved or remained stable with eplontersen compared to placebo

Physical health measured by SF-36 PCS score remained stable with eplontersen and decreased with placebo



1. Results from NEURO-TTRansform study, secondary endpoints at Week-66 compared to external placebo. CI, confidence interval; LSMD, least-squares mean difference; mBMI, modified body mass index; PCS, Physical Component Summary; SF-36, 36-item Short Form Survey; NSC, Neuropathy Symptom and Change; PND, Polyneuropathy Disability. 1 mBMI, calculated as BMI (kg/m2) × serum albumin (g/L), assesses nutritional status, with higher scores indicative of better nutritional status.
3. Published in *JAMA*.

Eplontersen Continued to Demonstrate a Favorable Safety and Tolerability Profile Through 85 Weeks[1,2]

Incidence, n (%)	Placebo	Eplontersen Week 66	Eplontersen Week 85
N	60	144	144
Any TEAE	60 (100)	140 (97.2)	141 (97.9)
Related to study drug	23 (38.3)	53 (36.8)	55 (38.2)
Leading to study drug discontinuation	2 (3.3)	6 (4.2)	8 (5.6)
TEAE of special interest	14 (23.3)	41 (28.5)	43 (29.9)
Ocular events potentially related to Vit A deficiency	12 (20.0)	39 (27.1)	41 (28.5)
— Ocular events excluding lab TEAEs of Vit A decrease or deficiency	9 (15.0)	24 (16.7)	26 (18.1)
Thrombocytopenia	1 (1.7)	3 (2.1)	3 (2.1)
Glomerulonephritis	2 (3.3)	0	0
Other TEAE of interest	48 (80.0)	87 (60.4)	93 (64.6)
Any serious TEAE	13 (21.7)	21 (14.6)	27 (18.8)
Related to study drug	1 (1.7)	0	0
Fatal TEAE	0	2 (1.4)	3 (2.1)
— Related to study drug	0	0	0

No SAEs
were related to study drug

No imbalance of ocular events
excluding vitamin A decrease or deficiency

3 non-drug related deaths
in the eplontersen group, all related to known sequelae of ATTR amyloidosis[3--7]

1. External placebo concluded at Week-66 while eplontersen patients remained on treatment and could accrue additional events; 2. Presented at AAN 2023. 3. Cavallaro et al, Neurology (2016) 87:750-1; 4.Yamada et al, Prog Mol Biol Transl Sci (2012) 107:41-78; 5.Yamashita et al, Neurology (2008) 70:123-28; 6.Ellie et al, Neurology (2001) 57:135-7; 7.Porcari et al, Cardiovasc Res (2023) 118:3517-35.

Eplontersen: Well Positioned to Address Underserved ATTRv-PN Patients Globally[1,2,3]

Attractive Clinical Profile[3]

Met co-primary and key secondary endpoints[4,5,6]

Halted neuropathic disease progression and **improved QoL** through Week 85[3-7]

Substantial number of patients **improved neuropathy impairment and QoL** through Week 85[3-7]

Favorable safety and tolerability profile[3]

Next Steps

Planning to **launch** first **in the US**; PDUFA December 22, 2023

Preparing additional OUS regulatory submissions this year and next year

— Currently under review in Canada

1. Timing expectations based on current assumptions and subject to change. 2. Assuming approval. 3. Based on data generated to date and published in *JAMA*. 4. Co-primary and secondary endpoints achieved at Week-66 compared to external placebo. Data reported at Week-85 are exploratory. 5. Primary endpoints at Week-66, Norfolk QoL was a secondary endpoint at Week-35. 6. mBMI, modified body mass index; PCS, Physical Component Summary; SF-36, 36-item Short Form Survey, NCS, neuropathy symptom and change, PND, polyneuropathy disability score. 7. Data reported at Week-85 are exploratory.

ATTR Cardiomyopathy & CARDIO-TTRansform

Largest, Most Comprehensive Phase 3 Study in Patients with ATTR Cardiomyopathy

cardio TTRansform

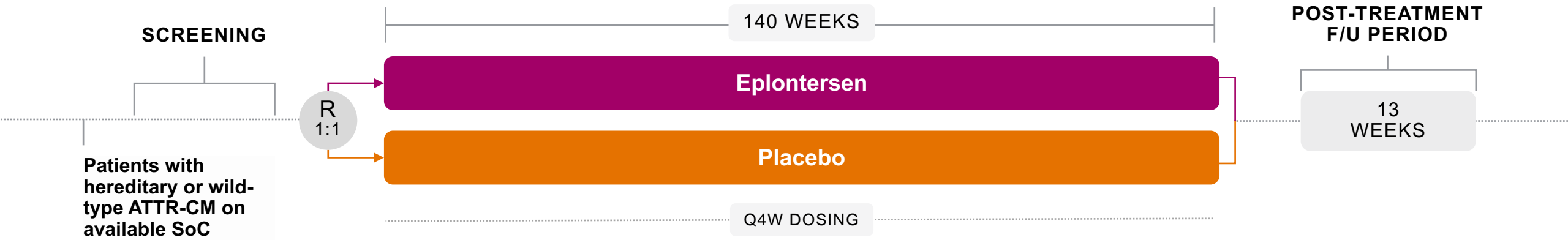
DESIGN

A global, randomized, double-blind, placebo-controlled study in >1,400 patients with hereditary or wild-type TTR amyloid cardiomyopathy

Imaging sub-studies in ATTR-CM to assess the effects on cardiac structure and function

PRIMARY ENDPOINT

Cardiovascular death & frequency of cardiovascular clinical events at Week 140 (~32 months)



Completed enrollment in July 2023 • Data as early as H1:2025[1]

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

Enhancing Studies: MRI Sub-Study

cardio TTRansform

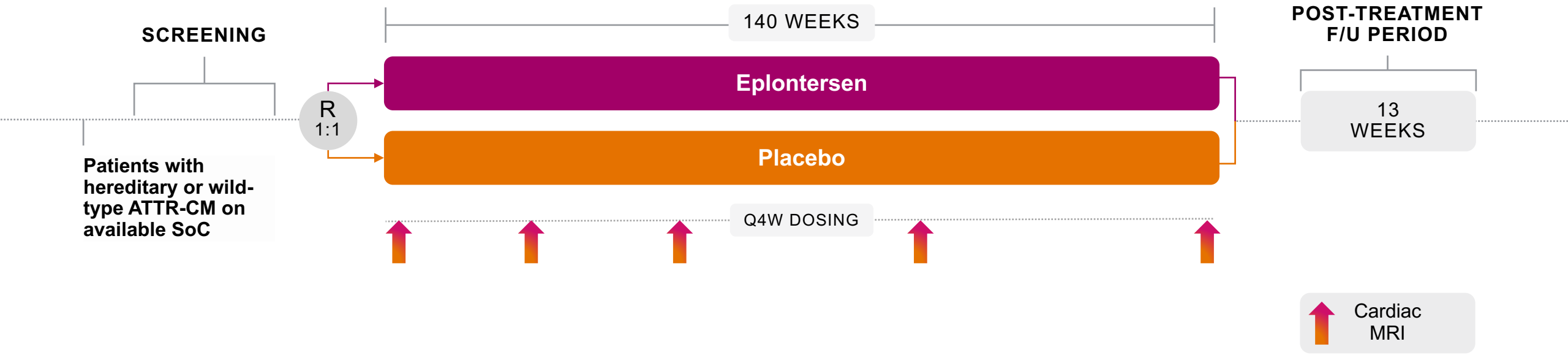
DESIGN

Imaging **sub-studies** in ATTR-CM to assess the effects on **cardiac structure** and **function**:

- 128 patients in CARDIO-TTRansform in US, EU and UK; fully enrolled
- Cardiac MRI at baseline, week 25, 49, 97 and 140

PRIMARY OBJECTIVE

To **measure amyloid burden** (extracellular volume, or ECV) over time



Enhancing Studies: Scintigraphy Sub-Study

cardio TTRansform

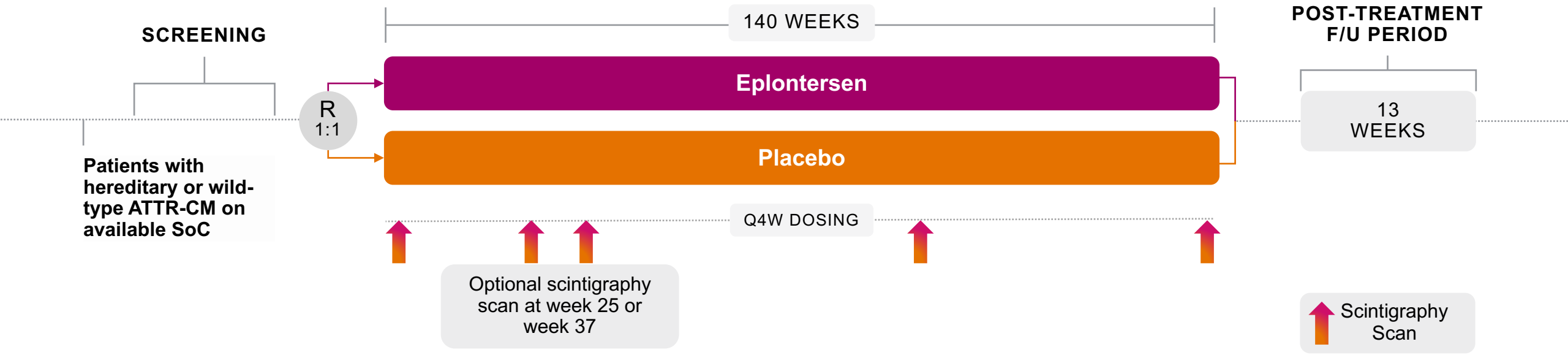
DESIGN

Imaging **sub-studies** in ATTR-CM to assess the effects on **cardiac structure** and **function**:

- In up to 150 patients in CARDIO-TTRansform in US, UK and Spain; underway
- Scintigraphy at baseline, week 25/37 (optional), week 97 and 140

PRIMARY OBJECTIVE

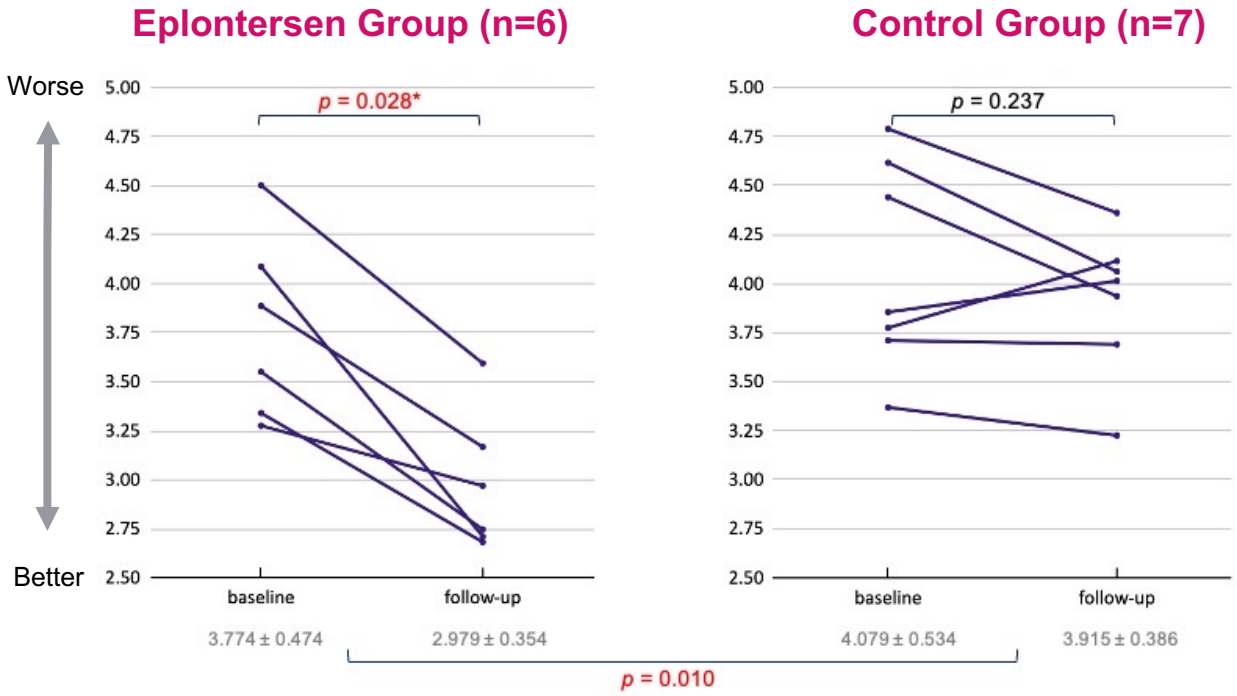
Examine **changes in amyloid myocardial burden** using the Perugini grade score method



Encouraging Taiwan Sub-Study Results from NEURO-TTRansform in ATTRv-Mixed Patients with Cardiac Involvement[1]

A Taiwanese site analyzed a cohort of ATTR-CM patients in NEURO-TTRansform along with a control group who had not received eplontersen, inotersen, tafamidis or patisiran

Changes in Volumetric Heart/Lung Ratio on 99mTc-PYP[2]



- Median follow-up: 544 days
- **Eplontersen-treated** group showed a **significantly greater decrease** in volumetric **H/L ratio** compared to the control group (-20.7% ± 7.8% vs -3.4% ± 8.1%, p = 0.010)

1. ESC presentation (2023). 2. 99mTc-PYP: technetium-99m-pyrophosphate

Robust Development Program & Compelling Data Generated Potentially Position Eplontersen to be the Preferred Treatment for ATTR

ATTRv Polyneuropathy

neuro TTRansform

ATTR Cardiomyopathy

cardio TTRansform

Ready to Bring Eplontersen to Patients

Onaiza Cadoret

Executive Vice President, Chief Global Product Strategy & Operations Officer

Positioned to Bring A Needed Advance to ATTR Patients

Underserved and **Growing Market**

Potential for Eplontersen to be Preferred Treatment

Global Partnership with **AstraZeneca** Complements **Ionis'** Rare Disease **Capabilities**

Eplontersen

A Potential Treatment of Choice for a Largely Underserved Patient Population[1,2,3]

Potential to be the **treatment of choice** for the **global ATTR population** with monthly **self-administered** auto-injector profile

Our goal is to become the **preferred choice for patients who are new to silencer treatment**

Expanding Patient Population

	Indication	Patients[3,4]
	ATTR	~500K
CM	wtATTR & ATTRv	300K-500K
PN	ATTRv-PN + Mixed	40K

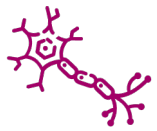
Currently <20% of ATTR patients are treated[2]

1. ATTRv-PN potential approval this year. 2. Market data on file.; 3.Conceição I et al. J Peripher Nerv Syst. 2016;21:5-9. 4. Ando Y et al. Orphanet J Rare Dis. 2013;8:31.

Eplontersen is Poised to be the Preferred Treatment Option for ATTR

Strong Clinical Profile[1]

Targeted Knockdown



Targeted TTR knockdown at the source with **consistent** and **sustained suppression**

Halted Disease Progression

Demonstrated **halting of neuropathy disease progression**

Sustained Benefit

Significant improvements in measures of **neuropathy** and **quality of life** in a substantial number of patients through **85 weeks**

Largest Data Set

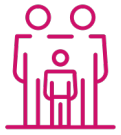
Largest clinical **trial** in **ATTR-CM** which will include **CV outcome data**

Significant Commercial Reach

Global Partnership

Alliance with a global footprint & **industry leader** in CVD medicines

Patient Support



Seamless **patient support** leveraging **Ionis' deep understanding** of these patients and the physicians who treat them

Administration Profile

Monthly **self-administration** with auto-injector

1. Based on data generated to date and published in *JAMA*.

Executing Successful Strategy to Provide Eplontersen for ATTR to Patients in Need [1,2,3]

IONIS + AstraZeneca

Deep expertise in ATTR, patient identification tools, and rare disease marketing

Vast global-scale and industry leader commercializing CVD medicines

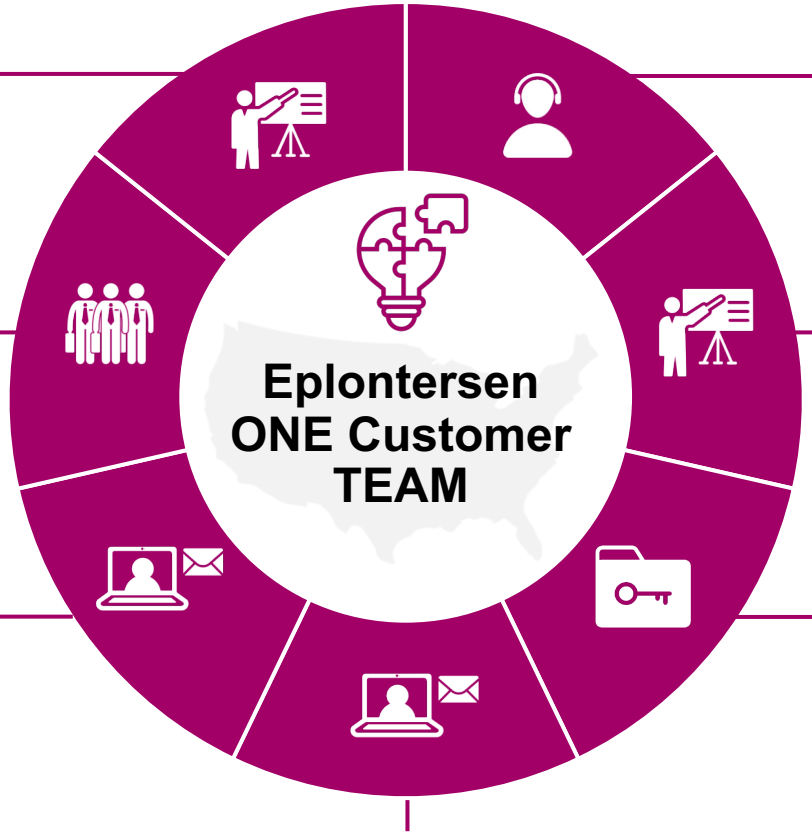
Shared Strategy to Bring Eplontersen to Patients with ATTR Around the Globe

ATTR Represents an Estimated >$10B Market Opportunity Worldwide[4]

1. Market data on file 2. Timing expectations and global peak sales estimates are based on current assumptions and are subject to change. 3. Assuming approval 4. Estimated overall market opportunity includes ATTRv-PN and ATTR-CM.

Commercial Operations Designed to Drive Rapid & Broad Uptake

Majority of Capabilities Deployed and in the Field



Field Medical Directors/ Medical Science Liaisons (MSLs)

Patient Education Managers (PEMs)

Field Sales

Access 360 Patient Case Managers

Regional Customer Directors

Payer and Integrated Delivery Network (IDN) Teams

Field Reimbursement Managers (FRMs)

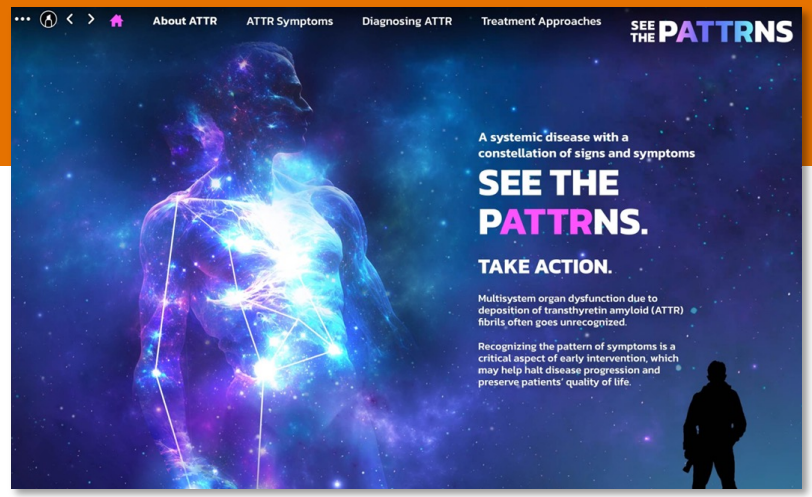
Omnichannel

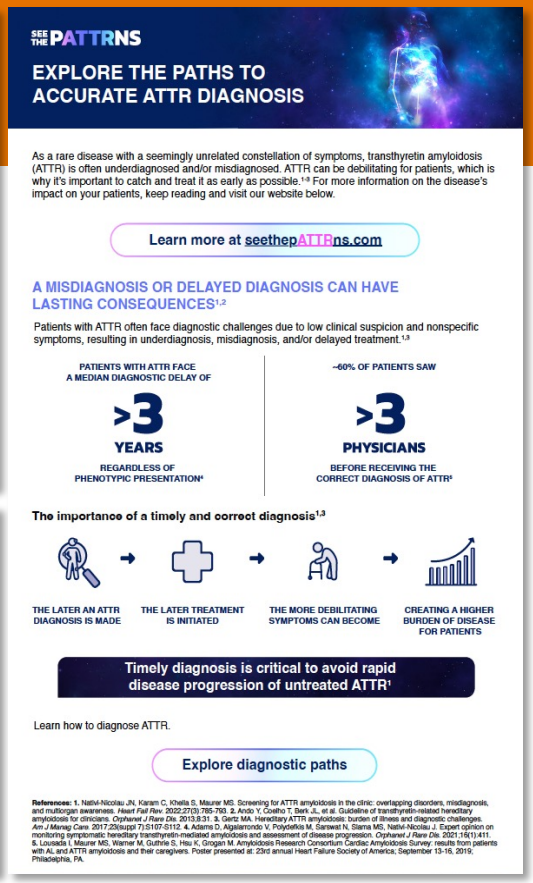
Building Launch Momentum Through Disease Awareness Campaign

JAMA | Original Investigation

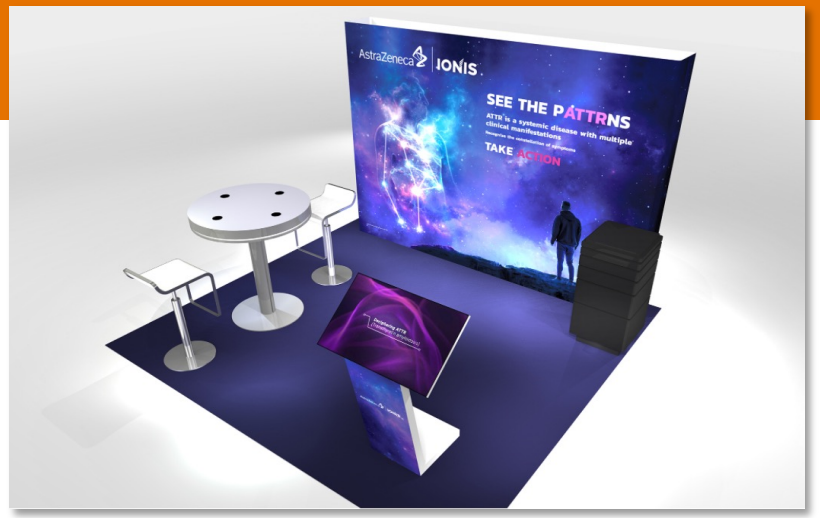
Eplontersen for Hereditary Transthyretin Amyloidosis With Polyneuropathy

Data Published in Top-Tier Journal





Extensive HCP Education



Robust Congress Presence

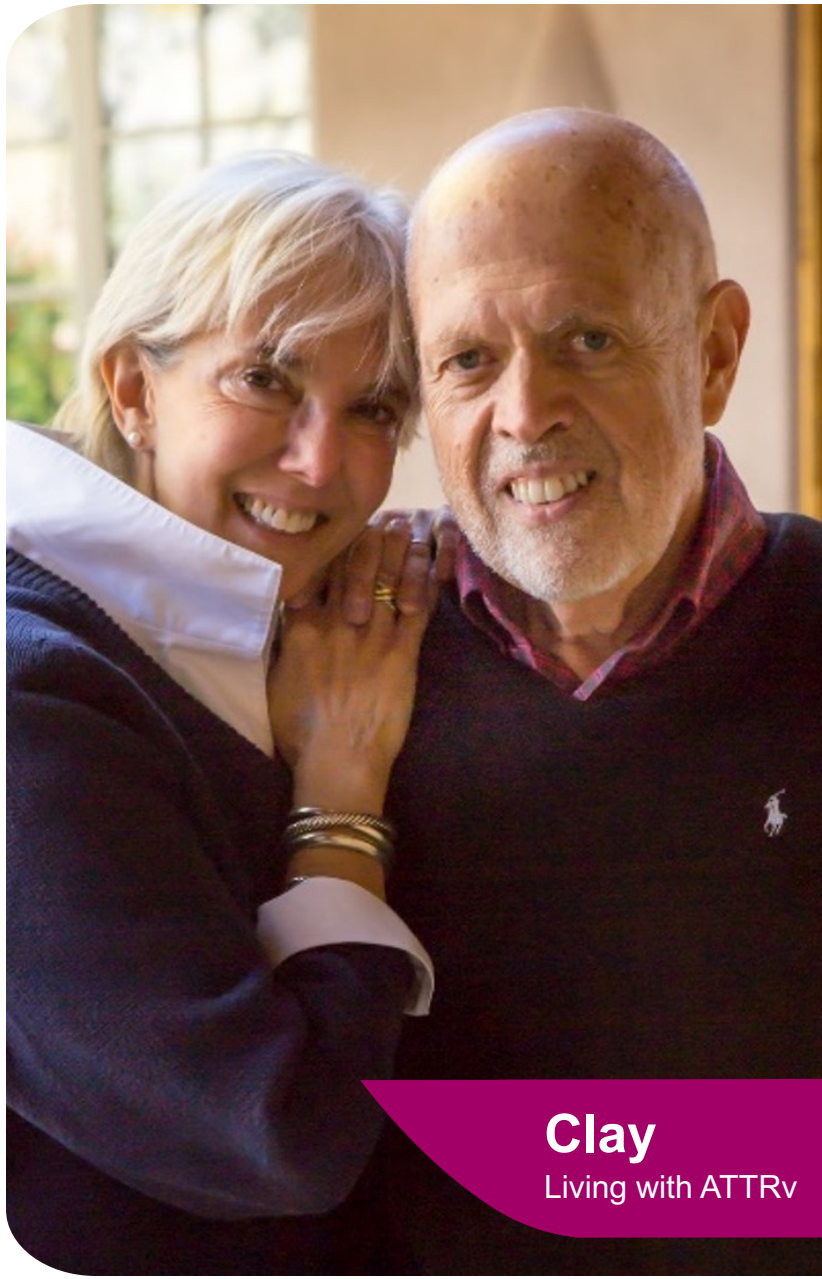
CLICK HERE: seethepatterns

Patient & Caregiver Support to Assist Patients Throughout Their Journey

Diagnostic support through **Genetic Testing**

Patient Education Managers to work closely with **Health Care Team** to deliver **Education and Customized Support** to patients

Self-Administration Training program to provide confidence to patients



Self-Administration Preferred by HCPs & For Patients it is the More Important Factor than Dosing Frequency[1]

66% of patients indicated that their primary caregiving need is to have someone **accompany them to the HCP office**

66% of HCPs believe that needing the assistance of a caregiver has **a significant negative impact on the lives of people living with ATTR**

48% of patients stated that traveling to and from an HCPs office for medication administration **negatively impacts their life**

ATTRv Patient Responses to Eplontersen's Anticipated Product Profile

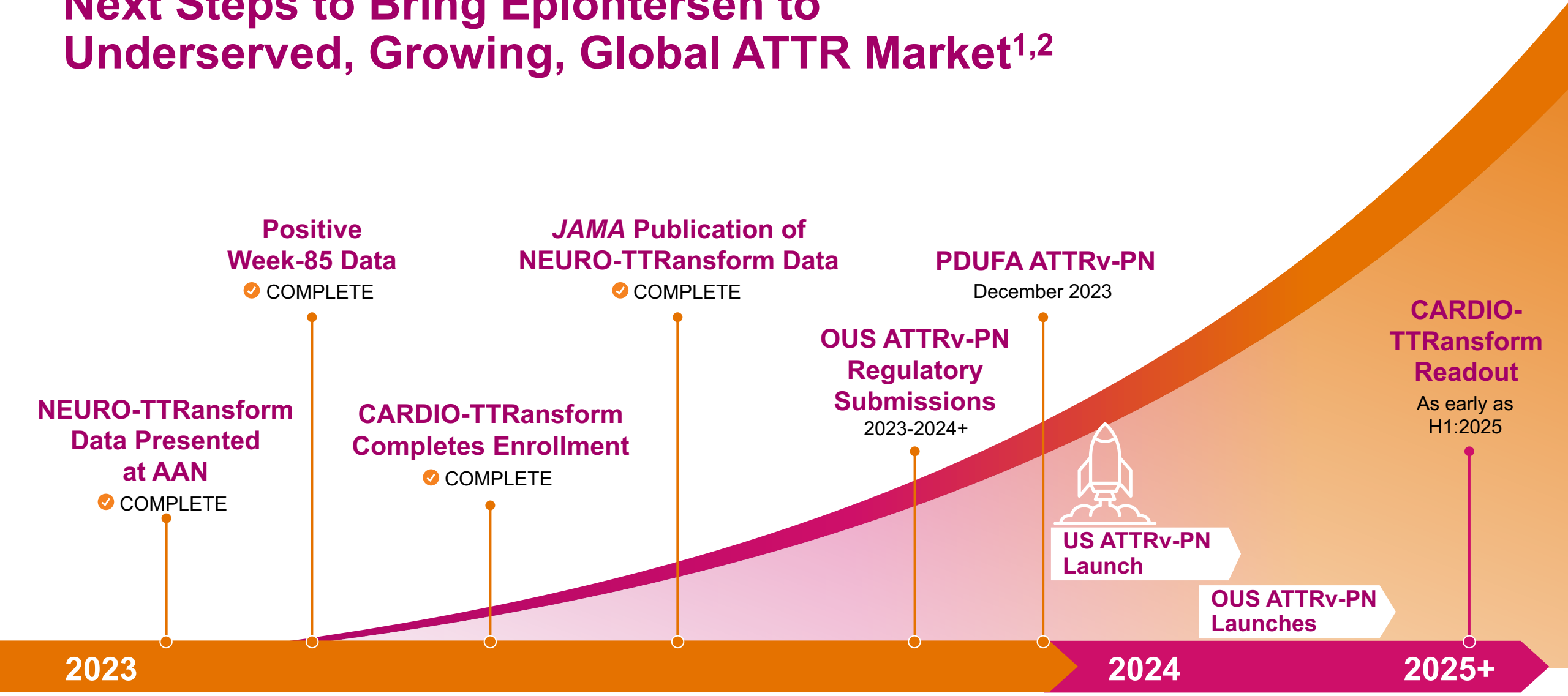
> With my current therapy I have to **miss my work for one entire day**. And I am also very tired in addition to the **financial burden**, because it's expensive to go back and forth.

> **I like the once-a-month dosing**. That's easy and practical to commit to. I have **no issues with self-administering.**

> … will **reduce the number of trips** I have to make to the clinic. At the same time, I don't have to rely on extra help. **I am able to manage the treatment myself.**

1. Market Research (Ipsos 2023).

Next Steps to Bring Eplontersen to Underserved, Growing, Global ATTR Market[1,2]



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

Coming Soon: Eplontersen, A Potential Treatment of Choice for ATTRv-PN

Halted neuropathy progression and improved QoL with favorable safety profile through Week-85[1]

At-home self-administration with autoinjector

Uniquely poised to **deliver benefit** to underserved patient population

"Not one day goes by where I'm not grateful that I'm **as healthy as I am** and I don't have to go through what my dad did."

1. Based on data generated to date and published in *JAMA*. 2. Subject to approval, PDUFA December 22,2023.

Olezarsen

A Potential New Standard-of-Care for FCS and SHTG

Severe Hypertriglyceridemia and Familial Chylomicronemia Syndrome: Unmet Needs and Current Treatment Landscape

Henry N. Ginsberg, M.D.

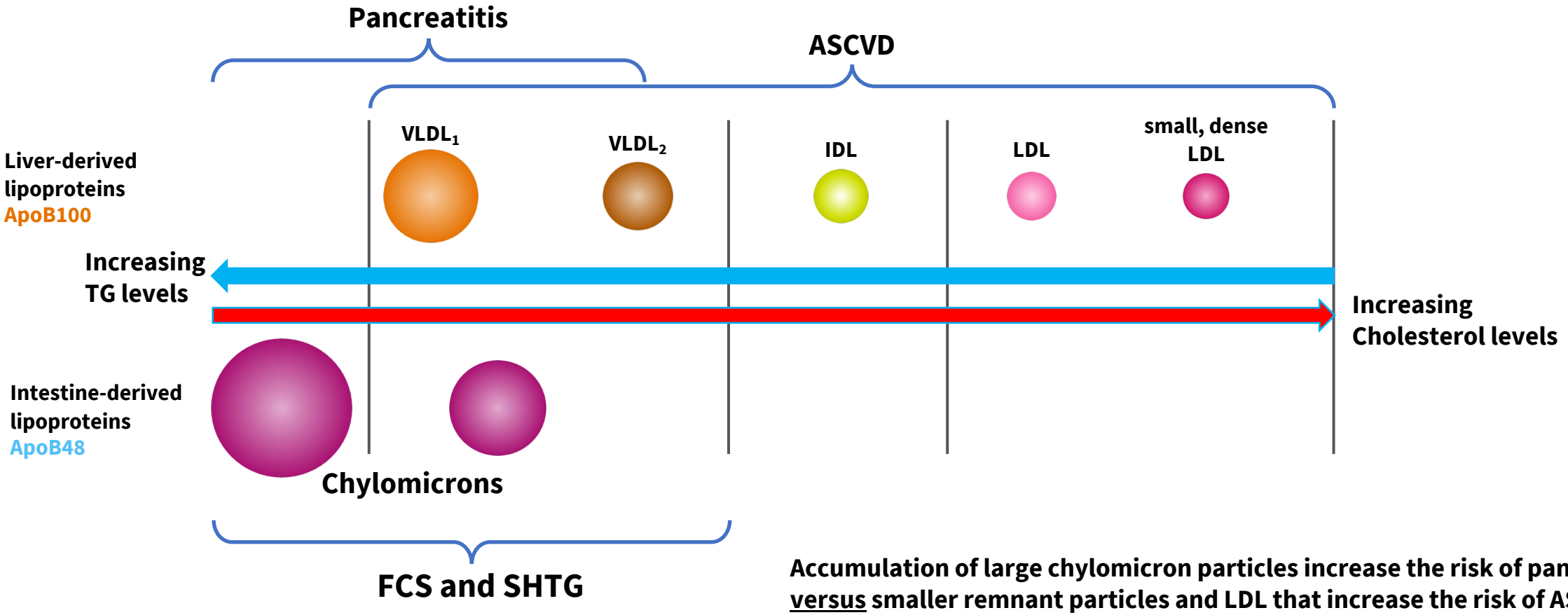
Irving Professor of Medicine

Past Director
Irving Institute for Clinical and Translational Research, Columbia University

Disclosures

- Paid consultant and advisor:
  - Ionis Pharmaceuticals, Merck, Silence Therapeutics, Kowa, AstraZeneca, Lexicon

Chylomicrons and VLDL are Prevalent in Patients with TGs > 500 mg/dL and Contribute to Risk for Acute Pancreatitis[1]



Accumulation of large chylomicron particles increase the risk of pancreatitis versus smaller remnant particles and LDL that increase the risk of ASCVD[2]

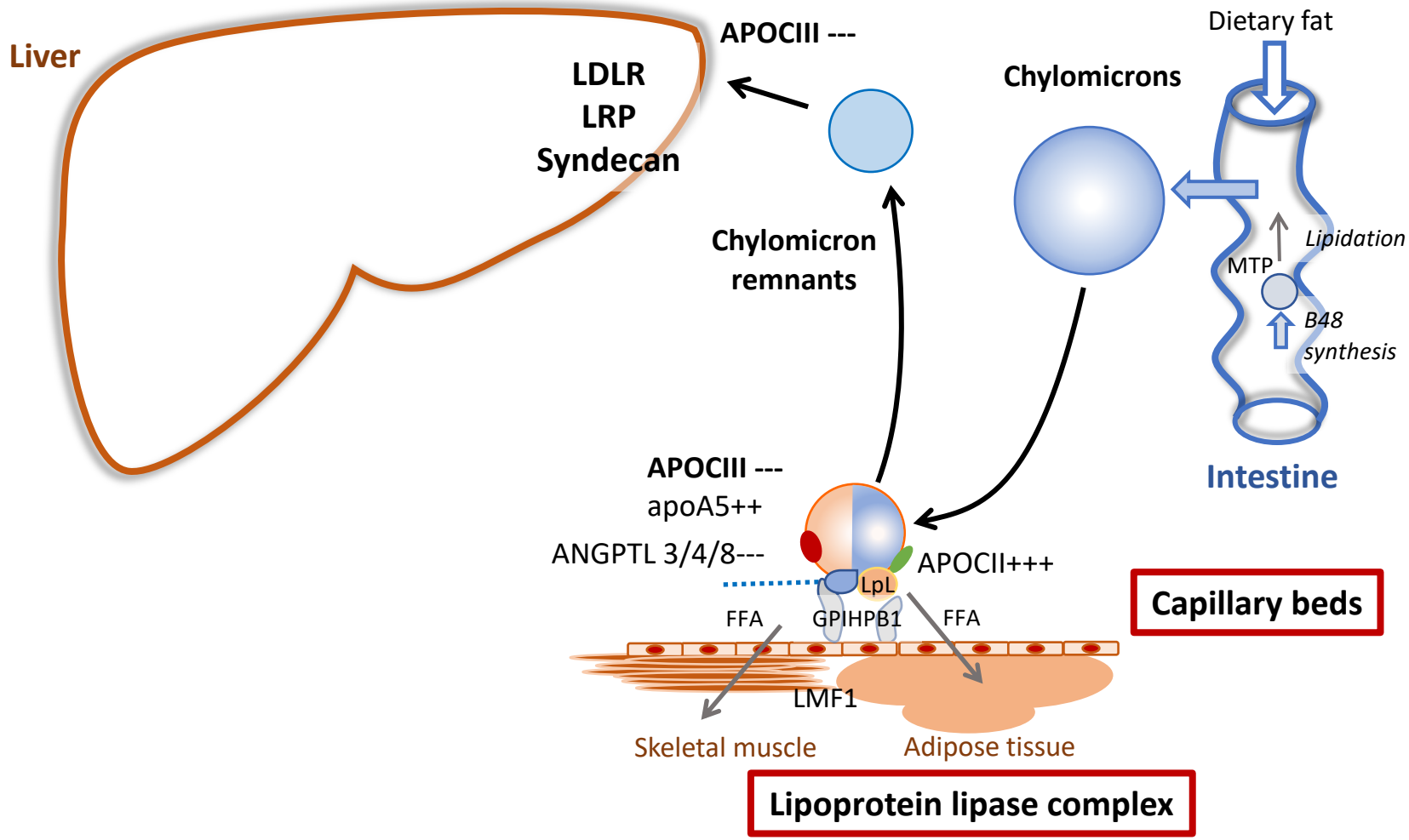
ApoB, apolipoprotein B-III; ASCVD, atherosclerotic cardiovascular disease; FCS, familial chylomicronemia syndrome; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; SHTG, severe hypertriglyceridemia syndrome; TG, triglyceride; VLDL, very low-density lipoprotein.1. Ginsberg HN. *Eur Heart J*. 2021;42(47):4791-4806. 2. Simha V. *BMJ*. 2020;371:m3109.

Role of APOCIII in TG Metabolism

- **APOCIII is a 79-amino acid glycoprotein synthesized principally in the liver**
  - Multiple APOCIII proteins on chylomicrons, VLDL and HDL particles
- **APOCIII plays key role in determining serum chylomicron and triglyceride levels**
  - Potent inhibitor of lipoprotein lipase (LPL)
  - Inhibits hepatic uptake of triglyceride-rich lipoproteins (TRLs)

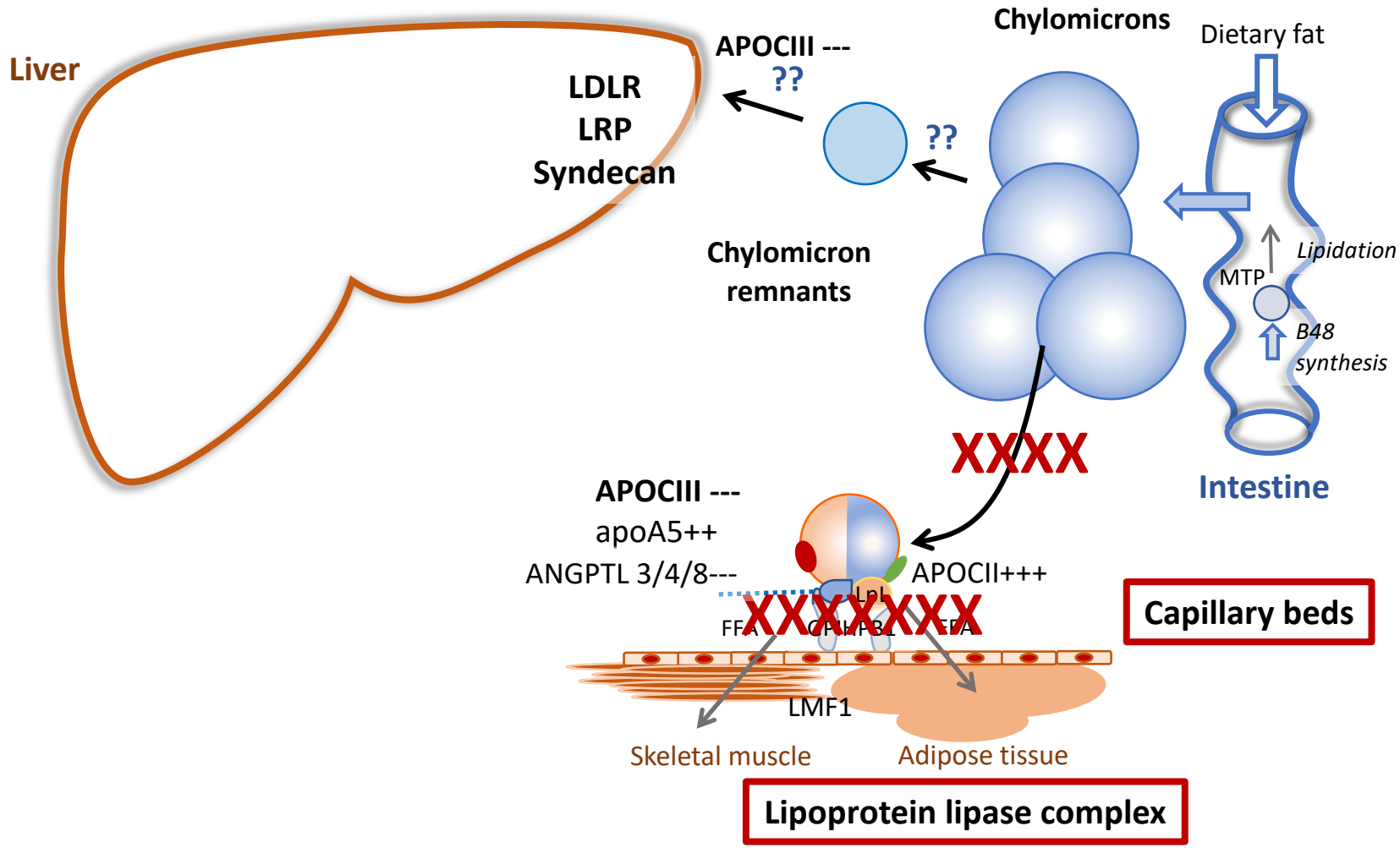
Gordts PL, et al J Clin Invest. 2016;126:2855-66

Normal Chylomicron Metabolism



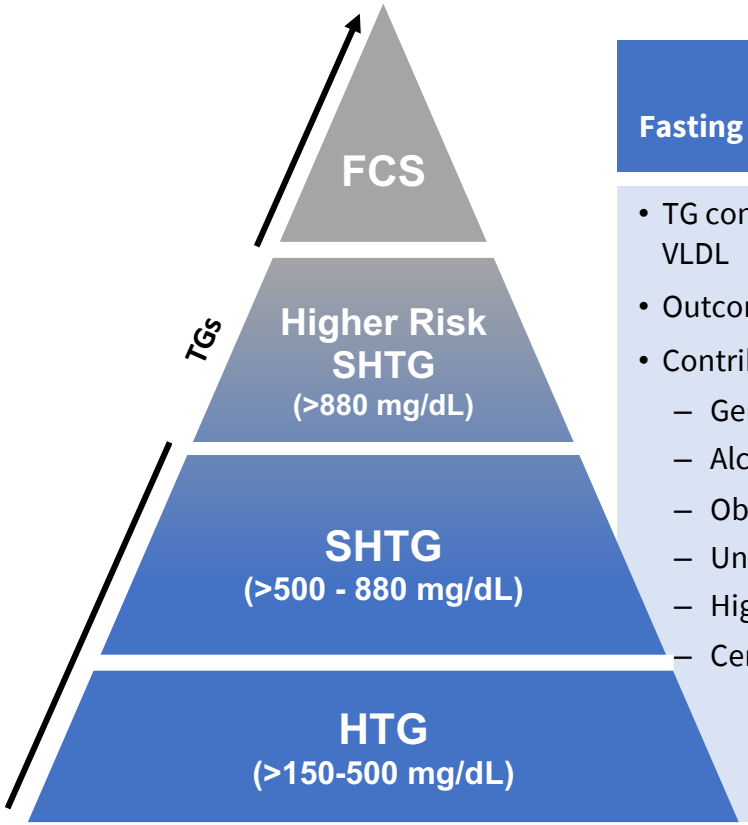
Eur Heart J. 2021 Dec 14;42(47):4791

Chylomicron Metabolism In The Complete Absence Of LPL Activity



Eur Heart J. 2021 Dec 14;42(47):4791

Multiple Phenotypes Associated with Elevated Triglycerides[1-5]



HTG Fasting TGs >150 - 500 mg/dL	SHTG Fasting TGs >500 - 880 mg/dL	SHTG w/ Higher AP Risk Fasting TGs >880 mg/dL	FCS Fasting TGs >880 mg/dL
• TG contained: remnants, VLDL • Outcomes: CVD • Contributing factors: – Genetics – Alcoholism – Obesity – Untreated diabetes – High fat/sugar diet – Certain medications	• TG contained: remnants, VLDL, chylomicrons • Outcomes: AP, CVD • Contributing factors: – Genetics – Alcoholism – Obesity – Untreated diabetes – High fat/sugar diet – Certain medications	• TG contained: VLDL, chylomicrons • Outcomes: AP, organ damage, higher mortality • Contributing factors: – Genetic – Alcoholism – Obesity – Untreated diabetes – High fat/sugar diet – Certain medications	• TG contained: chylomicrons • Outcomes: AP, organ damage, higher mortality • FCS presentation: – Refractory to TG lowering treatments – Earlier onset at younger ages – Diagnosis can include history of AP *or* abdominal pain *or* confirmed mutations

1. Simha V. BMJ. 2020;371:m3109; 2. Brahm AJ, Hegele RA. Nat Rev endocrinologist. 2015;11:352–362; 3. Miller M, et al. Circulation. 2011;123:2292-2333; 4. Hegele RA, et al. Curr Opin Lipidol. 2015;26:103-113;
5. Ewald et al.Clin research in cardiologistlogy supplements.

FCS: A Severe, Rare, Genetically Driven Disease

FCS Overview[1-4]

- 1 – 2 per million patients worldwide
- Monogenic, associated with deficient LPL activity caused by mutations in *APOA5, APOC2, GPD1, GPIHBP1, LMF1* or *LPL*
- TG levels often 10-100 times higher than normal levels

Associated with Multiple Debilitating Symptoms and Reduced QoL[2]

- Extreme risk for acute, potentially fatal, pancreatitis
- Causes daily, debilitating symptoms, including abdominal pain, neurocognitive impairment, eruptive xanthomas and poor QoL

FCS Represents Clear Unmet Medical Need[1,3]

- No approved treatments in the US
- FCS patients are refractory to triglyceride-lowering therapies
- Standard of care is limited to restrictive, extremely low-fat diet
  - 15 – 20g of dietary fat per day – equivalent to ~2 Tbsp olive oil; no alcohol

1. Pallazola et al. Eur J Preventive Cardiol 2020 27:2276-2278. 2. Gaudet D, et al. N Engl J Med. 2014;371:2200-2206. 3. Hegele, et al, Lancet Diabetes Endocrinology, 2014. 4. Warden et al. 2020; J Clin Lipidol 14:201-6

SHTG: Broad Population with Increased Risks for AP and ASCVD

SHTG: Complex Condition Representing Clear Unmet Need[1-7]

- SHTG represents a broad US patient population
  - ~1 million patients with TG >880 mg/dL
  - >2 million patients with TG 500-880 mg/dL
- Caused by a combination of genetics, diet and lifestyle

Greater Risk for Severe Diseases and Lower Quality of Life[8-10]

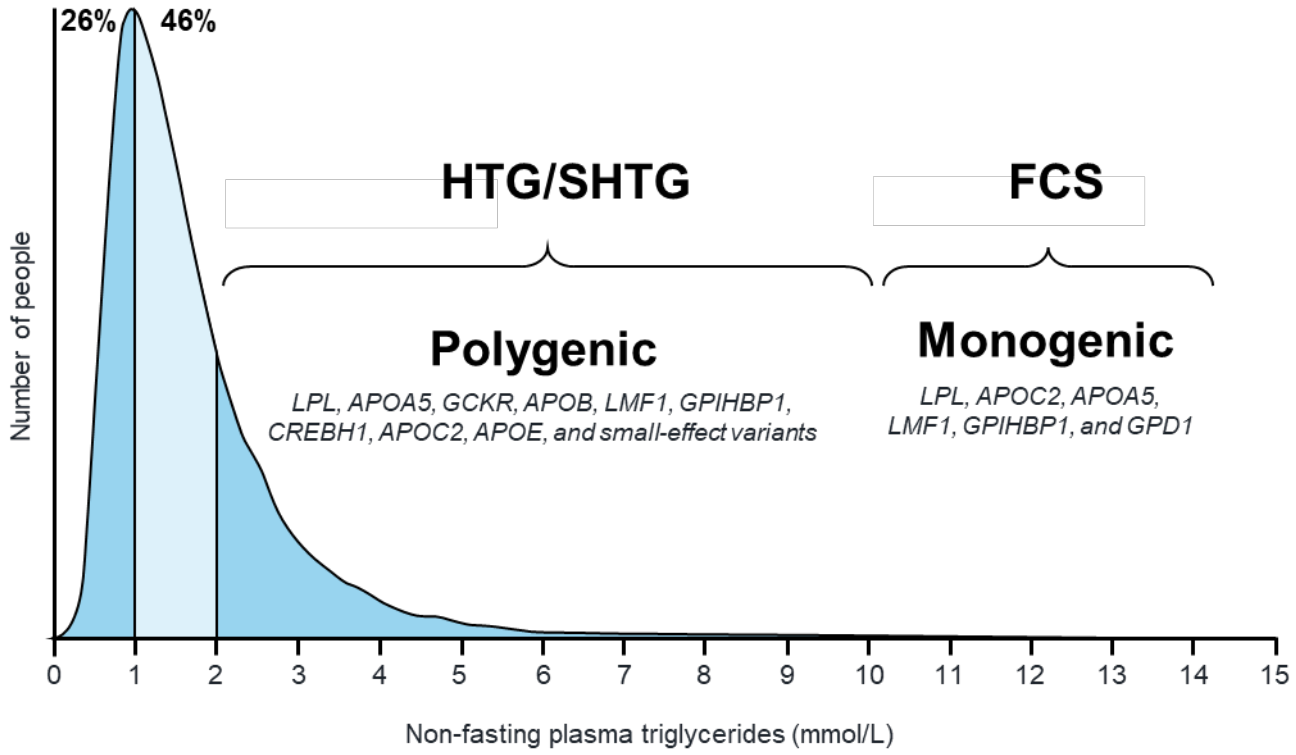
- Risk for acute, potentially fatal pancreatitis and ASCVD
- Associated with daily chronic symptoms, including abdominal pain, nausea and fatigue
- Patients report lower productivity and emotional well-being

Ineffective Standard of Care[10]

- Many SHTG patients unable to manage triglycerides and associated risks with current SOC
- Pregnancy, certain medications can increase triglyceride levels

1. Total addressable market. 2. Represents those with initial triglyceride levels >500 mg/dL. 3. Sanchez et al. Lipids in Health and Disease 2021;20:72. 4. Berberich et al. Lipids in Health and Disease 2021;20:98. 5. Fan et al., J Clin Lipidology 2019; 13:100-108. 6. Christian et al., Am J Cardiol 2011;107:891-897. 7. Hegele, et al, Lancet Diabetes Endocrinology, 2014. 8. Simha V. BMJ. 2020;371:m3109. 9. Yang AL, et al. Pancreatology. 2020;20(5):795-800. 10. Aquest Research, 2021.

FCS, HTG and SHTG Patients Have Distinct Genetic Profiles



1 mmol/L = ~89 mg/dL
1.6 mmol/L = ~150 mg/dL
5.6 mmol/L = 500 mg/dL

FCS (monogenic)

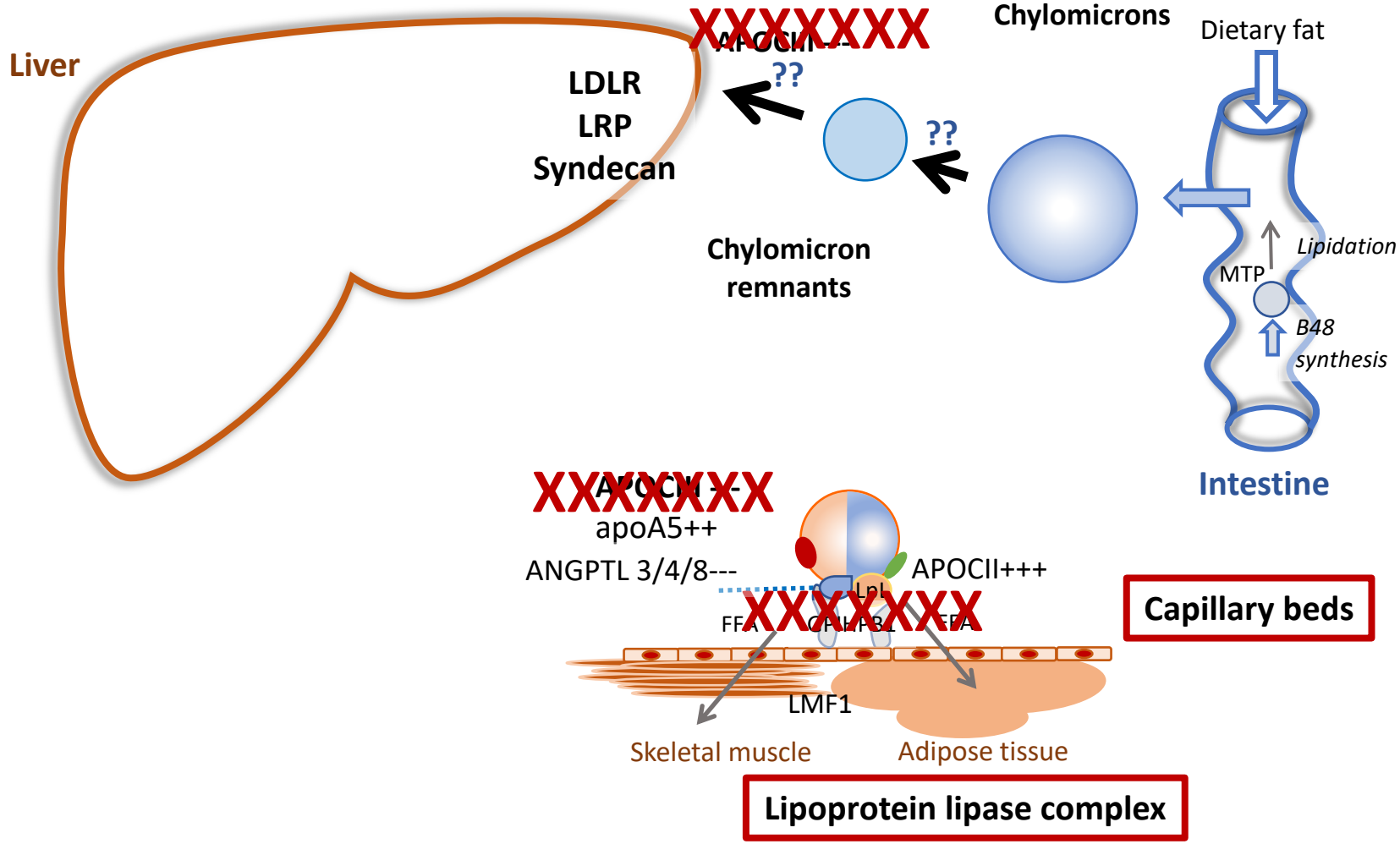
- Complete absence of LPL activity
- Markedly reduced TRL clearance

HTG/SHTG (polygenic)

- Functional but reduced LPL activity
- Functional but reduced TRL clearance

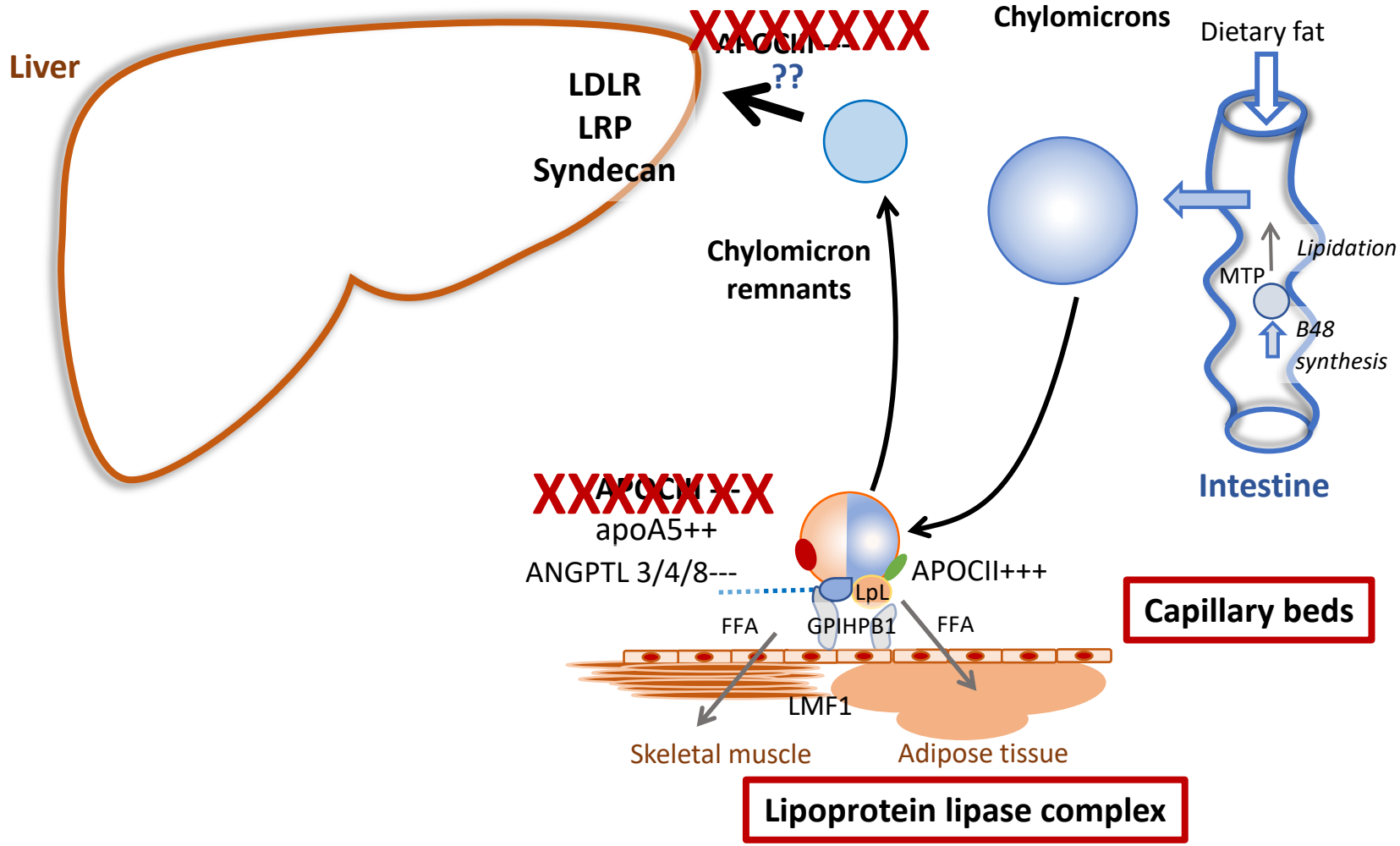
Hegele, et al, Lancet Diabetes Endocrinology, 2014

Effect of Olezarsen on Chylomicron Metabolism in FCS with a Complete Absence of LPL Activity



Eur Heart J. 2021 Dec 14;42(47):4791

Effect of Olezarsen on Chylomicron Metabolism in SHTG with Some LPL Activity

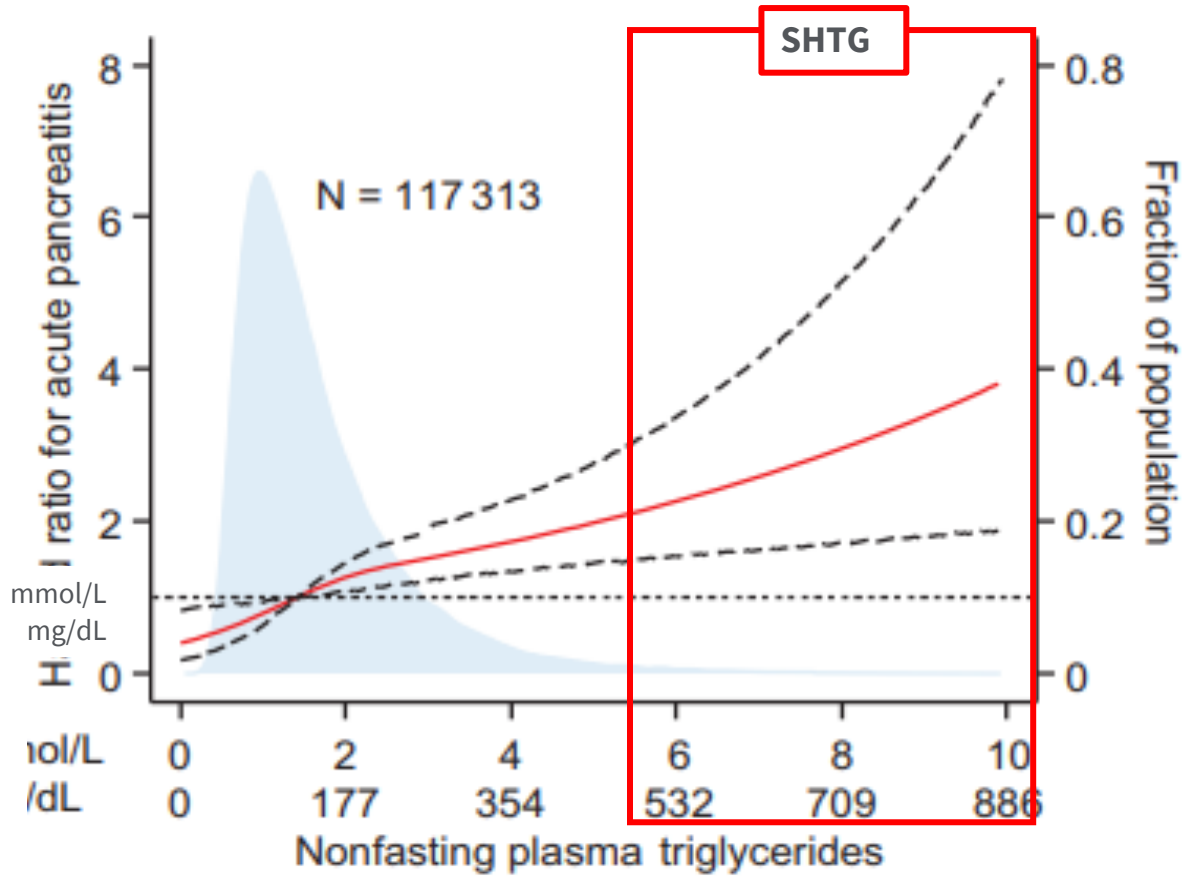


Eur Heart J. 2021 Dec 14;42(47):4791

AP Risk Increases Linearly in Patients with TGs >500 to 880 mg/dL

- High TGs are a well-established causal risk factor for AP for patients with LPL activity
- SHTG causes up to 22% of AP cases[1-4]
- AP risk increases linearly with TGs between >500-880 mg/dL[5]

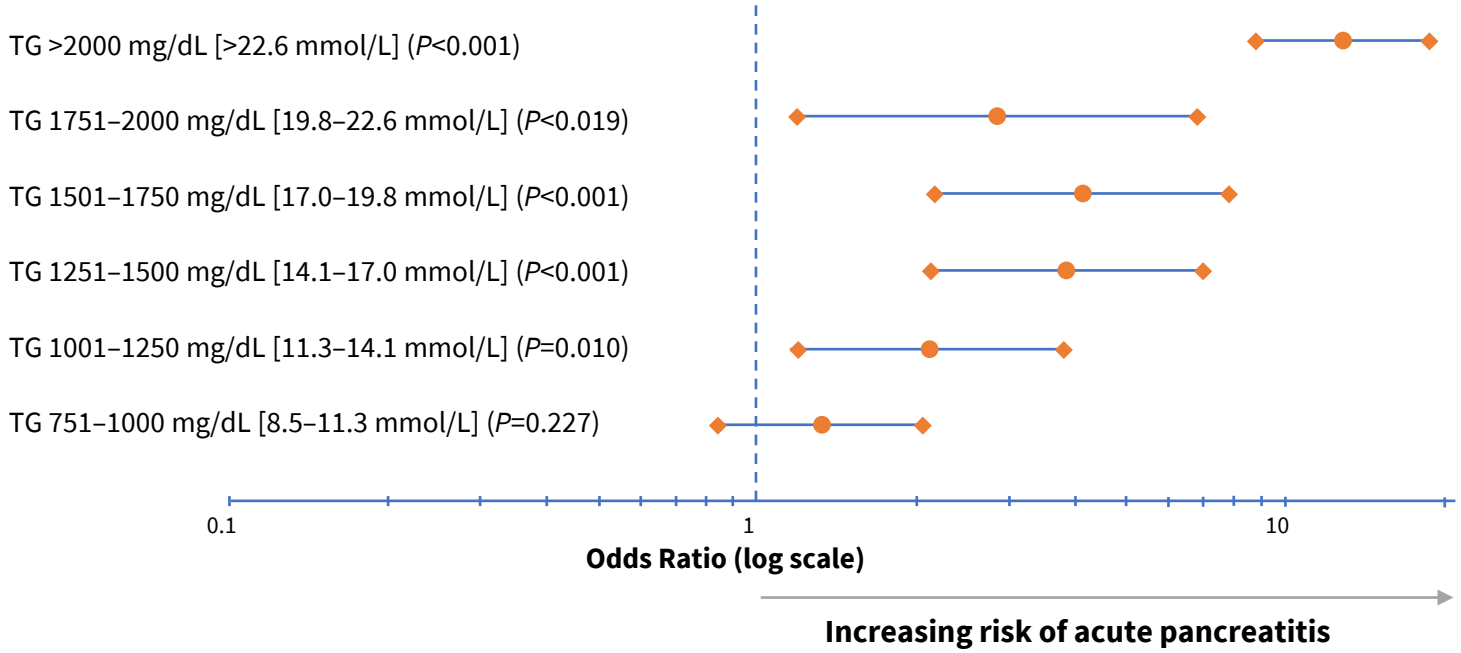
Triglycerides and the Risk of AP in the General Population[6]



1. Based on non-fasting triglyceride levels. 2. Jin M, et al. *J Clin Lipidol*. 2019;13(6):947-953.e1. 3. Whitcomb DC. *N Engl J Med*. 2006;354(20):2142-2150. 4. Papachristou GI, et al. *Ann Gastroenterol*. 2017;30(1):106-113.
5. Yang AL, et al. *Pancreatology*. 2020;20(5):795-800. 6. Hansen SEJ, et al. *Clin Chem*. 2019;65(2):321-332.

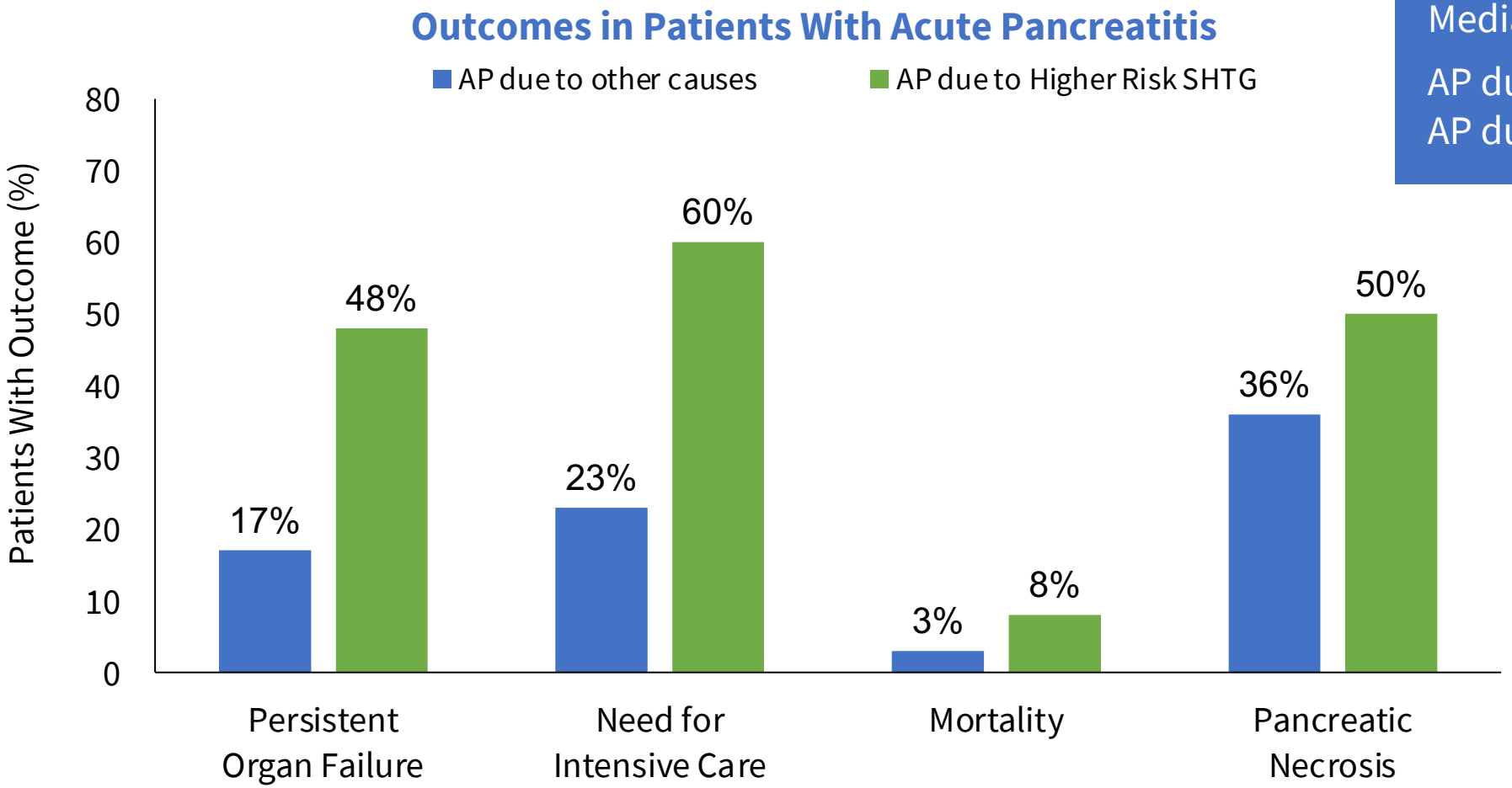
Risk of Acute Pancreatitis by Increasing TG Levels Above 880 mg/dL[1-3]

- Higher TG ranges were typically associated with a higher risk of acute pancreatitis than with lower TG ranges
- A significantly increased risk for acute pancreatitis in patients with TG levels >2000 mg/dL (22.6 mmol/L) OR 12.8; 95% CI 8.8–18.6; *P*<0.0001



1. Retrospective Cohort Study Based on US Insurance Claims Data (N=53,627). 2. Based on fasted triglyceride levels. 3. Toth PP, *et al*. *Atherosclerosis* 2014;237:790-797.

AP Due to Higher Risk SHTG Levels is Associated with Significantly Worse Outcomes Compared to AP Due to Other Causes



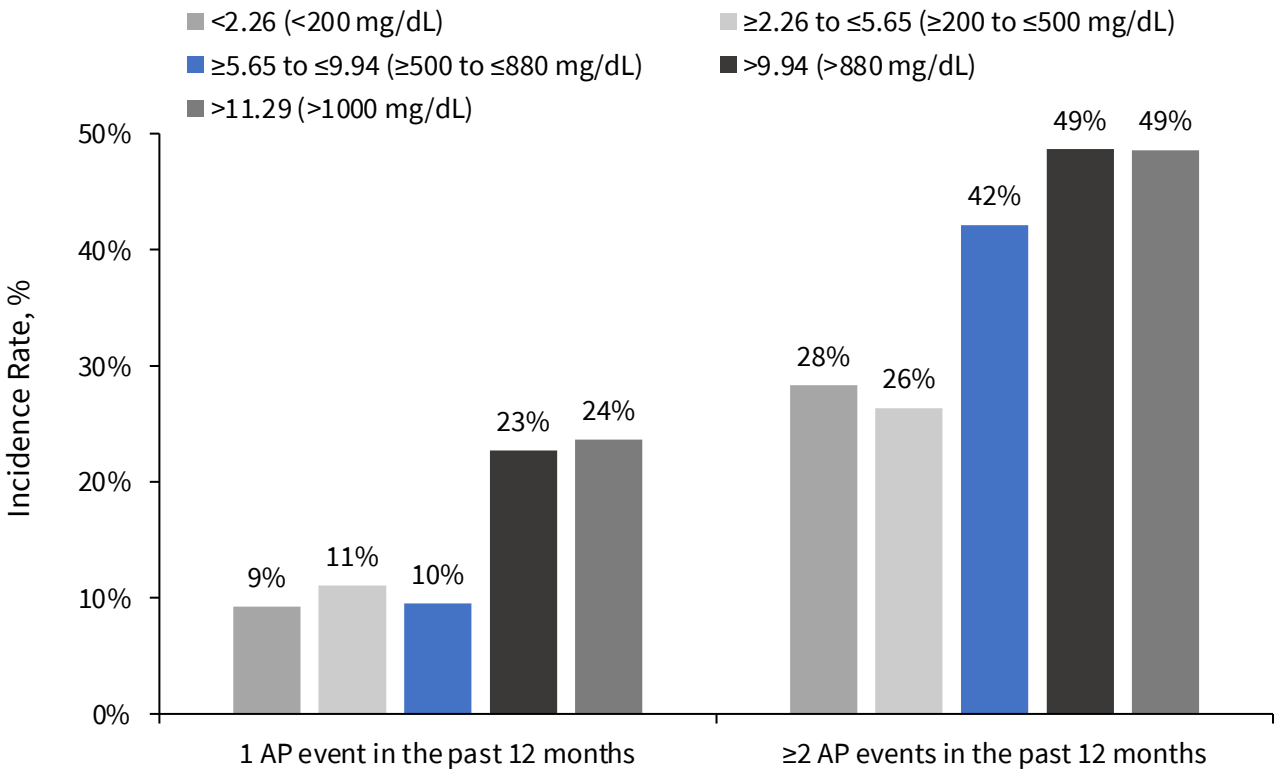
Median hospital stay:

AP due to other causes: 7 days
AP due to higher risk SHTG: 17 days

Nawaz H, et al. Am J Gastroenterol. 2015;110:1497-1503.

Risk for AP Increases with Each Event

Overview of Incidence Rate of AP by TG Concentration and Prior AP[1]



Risk of Recurrent AP

- Patients with higher risk SHTG (TG levels >880 mg/dL) have significant likelihood of **incurring another AP event**
- Patients who have incurred ≥2 AP events in the past 12 months are at **significantly increased risk of incurring another AP event**
  - **Patients with TG levels from 500 to 880 mg/dL demonstrate AP risk similar to those >880 mg/dL once >1 event occurs**

Patel RS, et al. Cardiovasc Diabetol. 2022;21(1):102. 2.

High Unmet Medical Need for Effective TG-Lowering Treatments[1-5]

Fibrates and Omega 3s

- Generally 1st and 2nd line treatments for patients with TGs > 500mg/dL
- Modest TG reductions (20-30%)
- TG reductions not sufficient for AP risk reduction in patients with SHTG, higher-risk SHTG

Statins

- First line treatment in patients at risk for ASCVD, including patients with HTG and SHTG
- Minimal TG reductions (10-30%)
- TG reductions not sufficient for AP risk reduction in patients with SHTG, higher-risk SHTG

GLP1 Receptor Agonists

- Widely used in patients with BMI > 27kg/m
- Class associated with increased risk for AP in patients with TGs > 400mg/dL or history of AP
- Minimal TG reductions (10-30%) seen alone or in combination with standard TG-lowering drugs
- TG reductions not sufficient for AP risk reduction in patients with SHTG, higher-risk SHTG

1. Ginsberg et al. Eur Heart J. 2021;42:4791-4806. 2. Mach et al. Eur Heart J, 2020;41:111–188. 3. Berglund L, et al. *J Clin Endocrinol Metab.* 2012;97:2969-2989. 4. Newman CB, et al. *J Clin Endocrinol Metab.* 2020;105:3613-3682.
5. ClearView Analysis, 2022.

FCS and SHTG Key Takeaways

- FCS and SHTG are both defined by very high triglyceride levels but have genetic and mechanistic differences
    - **FCS** patients have monogenic mutations that result in a **complete absence of LPL activity** but functional TRL clearance in the liver
    - **SHTG** patients have polygenic mutations that result in **reduced LPL activity and TRL clearance**
- Both patient populations are at **high risk for acute pancreatitis** and other serious symptoms driven by high triglyceride levels
- Current treatment options **do not provide adequate benefit** for FCS patients and for many SHTG patients

Phase 3 Balance Study Topline Results

Sam Tsimikas, M.D.

Senior Vice President, Global Cardiovascular Development

Olezarsen Targets APOCIII, a Key Regulator of Triglyceride Clearance and Metabolism[1,2]

APOCIII inhibits triglyceride metabolism and clearance via two mechanisms:

APOCIII inhibits LPL activity (metabolism)

APOCIII inhibits TRL clearance

By reducing APOCIII production, olezarsen is designed to increase both triglyceride metabolism and TRL clearance

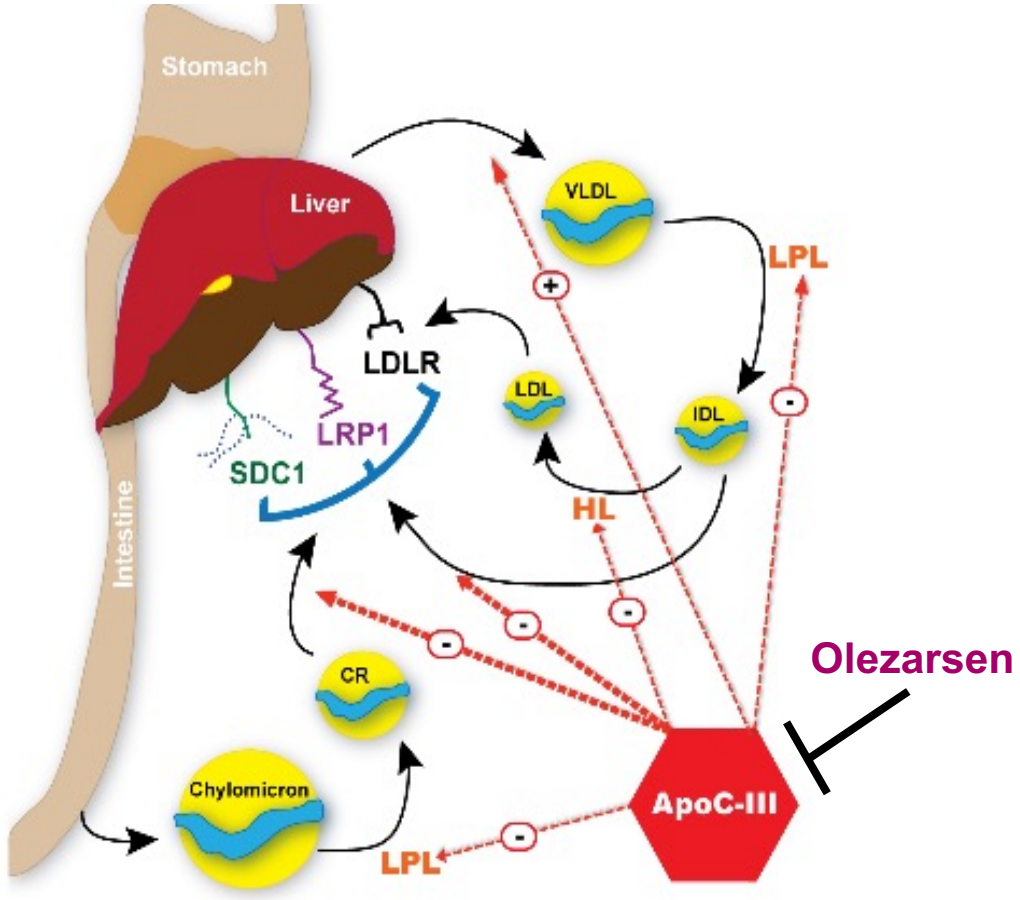


Image adapted from: Gordts PL, et al J Clin Invest. 2016;126:2855

1. Gordts PL et al. J Clin Invest 2016;126:2855–66. 2. Kohan AB. Curr Opin endocrinologistcrinol Diabetes Obes. 2015;22:119-125.

APOCIII Loss of Function Reduces Post-Prandial Triglycerides

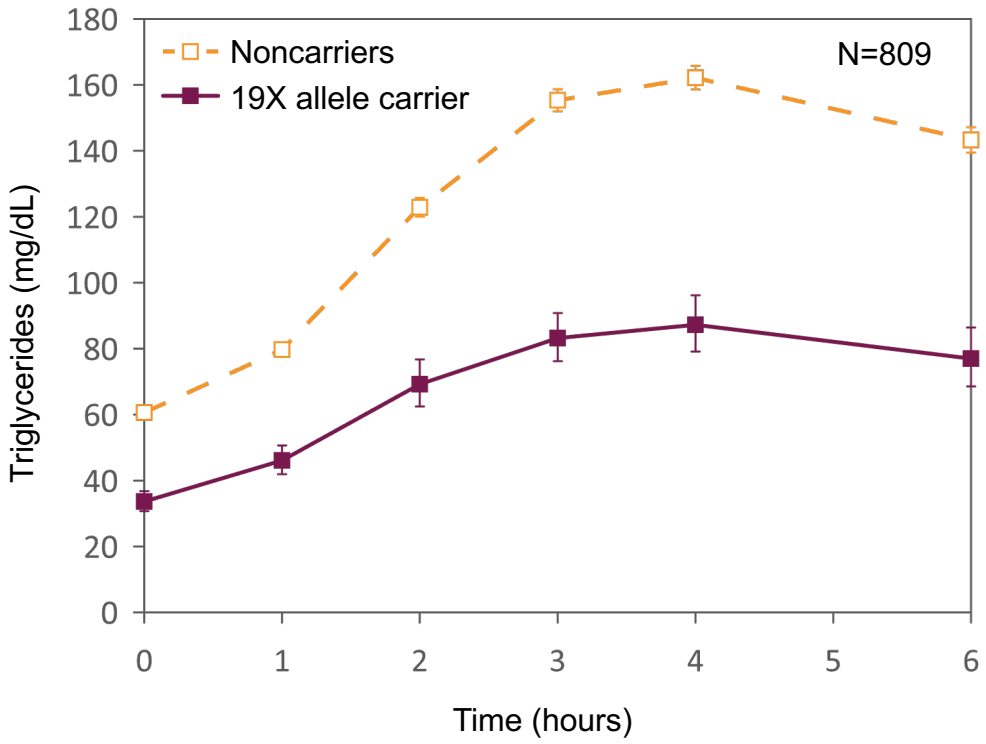
A Null Mutation in Human *APOC3* Confers a Favorable Plasma Lipid Profile and Apparent Cardioprotection

Toni I. Pollin,[1] Coleen M. Damcott,[1] Haiqing Shen,[1] Sandra H. Ott,[1] John Shelton,[1] Richard B. Horenstein,[1] Wendy Post,[2] John C. McLenithan,[1,3] Lawrence F. Bielak,[4] Patricia A. Peyser,[4] Braxton D. Mitchell,[1] Michael Miller,[1] Jeffrey R. O'Connell,[1] Alan R. Shuldiner[1,3]

Key Results:

- Reduced APOCIII levels in heterozygotes by 50%
- Decreased fasting and postprandial TGs
- Decreased non-HDL-C, LDL-C, VLDL-C, IDL-C

TG Levels Before and During High-fat Challenge by R19X *APOCIII* Genotype



Pollin TI, et al. Science. 2008;322:1702-1705.

Olezarsen Development Program Designed to Generate Robust Data in Patients with FCS and SHTG[1]

FAMILIAL CHYLOMICRONEMIA SYNDROME (FCS)

Balance
a familial chylomicronemia syndrome study

- Significant reductions in TGs, clinically meaningful reductions in AP, favorable safety and tolerability
- OLE progressing well
- Ph 2b study supporting FCS NDA exposure database, on track to complete 2H:2023
- On track for US and EU filings in 2024
- Launch preparations underway

SEVERE HYPERTRIGLYCERIDEMIA (SHTG)

CORE
a hypertriglyceridemia study

- First pivotal study in patients w/ TGs ≥500 mg/dL enrolling
- Pivotal registrational study
- ~540 patients

CORE2
a hypertriglyceridemia study

- Confirmatory study in patients w/ TGs ≥500 mg/dL enrolling
- Pivotal registrational study
- ~390 patients

Essence
TIMI-73b

- Supportive Ph3 study in patients w/ TGs ≥200 mg/dL
- Adds to patient exposure database
- ~1,300 patients

---------- *Data expected in late 2024/early 2025* ----------

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

Phase 3 Balance Study in Patients with FCS

Balance
a familial chylomicronemia syndrome study

DESIGN

Randomized, double-blind, placebo-controlled study of monthly subcutaneous olezarsen in 66 patients with FCS, fasting TG ≥ 880 mg/dL (10 mmol/L) and a history of pancreatitis

– Patients were expected to be on background lipid-lowering therapy

ENDPOINTS

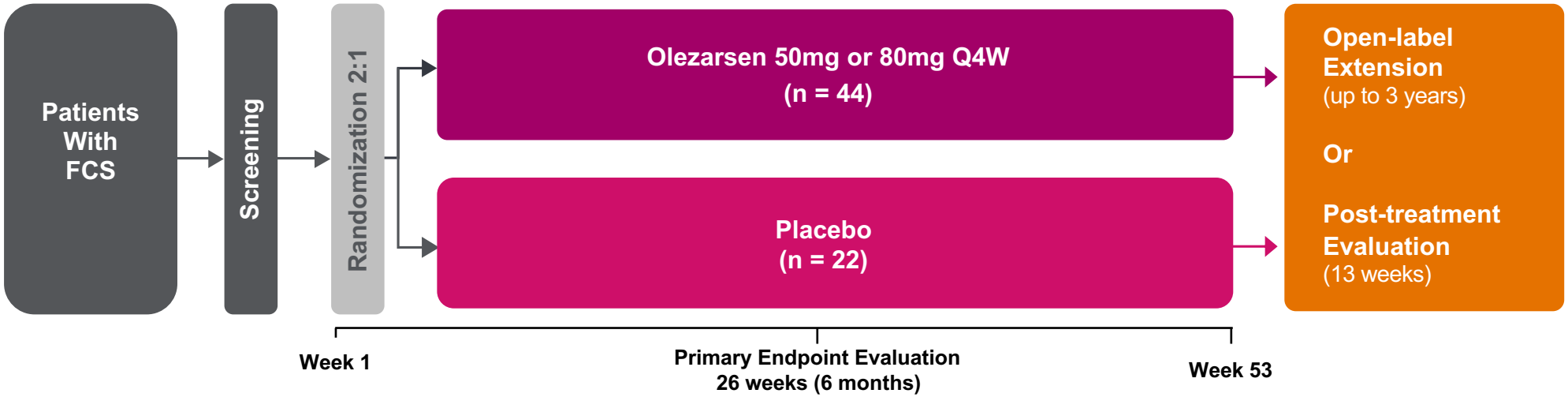
Primary outcome measure:

Percent change in fasting triglycerides (TG) from baseline to 6 months

Key secondary endpoints:

Change from baseline: fasting TG (12 months)

Reduction in pancreatitis events



Patient Disposition: >90% of Patients Completed Study

	Placebo	Olezarsen 50 mg	Olezarsen 80 mg
N	23	21	22
Completed Treatment	22 (95.7%)	19 (90.5%)	19 (86.4%)
Discontinued Study Treatment	1 (4.3%)	2 (9.5%)	3 (13.6%)
Voluntary withdrawal	0	1 (4.8%)	1 (4.5%)

100% of Patients who Completed the Study Chose to go into the Open Label Extension Study

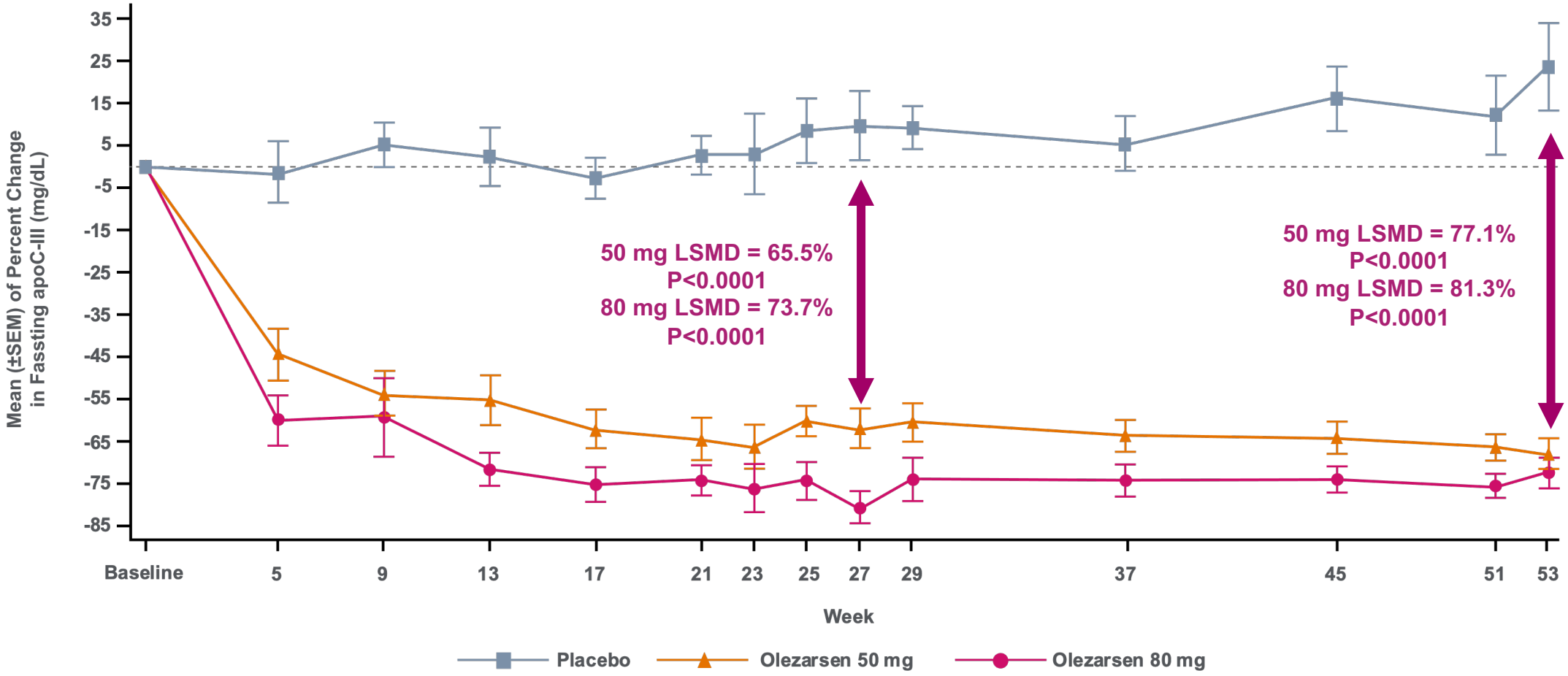
Baseline Characteristics

Baseline Characteristics	Placebo (n=23)	Olezarsen 50 mg (n=21)	Olezarsen 80 mg (n=22)
Age, Mean years (SD)	44.0 (14.67)	43.2 (12.11)	47.7 (13.30)
Age Category, n (%) • < 65 • ≥ 65	 20 (87.0%) 3 (13.0%)	 20 (95.2%) 1 (4.8%)	 20 (90.9%) 2 (9.1%)
Sex, n (%) • Female • Male	 12 (52.2%) 11 (47.8%)	 15 (71.4%) 6 (28.6%)	 11 (50.0%) 11 (50.0%)
Race, n (%) • White • Asian • Native Hawaiian/other Pac Islander • Other	 22 (95.7%) 0 0 1 (4.3%)	 17 (81.0%) 3 (14.3%) 1 (4.8%) 0	 17 (77.3%) 3 (13.6%) 0 2 (9.1%)
Body Weight (kg), Mean (SD)	67.8kg (16.1)	61.2 (11.6)	68.4 (16.7)
BMI (kg/m^2), Mean (SD)	24.2 (4.1)	22.4 (3.5)	25.1 (6.0)

Baseline Characteristics	Placebo (n=23)	Olezarsen 50 mg (n=21)	Olezarsen 80 mg (n=22)
History of AP, prior 10 years, n (%)	15 (65.2%)	15 (71.4%)	17 (77.3%)
≥2 documented AP events, prior 5 years, n	9	6	6
Fasting TG ≥ 880 mg/dL at Baseline, n (%)	21 (91.3%)	20 (95.2%)	21 (95.5%)
Previous treatment with volanesorsen	10 (43.5%)	8 (38.1%)	8 (36.4%)

Baseline demographics and clinical characteristics were generally well balanced between groups

Olezarsen Treatment Resulted in Robust and Significant Reduction in Serum APOCIII Levels at 6 and 12 Months



LSMD = Least squares mean difference

Positive Results For Primary and Key Secondary Endpoints

Measurement	Time
Triglyceride (TG):	**Month 6***
Percent change in fasting TG (80 mg)	**p=0.0009**
Percent change in fasting TG (50 mg)	p=0.0775
Pancreatitis:	**Weeks 1-53**
Reduction in pancreatitis events (80 mg)	**100%** (olezarsen: 0 events, placebo: 11 events**)
Reduction in pancreatitis events (50 mg)	**92%** (olezarsen: 1 event, placebo: 11 events**)

*Primary endpoint. P-values are based on differences in least-squares mean change from baseline **There were a total of 8 patients in the study who had one or more pancreatitis events

Olezarsen Safety and Tolerability Profile

- More TEAEs were seen in the placebo group compared to the olezarsen groups, primarily due to a higher number of pancreatitis events in the placebo group
- No serious TEAEs related to study drug
- No clinically meaningful thrombocytopenia, renal or hepatic safety signals
- Low incidence of mild injection site reactions
- 1 non-drug related death in olezarsen treatment group

Incidence, n (%)	Placebo	Olezarsen 50 mg	Olezarsen 80 mg
N	23	21	22
Any TEAE[1]	22 (95.7)	18 (85.7)	19 (86.4)
Related to study drug	5 (21.7)	6 (28.6)	7 (31.8)
Leading to study drug discontinuation	0	1 (4.8)	2 (9.1)
Any Serious TEAE	9 (39.1)	4 (19.0)	3 (13.6)
Related to study drug	0	0	0
Fatal TEAE	0	1 (4.8)	0
Related to study drug	0	0	0

1. Treatment emergent adverse event (TEAE) is defined as an adverse event that first occurred or worsened after the first dose of investigational product.

Olezarsen: Potential New Standard-of-Care Treatment for FCS Patients[1,2]

Attractive Clinical Profile[3]

Robust, dose-dependent reductions in APOCIII

Statistically significant reductions in triglycerides at 80mg dose

Substantial reduction in acute pancreatitis attacks at 80 mg dose

Favorable safety and tolerability profile

Next Steps

Phase 2b study supporting FCS NDA exposure database **on track to complete 2H:2023**

Initiate **expanded access** program for patients with FCS in 2024

On track for **US and EU regulatory filings** in 2024

Launch preparations underway

1. Timing expectations based on current assumptions and subject to change. 2. Assuming approval. 3. Based on Phase 3 Balance study topline results.

Broad Clinical Program for Olezarsen in Patients with SHTG

Olezarsen CORE and CORE2 Phase 3 Studies

Pivotal Studies in Patients with SHTG

CORE a hypertriglyceridemia study

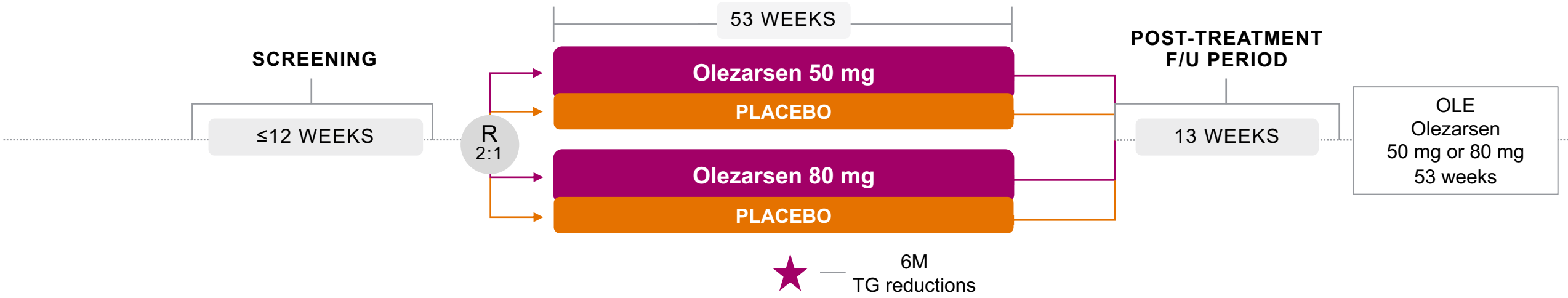
CORE2 a hypertriglyceridemia study

DESIGN

A global, randomized, double-blind, placebo-controlled study of monthly subcutaneous injections of **olezarsen** in up to **540 patients** (CORE) **and 390 patients** (CORE2) with TGs ≥ 500 mg/dL

PRIMARY OUTCOME

Percent change in fasting TG from baseline compared to placebo at 6 Months (average of weeks 25 & 27)



★ Primary Endpoint

Data expected in late 2024 or early 2025[1,2]

1. Timing expectations are based on current assumptions and are subject to change. 2. Based on enrollment.

Olezarsen ESSENCE Phase 3 Study

Essence TIMI-73b

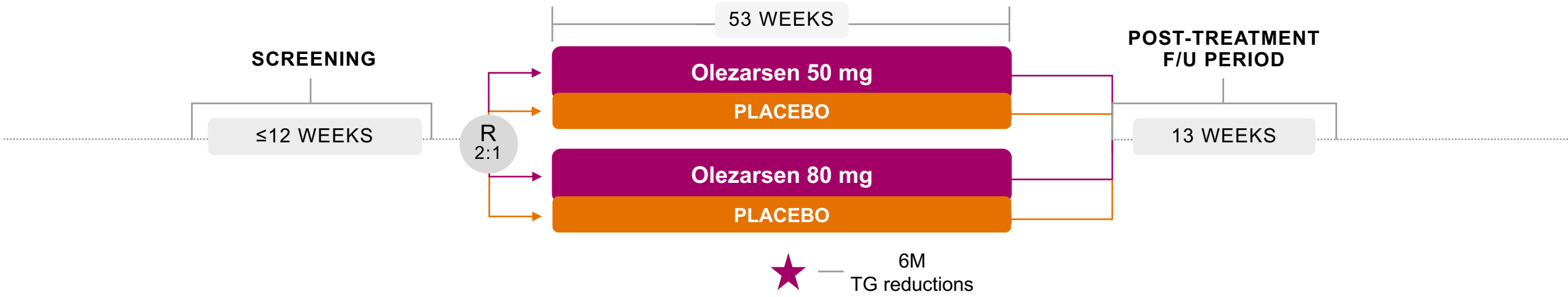
Supportive Exposure Study

DESIGN

A global, randomized, double-blind, placebo-controlled study of monthly subcutaneous injections of **olezarsen** in up to **1,300 patients** with TGs ≥ 200 mg/dL

PRIMARY OUTCOME

Percent change in fasting TG from baseline compared to placebo at 6 Months (average of weeks 25 & 27)



Data expected in late 2024 or early 2025[1,2]

1. Timing expectations are based on current assumptions and are subject to change. 2. Based on enrollment.

Olezarsen: Positioned to Address Underserved Patients with FCS and SHTG[1,2]

Phase 3 Balance study **demonstrated**:

- **Robust, dose-dependent reductions in APOCIII**
- **Statistically significant reductions in triglycerides** at 80 mg dose
- **Substantial reduction in acute pancreatitis attacks** at 80 mg dose

Favorable Safety and Tolerability Profile

On track to submit regulatory filings for the treatment of FCS in US and EU in 2024

Phase 3 CORE, CORE2 and ESSENCE studies in SHTG **progressing well**

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

Olezarsen: Bringing it to Patients

Onaiza Cadoret

Executive Vice President, Chief Global Product Strategy & Operations Officer

Olezarsen: Addressing Two Distinct Populations of Patients with Urgent Unmet Need[1-3]

Familial Chylomicronemia Syndrome

- **No approved treatments** in the US
- **Significant risk** for acute, potentially fatal pancreatitis
- **First-mover** advantage
- **Potential first indication** launch for olezarsen

Severe Hypertriglyceridemia

- Significant **unmet need**
- **Treatment guidelines** recommend preventative treatment
- **Clear** regulatory path
- **Large addressable** market

Olezarsen Represents a Blockbuster Opportunity

1. Timing expectations and peak sales estimates based on current assumptions and subject to change. 2. Assuming approval. 3.Applies to total addressable market.

FCS is a Severe, Rare Disease of Significant Unmet Need[1-3]

FCS

It is Rare: Estimated 1-2 per million patients worldwide

It is Severe: Acute, potentially fatal pancreatitis is the most severe manifestation

It is Debilitating: Patients suffer chronic, debilitating physical, cognitive and emotional symptoms that impact relationships, employment and well-being

It Has No Effective Treatments: Patients in the US have no effective treatments

1. Warden et al. 2020; J Clin Lipidol 14:201-6. 2. Gaudet D, et al. N Engl J Med. 2014;371:2200-2206. 3. Williams L, et al. J Clin Lipidol. 2018;12:908-919.

Market Research Supports Unmet Needs of FCS Patients and Support for Olezarsen from HCPs and Payers[1,2]

> "I don't even have to have my TG levels checked. When I am in danger, my body tells me. And there's very little I can do about it." – *FCS patient*

> "Patients are scared of having an acute pancreatitis attack and are very motivated to take action." – *KOL Endocrinologist*

> "A trend in improving acute pancreatitis would be great… outcomes data would be a homerun." – *PBM*

Patients report FCS **impacts all aspects of life** (i.e., fear, depression, difficulty maintaining jobs, relationships, etc.)

HCPs are **motivated to prevent acute pancreatitis** attacks and improve QoL in patients with FCS

Payers **recognize the value of preventing acute pancreatitis** and **minimizing other chronic symptoms** associated with FCS

1. Aquest Research. 2. US Pricing Research.

FCS Patients are at Increased Acute Pancreatitis Risk, Suffer Worse Outcomes Compared to Patients with Normal TGs[1]

Acute pancreatitis is a significant burden for patients with FCS

Higher AP Risk[2]

67% of FCS Patients

Have experienced an AP event in their lifetime

Higher Recurrence[3]

Up to 10-fold

Increased risk of recurrent attacks

More Deadly[1]

~2 times

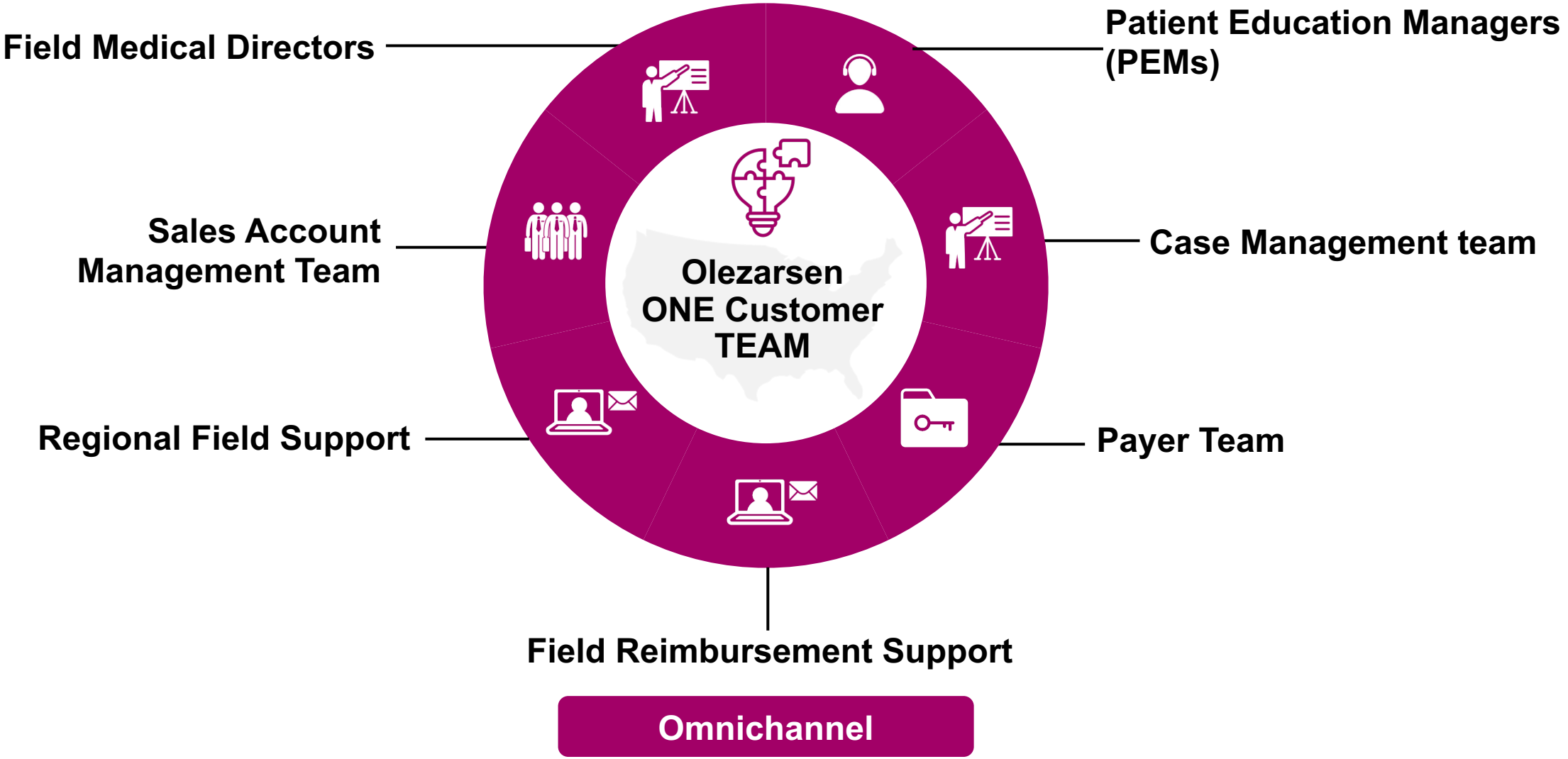
More likely to result in death vs. other AP causes

1. Nawaz H, et al. *Am J Gastroenterol.* 2015;110:1497-1503. 2. Gaudet D, et al. N Engl J Med. 2014;371:2200-2206. 3. Toth PP, *et al. Atherosclerosis* 2014;237:790-797.

Delivering Olezarsen to FCS Patients

Potential Approval

Commercial and Medical Affairs Operations Designed to Deliver Exceptional Customer Experience



SHTG is a Severe, Common Disease of Significant Unmet Need[1-9]

It is Common

Estimated
>3 million patients
in the US

It is Severe

Acute, potentially fatal pancreatitis is the most severe manifestation

It Has a High Disease Burden

Patients suffer from chronic physical symptoms and reduced QoL

Patients are Underserved

Many patients are underserved by current treatment options

1. Total addressable market. 2. Represents those with initial triglyceride levels >500 mg/dL. 3. Sanchez et al. Lipids in Health and Disease 2021;20:72. 4. Berberich et al. Lipids in Health and Disease 2021;20:98. 5. Fan et al., J Clin Lipidology 2019; 13:100-108. 6. Christian et al., Am J Cardiol 2011;107:891-897. 7. Simha V. BMJ. 2020;371:m3109. 8. Yang AL, et al. Pancreatology. 2020;20(5):795-800. 9. Aquest Research, 2021.

Targeting Patients with Severely Elevated Triglycerides with the Highest Degree of Unmet Need[1-7]

Higher-Risk SHTG
TGs >880mg/dL

SHTG
TGs >500mg/dL

HTG
TGs >150-500mg/dL

1. Represents initial TGs >500 mg/dL 2. Total addressable market. 3. Sanchez et al. Lipids in Health and Disease 2021;20:72. 4. Berberich et al. Lipids in Health and Disease 2021;20:98. 5. Fan et al., J Clin Lipidology 2019; 13:100-108. 6. Christian et al., Am J Cardiol 2011;107:891-897. 7. Fan P, et al. Cardiology and Therapy, 2020; 9(1), 207–213. Figure not to scale.

Guidelines Recommend Reducing Triglycerides to Below the Key Threshold for AP Risk[1-6]

Recommendations for High-risk SHTG (TGs >880 mg/dL)

- Weight loss and diet, lifestyle modifications
- Treat diabetes and other secondary factors
- Initiate treatment fibrates to reduce triglycerides

Recommendations for SHTG (TGs >500-880 mg/dL)

- Weight loss and diet, lifestyle modifications
- Statin therapy to reduce CV risk
- Initiate treatment with fibrates or omega-3 fatty acids to reduce triglycerides

American Heart Association. | AMERICAN COLLEGE of CARDIOLOGY | ESC European Society of Cardiology | UpToDate® | ENDOCRINE SOCIETY | nla NATIONAL LIPID ASSOCIATION | EAS

1. Berglund L, et al. *J Clin endocrinologist Metab.* 2012;97:2969-2989. 2. Newman CB, et al. *J Clin endocrinologist Metab.* 2020;105:3613-3682. 3. Virani SS, et al. *J Am Coll cardiologist.* 2021;78:960-993. 4. Ginsberg HN, et al. Eur Heart J. 2021;42:4791-4806. 5. UpToDate. Hypertriglyuceridemia in adults: Management. Updated June 2023. 6. Nutrition Interventions for Adults with Dyslipidemia: A Clinical Perspective from the NLA.

Market Research Supports SHTG Opportunity

200+ HCPs
representing 30,000+ patients[1]

Association between TGs and acute pancreatitis, ASCVD well understood

Most HCPs agree current treatments are ineffective in many patients

20 US Payers
representing 100M+ covered lives[1]

Payers viewed target product profile favorably, suggesting potential for broad access

600+ Patients
with SHTG[2]

Patients understand the underlying medical need, are motivated to take a new medication

1. Data on file. 2. Aquest Patient Journey, 2021.

Patients with SHTG Report Reduced Quality of Life

Activities of Daily Living

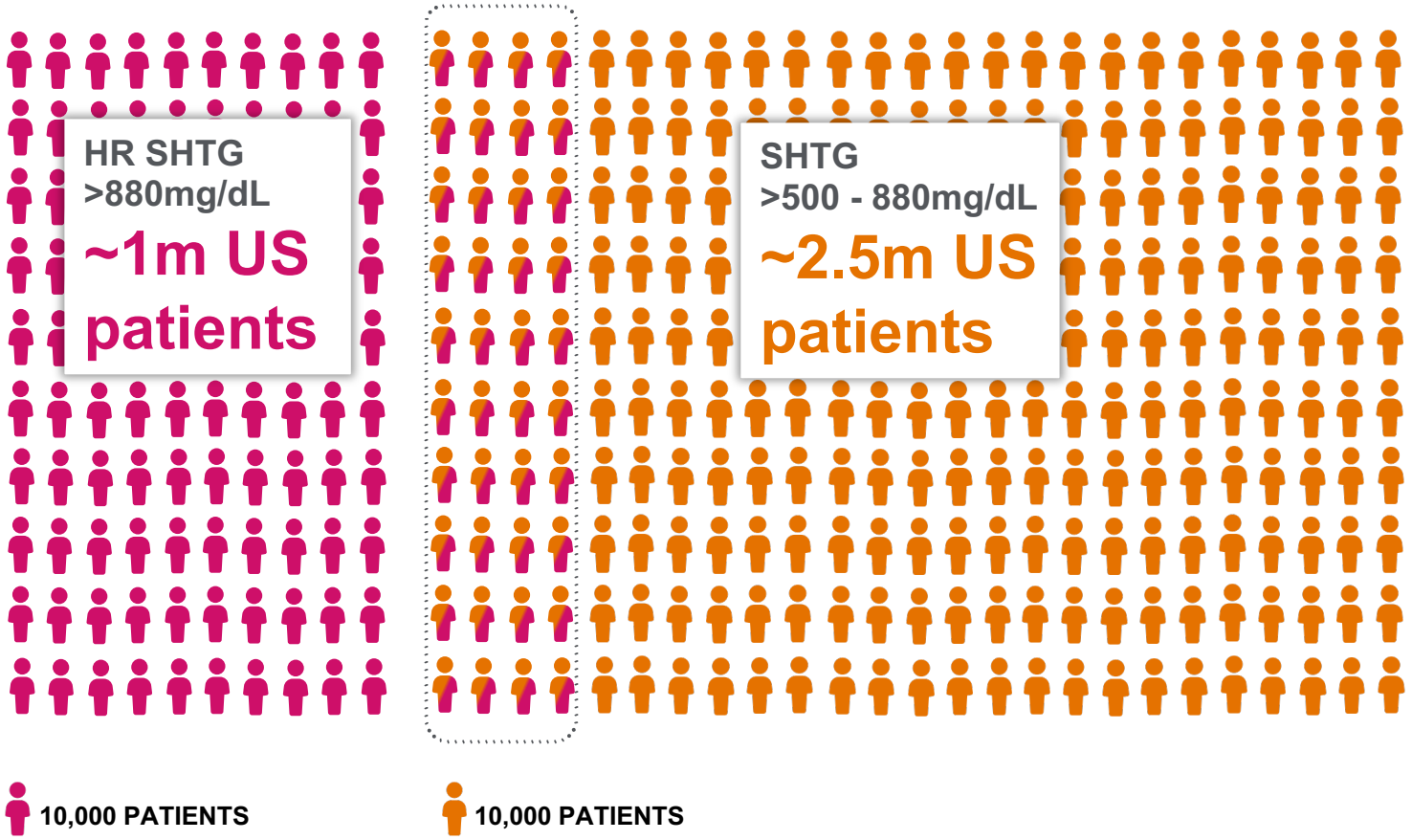
Element	% of Patients
Increased Stress	49%
Sleep Quality	43%
Ability to Work	36%

Emotional Journey

Element	% of Patients
Worried	56%
Sad or Depressed	35%
Frustrated	53%

Aquest Patient Journey, 2021

Preparing to Address Patients with SHTG and Higher-Risk SHTG in Parallel as a Single Indication[1-6]



- **Significant movement** can occur between **segments** due to post-prandial TG fluctuations
- Once patients are in the **higher-risk** segment, they are often **unable to reduce TGs** and remain a higher-risk patient
- Our plan is to **address both SHTG segments in parallel**, with **rapid adoption** expected among high-risk patients

1. Represents initial TGs >500 mg/dL. 2. Market data on file. 3. Sanchez et al. Lipids in Health and Dis. 2021;20:72. 4. Berberich et al. Lipids in Health and Disease 2021;20:98.
5. Fan et al., J Clin Lipidology 2019; 13:100-108. 6. Christian et al., Am J Cardiol 2011;107:891-897.

Priority Launch Segment Focuses on Prescribers Most Motivated for Olezarsen

SHTG Prescriber Base

Prescriber Segment	TG 1st Line Treatment	Launch Stage
Aggressive	Treat TGs >500	Priority
Active	Treat TGs >880	
Passive	Diet, lifestyle modifications	Growth

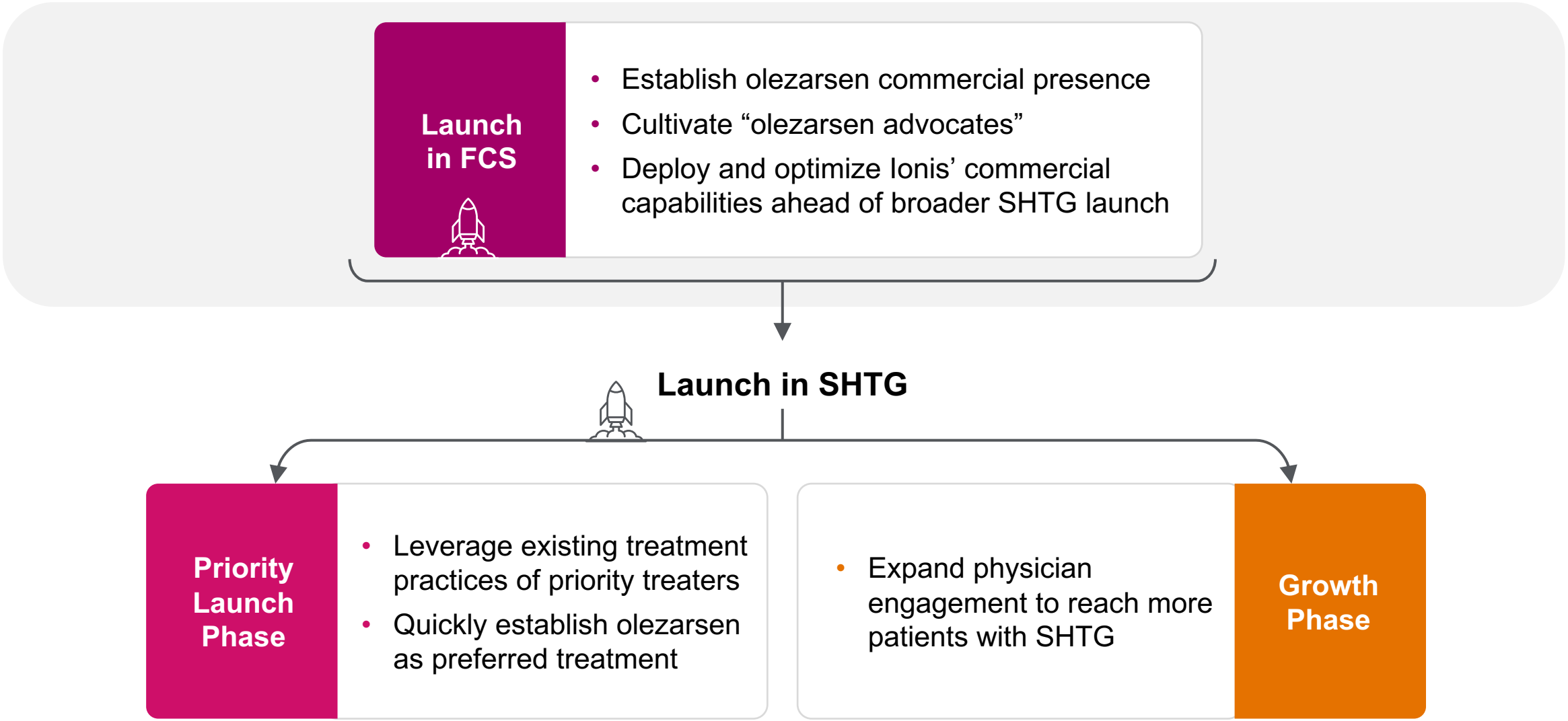
Key Attributes of Priority SHTG Treaters

- **Highly dissatisfied with current SHTG lowering therapies**
- **Strong belief in the importance of managing non-fasting TG levels**
- **Motivated to start all patients on new TG-lowering therapy**

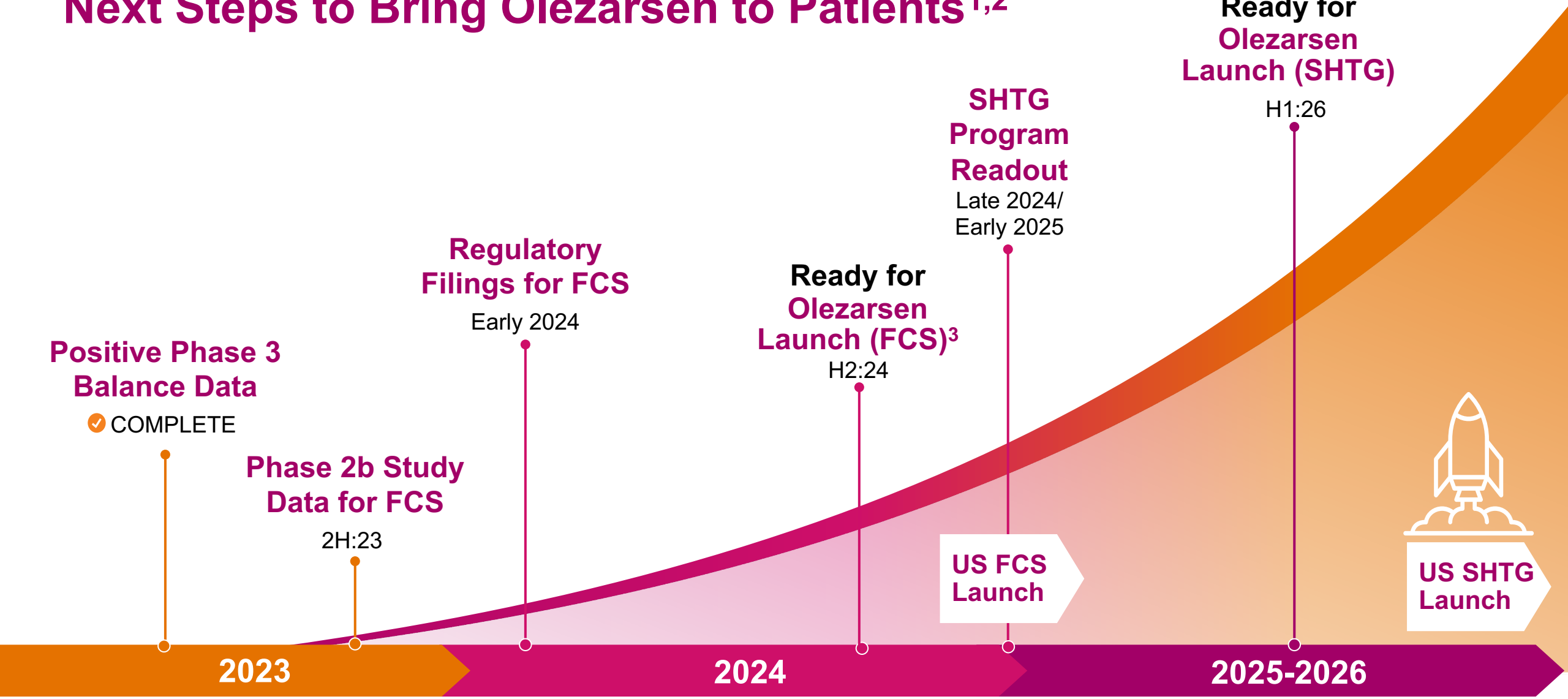
"Could be life-changing for patients - HCP"

SHTG Segmentation Research, June 2023.

Olezarsen Launch is Designed for Commercial Success



Next Steps to Bring Olezarsen to Patients[1,2]



1. Timing expectations based on current assumptions and subject to change 2. Assuming approval. 3. Assuming priority review.

Olezarsen: A Potential New Standard-of-Care Treatment for Patients with FCS and SHTG[1,2]

FCS and SHTG patients have a clear and **urgent unmet medical need**

Robust APOCIII reductions, **significant TGs reductions** and **substantial reductions in acute pancreatitis** in Balance Phase 3 study

FCS regulatory filings planned for 2024; **SHTG** Phase 3 study readouts expected **late 2024/early 2025** depending on enrollment

Olezarsen is the **first of many medicines** expected to launch from our **wholly owned pipeline**

1. Based on data generated to date. 2. Assuming approval.

Donidalorsen

A Potential Advance in Prophylactic Treatment for Hereditary Angioedema

Hereditary Angioedema

An Unpredictable, Debilitating and Potentially Life-threatening Disease

Raffi Tachdjian, M.D., MPH, FAAAAI, FACAAI

Associate Clinical Professor of Medicine and Pediatrics, UCLA School of Medicine;
Chief, Division of Allergy and Immunology, Providence St. John Medical Center

Disclosures

- **Speaking and advisory honoraria**: Biocryst, CSL Behring, Ionis, Kalvista, Pharming, Takeda
- **Research/Grants**: Astria, Biocryst, CSL Behring, Ionis, Kalvista, Pharming, Pharvaris, Takeda

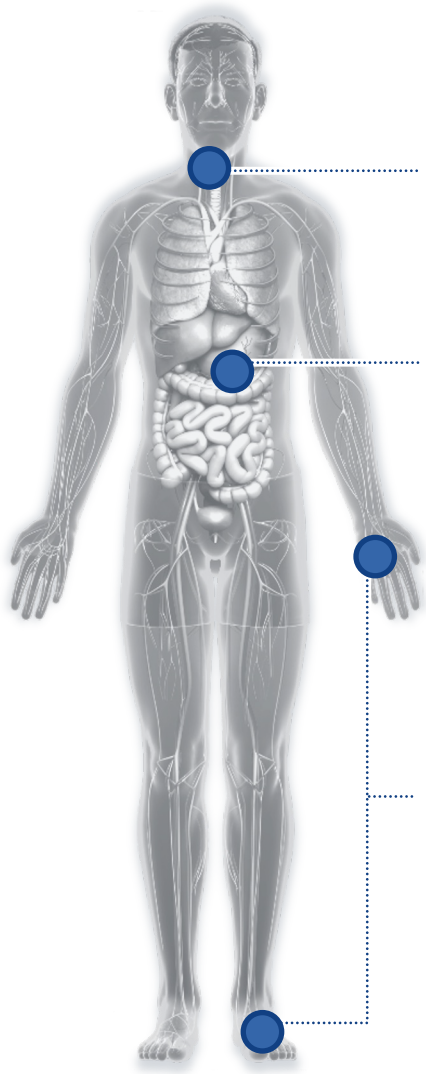
Hereditary Angioedema (HAE) Disease Overview[1-6]

A rare and potentially life-threatening **genetic disease** that often runs across family members

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

Inadequate C1 esterase inhibitor (C1-INH) activity causes aberrant activation of the kinin-kallikrein system

- Plasma prekallikrein (PKK) is produced in the liver and is the precursor of kallikrein
- Uncontrolled kallikrein activation leads to elevated bradykinin levels and HAE symptoms mediated through BK2 receptor activation



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.

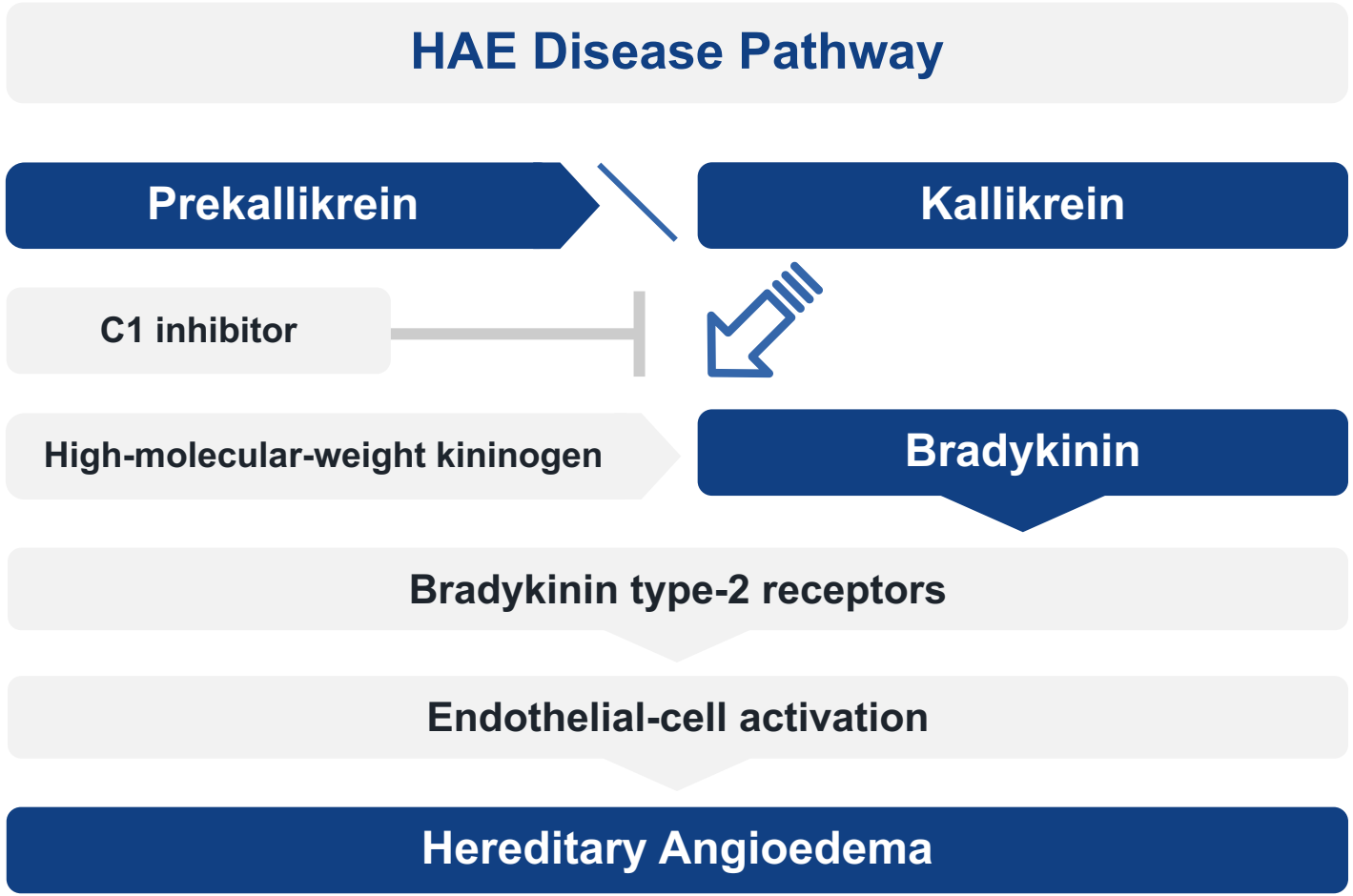
Overactivity of the Prekallikrein Pathway in HAE[1]

Insufficient or Dysfunctional C1-Inhibitor Results in:

Overactivity of the PKK pathway

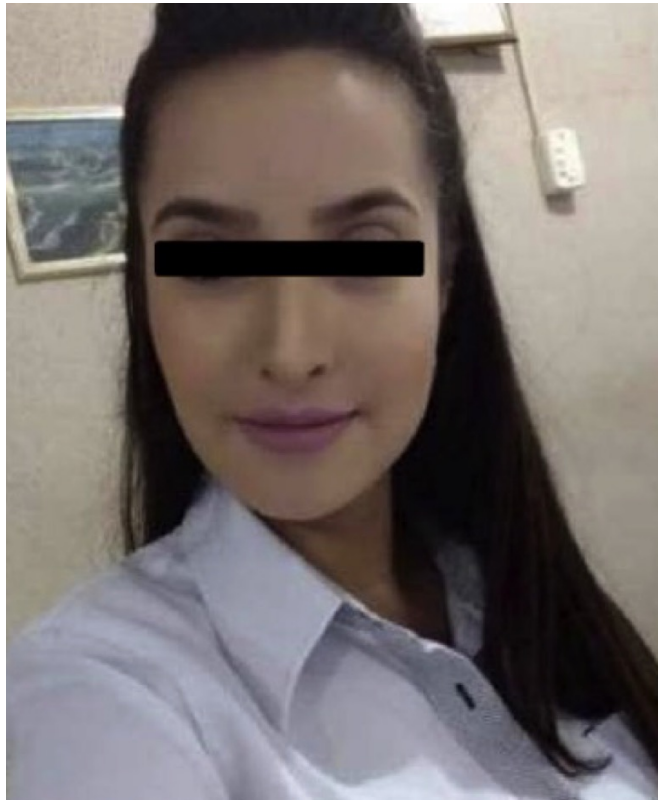
Excessive bradykinin production

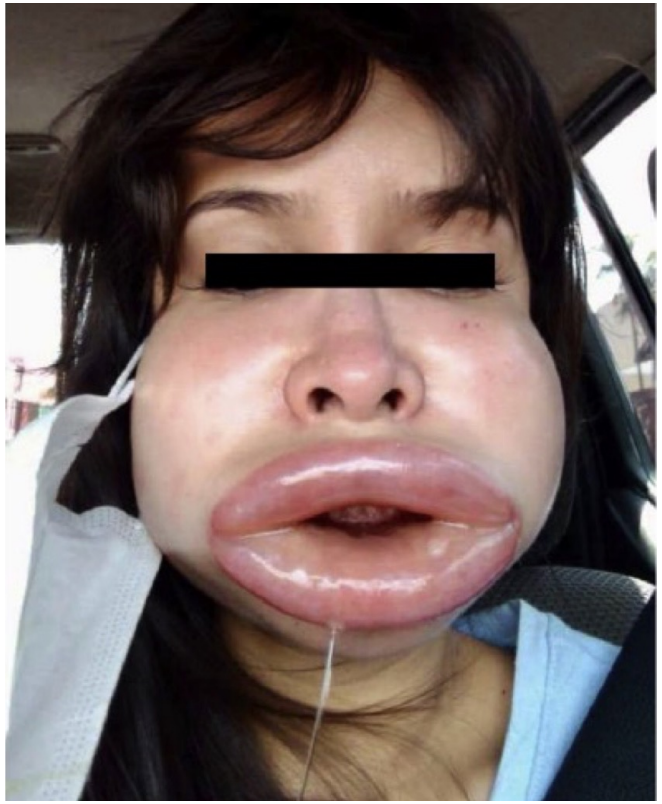
Severe swelling, characteristic of HAE

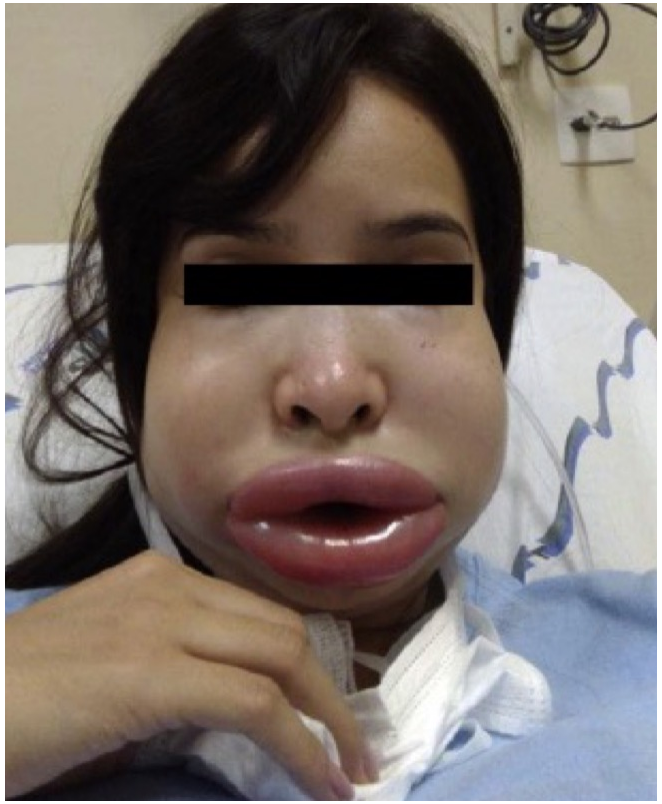


1. Lumry (2103) Am. J. Manag. Care. 19:S103-S110

HAE Attacks are Unpredictable, Debilitating and can be Fatal[1]







Images from Arruda LK,et al. J Aller Clin Immun 2021. https://doi.org/10.1016/j.jaci.2021.05.023.

1. Busse, P.J. and Christiansen, S.C., 2020 NEJM.

HAE: Prevalence and Types[1-6]

>20K

Patients in the US and Europe with HAE[1]

Estimated incidence of 1:50,000

HAE due to C1-INH Deficiency

Type I

Caused by loss of C1-INH **~80-85% of HAE patients**

Type II

Caused by improper function of C1-INH **~15-20% of HAE patients**

HAE with normal C1-INH

Poorly defined, but sometimes caused by an activating mutation in FXII

Extremely Rare (<1%)

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.

HAE: Disease Onset and Diagnosis[1-7]

Age of HAE onset varies[3,4]

50% of people experience an attack before the age of 10

Most experienced their first attack **before the age of 18**

10% report initial symptoms between the ages of 18-25

HAE attacks have been reported in children **as young as 1 year old**

Challenging Diagnosis[4]

Patients experience an average of **5 years to diagnosis**, with patients between 40-60 years old **averaging 8 years** and patients **older than 60 averaging 15.5 years**

Diagnostic tests[7]

Common: Blood tests (C1-INH quantitative, C1-INH functional, C4)

Uncommon: SERPING1 gene testing (blood, saliva or buccal)

Normal C1-INH: no approved diagnostic test[4]

25% of patients diagnosed **do not** have a family history of HAE

1. Busse, P.J. and Christiansen, S.C., 2020 NEJM ; 2. Busse 2020 J Allergy Clin Immunol Pract; 3. HAEI; 4. Sandra C. Christiansen MD , Joyce Wilmot MS , Anthony J. Castaldo MPA , Bruce L. Zuraw MD, For the US HAEA Medical Advisory Board members, The US HAEA Scientific Registry: Hereditary Angioedema Demographics, Disease Severity, and Comorbidities, Annals of Allergy, Asthma Immunology (2023)
5. Banerji, A. et al., 2020 Ann Allergy Asthma Immunol; 6. Banerji, A. et. al. 2015 Allergy & Asthma. 7. HAEA.

Attacks Can Significantly Impact People with HAE[1,2]

HAE Attack Impact on Patients[1]

87%	have gone to the ER
67%	have been hospitalized
16%	have been intubated (ICU admission)
16%	have had inappropriate abdominal surgery

Attacks may last from 1–5 days, if untreated

Attacks can **interfere** with patients' **daily activities,** including attending work or school

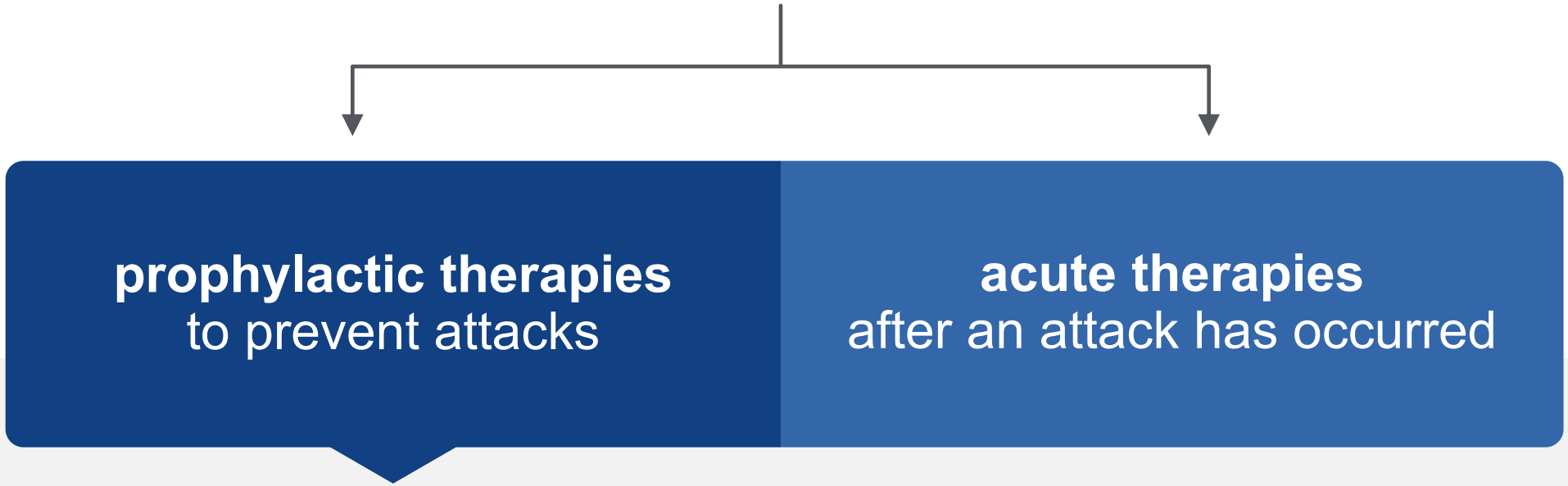
Unpredictable attacks can **reduce quality of life**

"I have been **intubated** three times. The very first time they had to **resuscitate me** because they had trouble getting the tube down. I stayed in the **ICU** for **three days**…"

1. Sandra C. Christiansen MD , Joyce Wilmot MS , Anthony J. Castaldo MPA , Bruce L. Zuraw MD , For the US HAEA Medical Advisory Board members, The US HAEA Scientific Registry: Hereditary Angioedema Demographics, Disease Severity, and Comorbidities, Annals of Allergy, Asthma Immunology (2023) 2. HAEI.

Current Treatment Landscape[1]

Treatments Are Divided Into:



Approved prophylactic therapies require frequent administration

(daily, twice weekly, bi-weekly, with limited patients dosed every 4 weeks)

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

New Treatment Options for HAE Still Needed[1]

Patient reported data collected by the US HAEA across **>500 participants** showed:

57% of those surveyed reported **using a prophylactic medication in the past 12 months**

34% of those surveyed reported **> 2 attacks per month**

13% reported they have **good control of their disease with ≤1 attack reported per year**

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

Key Takeaways

Sense of **urgency** in **HAE community** to help patients who's lives can be significantly impacted by their **unpredictable disease**

On **average** it takes **multiple years** for patients to be **diagnosed** with **25%** of patients with **no family history**

Despite **approved prophylactic treatments** on the market today, **less than 15% of patients report having good control** over their disease

---

Patients are **looking for better treatments** to **reduce disease** and **treatment burden**

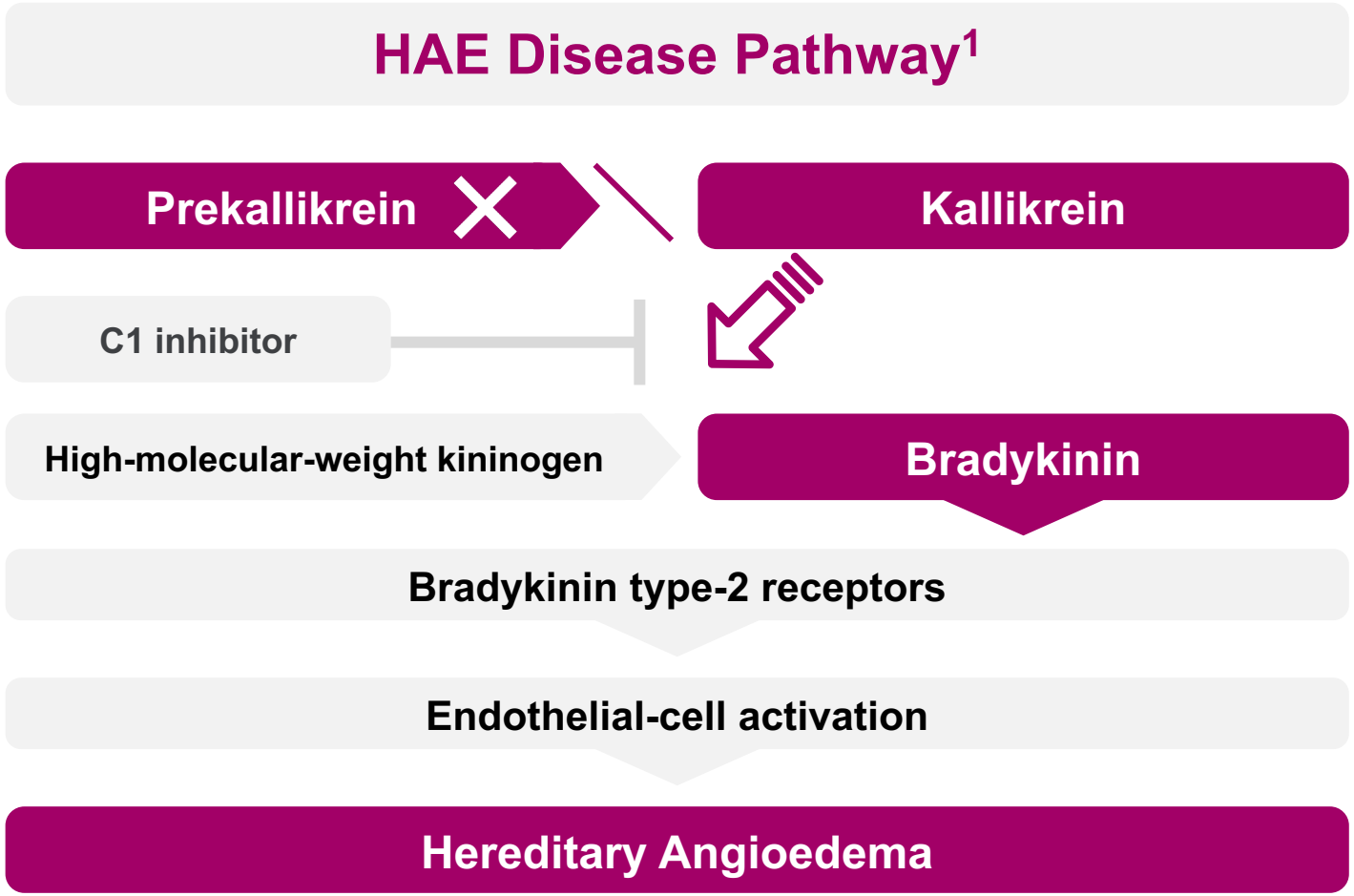
Donidalorsen: A Potential Advance in Prophylactic Treatment for HAE

Kenneth Newman, M.D.

Senior Vice President, Clinical Development

Donidalorsen is Designed to Reduce the Production of PKK, The Root Cause of HAE

Donidalorsen



1. Lumry (2103) Am. J. Manag. Care. 19:S103-S110.

Positioned to Demonstrate Compelling HAE Prophylactic Profile as a Once Monthly Treatment[1,2]

Donidalorsen

Positive Phase 2 data published in *New England Journal of Medicine*

Positive Phase 2 1-year OLE data, including positive QoL data reported

New 2-year Phase 2 OLE data reinforce donidalorsen's **compelling profile**

OASIS

Phase 3 study ongoing
Fully enrolled

Data expected in H1:2024

OASIS plus

Switch study underway
in patients previously treated with other prophylactic therapies

Phase 3 OLE study underway
in patients who have completed OASIS

1. Based on double blind Phase 2 study data published in NEJM in 2022 and Phase 2 OLE data. 2. Timing expectations based on current assumptions and subject to change.

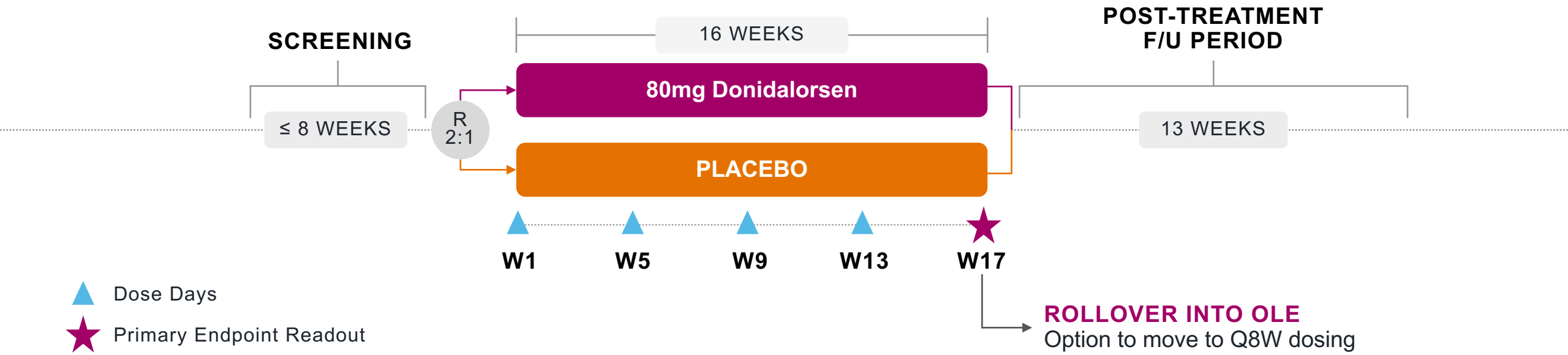
Donidalorsen Phase 2 Study in Patients with HAE

KEY INCLUSION CRITERIA

Randomized, double-blind, placebo-controlled study of monthly subcutaneous injections **of donidalorsen or placebo** in 20 patients, age 18 and above, with HAE Type 1 and Type 2 who had two or more attacks during screening

PRIMARY ENDPOINT

Time-normalized number of HAE attacks (per month)



Donidalorsen Phase 2 Study Results: Compelling HAE Prophylaxis Profile[1]

Rapid and **Sustained** Reductions in HAE Attacks[1]

Statistically and Clinically **Significant Improvement** in **QoL**[1]

Favorable Safety and Tolerability Profile[1]

90%

Mean Reduction in Monthly HAE Attacks vs. Placebo

WEEKS 1-17

97%

Mean Reduction in Monthly HAE Attacks vs. Placebo

WEEKS 5-17

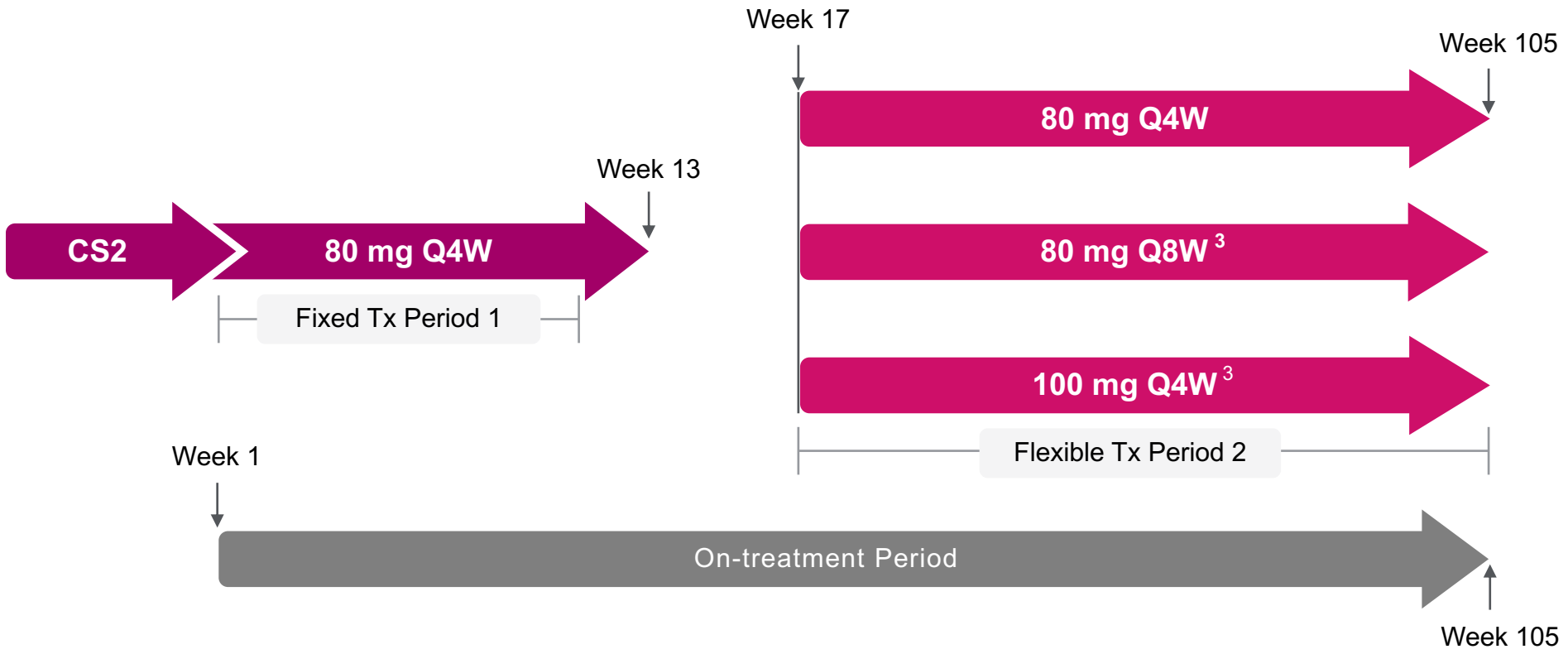
92%

Treated Patients Were Attack-Free vs. **0%** Patients on Placebo

WEEKS 5-17

1. Based on double blind Phase 2 study data published in NEJM in 2022 and Phase 2 OLE data.

Phase 2 Open-Label Extension Study Design & Patient Disposition Through 2 Years of Treatment[1,2]



Patients 18 years or older who completed the randomized **Phase 2 study (CS2) through week 17** were **eligible** for enrollment

OLE on-treatment study periods were composed of a **fixed dosing period (Weeks 1-13)** and a **flexible dosing period (Weeks 17-105)**

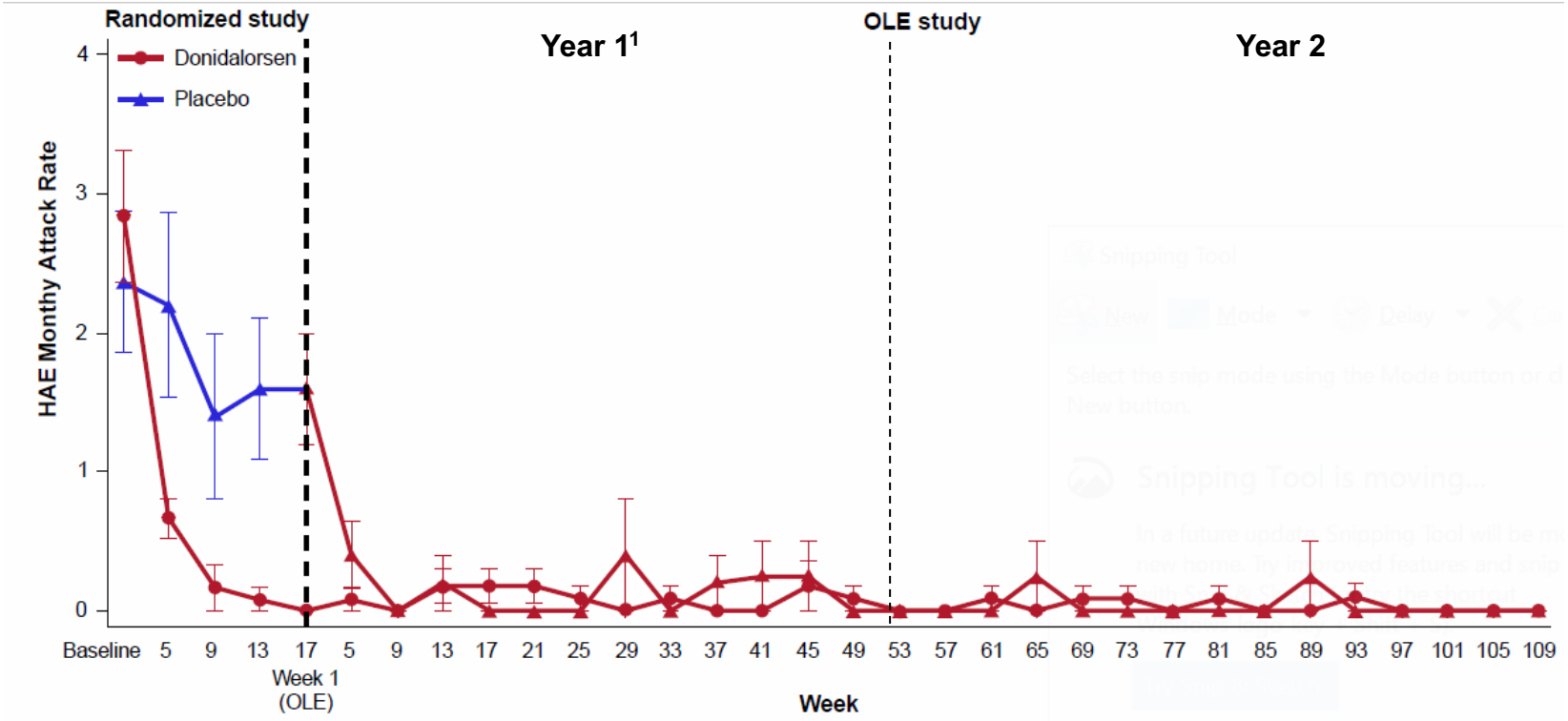
1. CS2, Phase 2 randomized study; Q4W, every 4 weeks; Q8W, every 8 weeks; Tx, treatment; OLE, open-label extension. 2. Bordone L, et al. Poster presented at 2023 American Academy of Allergy Asthma Immunology Annual Meeting; February 26, 2023. San Antonio, TX 3. Switch in dosing regimen as per the principal investigator.

Consistent and Sustained Protection from HAE Attacks Demonstrated Through 2 Years

Phase 2 two-year OLE Data showed donidalorsen treatment resulted in:

96%

overall sustained **mean reduction** from baseline in HAE attack rates



1. 1-year data: Bordone L, et al. Poster presented at 2023 American Academy of Allergy Asthma Immunology Annual Meeting; February 26, 2023. San Antonio, TX; HAE, hereditary angioedema; OLE, open-label extension. Bolded dashed black line indicates the end of the randomized phase 2 study and the beginning of the OLE study.

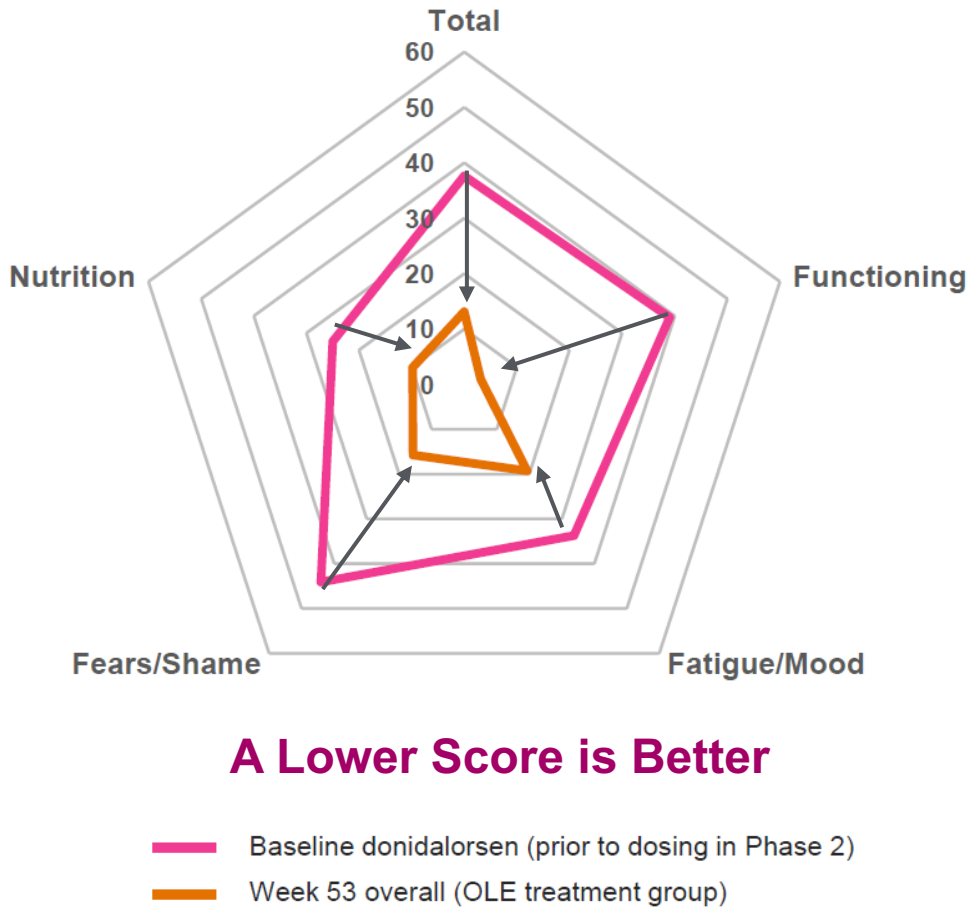
Phase 2 OLE Data Showed Clinically Significant Improvement in Quality of Life after 1 Year of Treatment[1]

Angioedema Quality of Life Questionnaire (AE-QoL) total score **improved by a mean change of 24.0 points** from baseline after 1 year, with improvements observed across all domains

- An improvement of 6 points or more is considered clinically meaningful[1]

12/14 patients had a clinically significant improvement, defined as at least a 6-point change in AE-QoL total score

- One patient did not complete the AE-QoL at Week 53



1. Bordone L, et al. Poster presented at 2023 American Academy of Allergy Asthma Immunology Annual Meeting; February 26, 2023. San Antonio, TX; CS2, randomized phase 2 study; CS3, open-label extension of the randomized phase 2 study; OLE, open-label extension. All patients received donidalorsen in the OLE study.

Donidalorsen Treatment Data Demonstrated Favorable Safety and Tolerability in the Phase 2 Study and continuing through 2 years in the OLE[1]

No serious adverse events (SAEs)

No treatment-emergent adverse events (TEAEs) led to discontinuation

- Injection site reactions / discolorations (n=2) were the only TEAEs reported in more than one patient
- Most common TEAEs unrelated to study drug were COVID-19 infection, UTI, and headache

No changes in electrocardiograms and no clinically significant changes in any laboratory parameters

1. Bordone L, et al. Poster presented at 2023 American Academy of Allergy Asthma Immunology Annual Meeting; February 26, 2023. San Antonio, TX
Newman KB, et al. Poster presented at 2023 American Academy of Allergy Asthma Immunology Annual Meeting; February 26, 2023. San Antonio, TX
Tayefeh L, et al. Poster presented at 2023 American Academy of Allergy Asthma Immunology Annual Meeting; February 26, 2023. San Antonio, TX

Donidalorsen OASIS-HAE Phase 3 Study

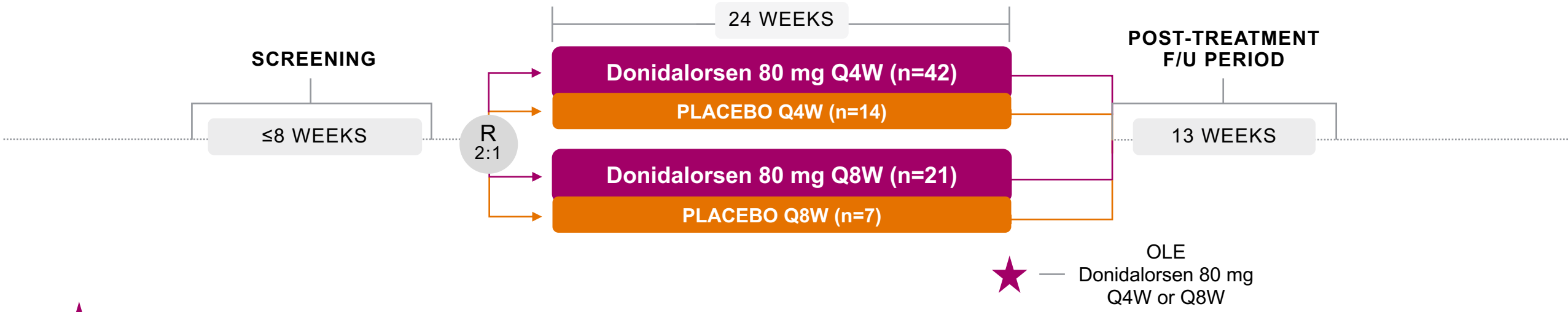
Pivotal Study in Patients with HAE

DESIGN

A global, randomized, double-blind, placebo-controlled study of monthly and bi-monthly subcutaneous injections **of donidalorsen or placebo** in 91 patients, age 12 and above, with HAE Type 1 and Type 2

PRIMARY OUTCOME

Time-normalized number of HAE attacks (weeks 1 - 25)



Fully Enrolled with 91 Patients; Data in H1:2024[1]

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

Donidalorsen OASIS Plus Phase 3 Study OLE

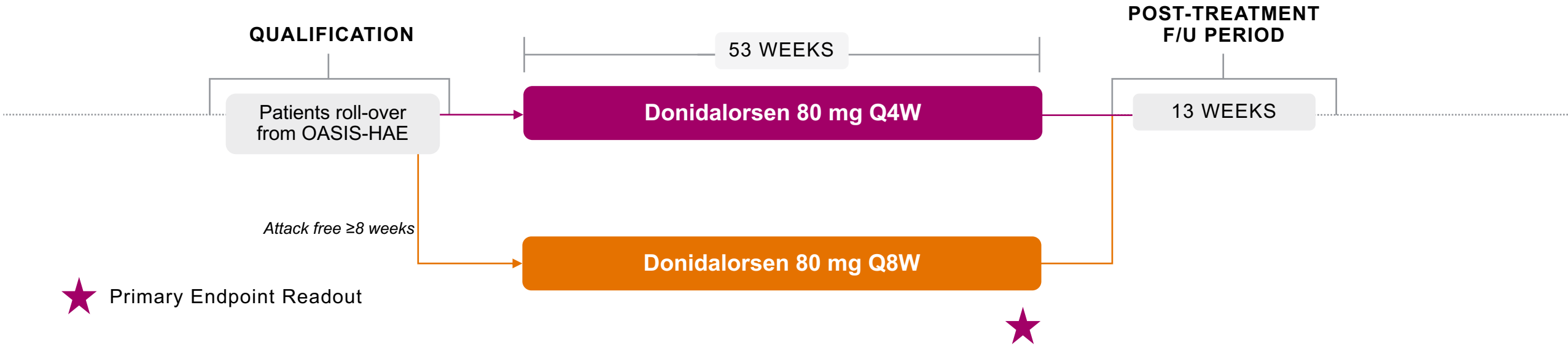
OLE in Patients with HAE

DESIGN

Open label extension study of every 4 weeks or every 8 weeks subcutaneous injections **of donidalorsen** in 91 patients, age 12 and above, **with HAE Type 1 and Type 2**

PRIMARY OUTCOME

Incidence and severity of **treatment-emergent adverse events (TEAEs)**



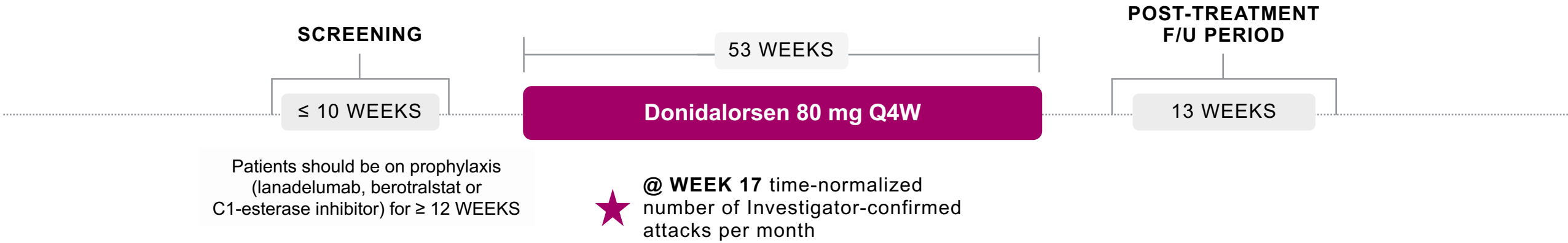
Donidalorsen OASIS Plus Phase 3 Switch Study

DESIGN

An Open Label study of every 4 weeks subcutaneous injections **of donidalorsen in up to 60 patients, age 12 and above, with HAE Type 1 and Type 2**

OBJECTIVES

- Show comparative efficacy with other prophylactic HAE medications
- Demonstrate how to switch to donidalorsen without loss of control or adverse events
- Evaluate patient satisfaction and preference for donidalorsen vs other therapies



★ Primary Endpoint Readout

Switch Data Planned Mid-2024[1]

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

Donidalorsen: A Potential Advance in Prophylactic Treatment for Hereditary Angioedema

Compelling Data Generated To Date Demonstrating Rapid and Sustained Reductions in HAE Attacks[1]

Clinically Significant Improvement in QoL[1]

Favorable Safety and Tolerability Profile[1]

Phase 3 Data Planned for H1:2024[2]

1. Based on double blind Phase 2 study data published in NEJM in 2022 and Phase 2 OLE data. 2. Timing expectations are based on current assumptions and are subject to change.

Donidalorsen: Bringing it to Patients

Onaiza Cadoret

Executive Vice President, Chief Global Product Strategy & Operations Officer

HAE Market Dynamics Underscore Donidalorsen Potential[1,2]

Well Defined
Patient Population

Rapidly
Increasing Rate
of Prophylaxis
Treatment

Patients
Have Shown
Willingness to Switch

Concentrated
Prescriber Base
in the US

Efficient
Commercial Model

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.

Donidalorsen

A Once-Monthly Self- Administered Potential Advance in Prophylactic Treatment for Hereditary Angioedema

>20K

Patients in the United States and Europe suffering from HAE[1]

Indication	Peak Sales[2]
HAE	>$500 Million

Designed to **Reduce** the Production of PKK, **the Root Cause of HAE**

Studies Showed **Rapid and Sustained Reductions** in HAE **Attacks**[3]

Positioned to Demonstrate **Compelling HAE Prophylaxis Profile**[3]

1. Market data on file. 2. Ionis peak sales estimates are based on current assumptions and are subject to change. 3. Based on Phase 2 and Phase 2 OLE data.

Significant Need Remains Despite Multiple Approved Therapies

Donidalorsen Showed Rapid, Sustained Protection from Attacks with 96% Mean Reduction in Attacks through 2 Years of Treatment[1]

Patients **still experience breakthrough attacks** with current medications

Approved prophylactic therapies require frequent administration (daily, weekly or bi-weekly) that can negatively impact patient compliance

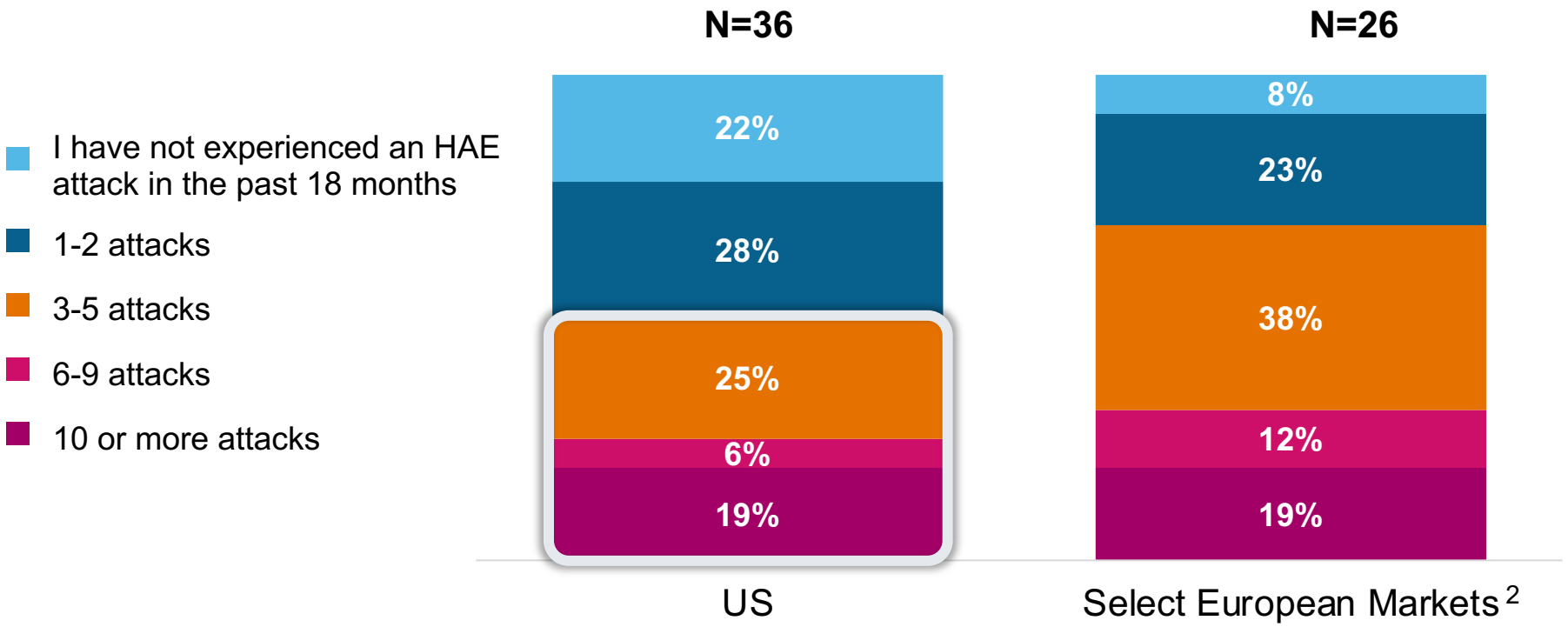
Patients seek to **regain their freedom** from the disease and **improve their quality of life**

Continued **need** for a **prophylactic treatment** offering HAE patients **greater efficacy** and **tolerability** that is **easy to use**

1. Based on Phase 2 and Phase 2 OLE data.

Most Patients Still Experience Attacks on Currently Approved Prophylactic Treatment[1]

Patient-Reported Number of HAE Attacks in Past 18 Months[1]

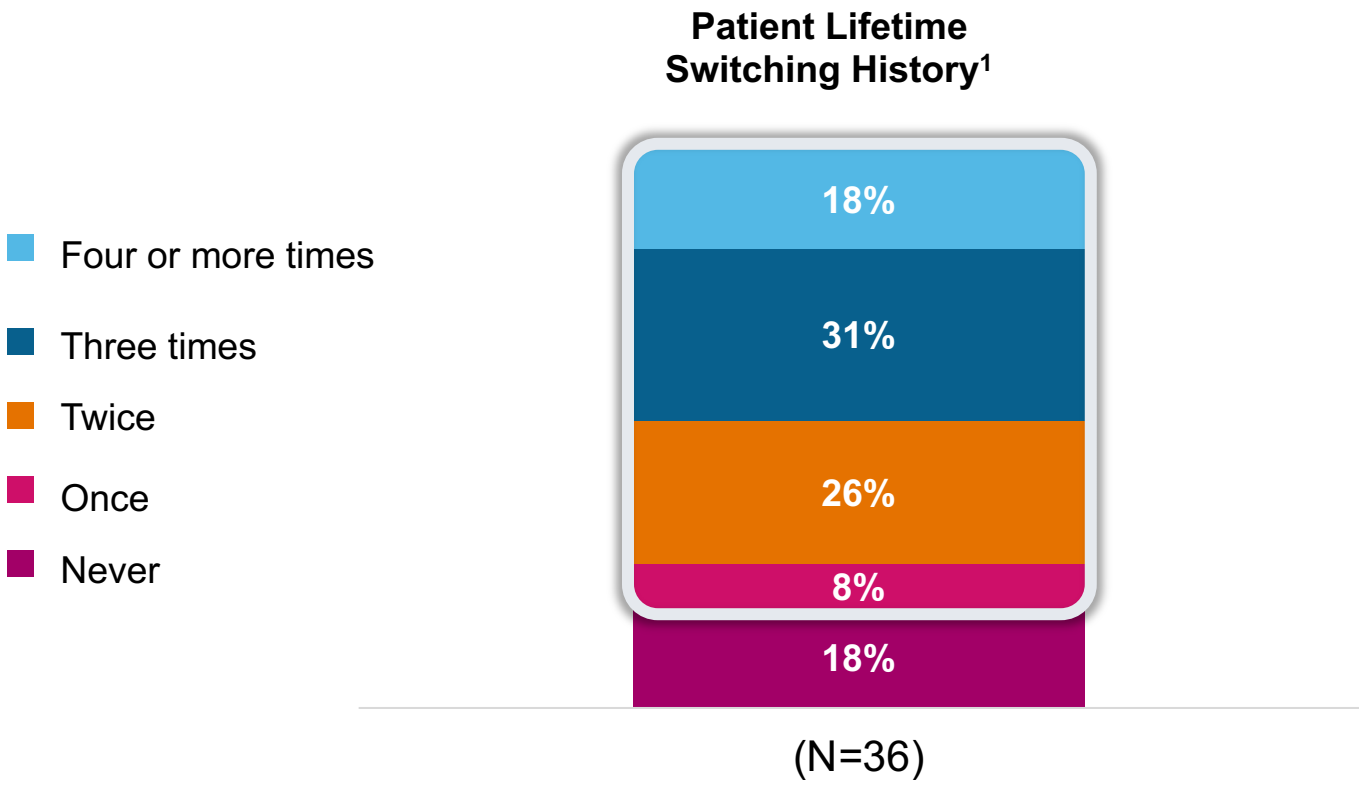


50%
of US Patients had 3 or More Attacks in the Past 18 Months[1]

1. Ionis primary qualitative market research mid-2022; 2. European markets include: UK, Germany and Spain.

Patients Demonstrate Willingness to Switch Prophylactic Treatments[1]

>80% of Patients Have **Switched Treatments[1]**



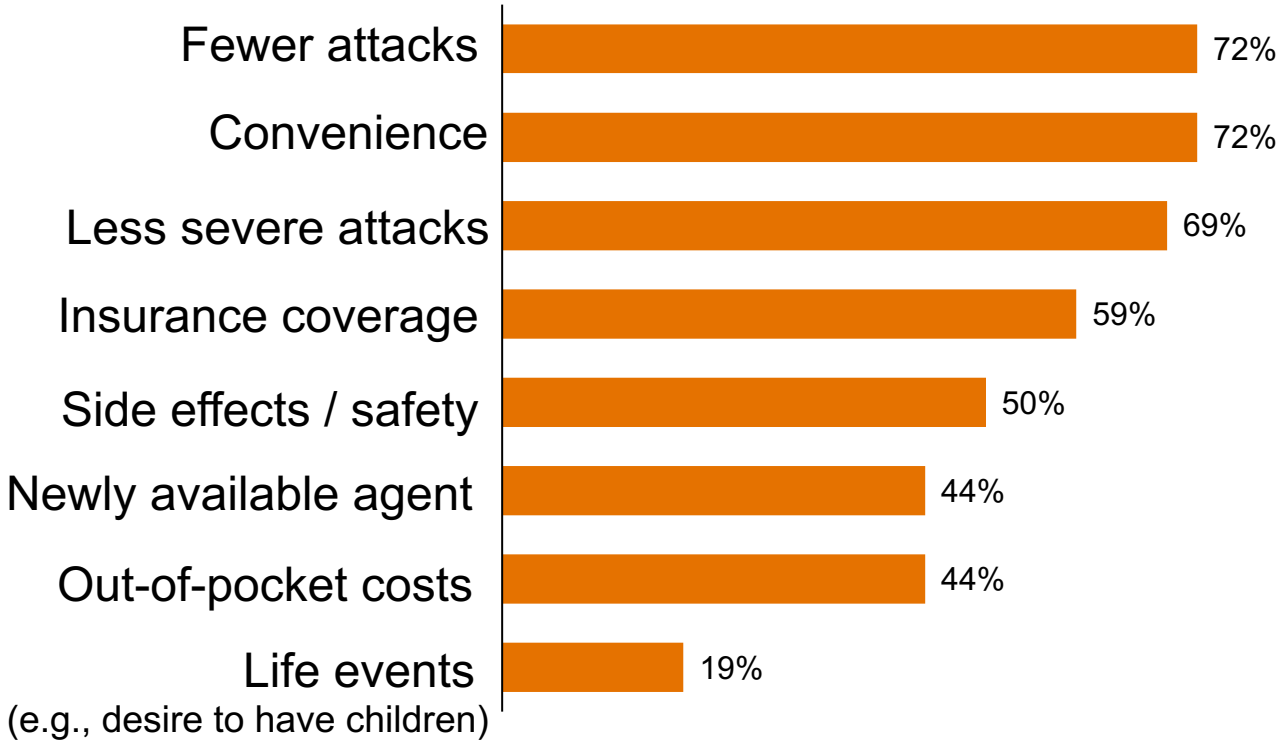
Patient Switching Driven By[1]:

- Improved efficacy (fewer attacks)
- Improved convenience
- Less severe attacks

1. Ionis primary qualitative market research, 2022.

Top Drivers for Patients Switching Treatments: Efficacy, Convenience, Insurance Coverage[1]

Patient Triggers of Most Recent Switch



> **"My prior medication didn't work properly. I would have breakthrough attacks"**

> **"The previous medication […] I was on just really hurt when administered it, and I had to do it myself, obviously. So I switched and also had to be stored in the fridge. It's just very complicated."**

1. Ionis primary qualitative market research 2022; N = 32 Patients.

Patients Have Strong Interest in Donidalorsen[1,2]

When presented a blinded profile of donidalorsen during market research, **almost all patients (~98%[1])** were moderately or very **enthusiastic** about **donidalorsen**

> Going to dosing once every two weeks has been great! **So once every four and with a small injection sounds even better.**

> I would be extremely interested. If it was available tomorrow, I'd go ask my doctor about it. (To switch) It wouldn't take much… **Taking it once a month, and potentially only once every two months is very attractive.**

1. Ionis primary qualitative market research , 2022. N = 36 Patients. 2. Ionis primary qualitative market research 1Q2021

HCPs View Donidalorsen Expected Target Product Profile (TPP) as a Potentially Meaningful Advance in Treating HAE[1,2]

When presented a blinded **expected target product profile** (TPP) of donidalorsen during market research all physicians viewed donidalorsen as **favorable across all dimensions**, including:

- Reduced Attack Frequency
- Reduced Attack Severity
- Attack Free Rate
- Onset of Action
- Expected Patient Compliance
- Dosing Frequency
- Ease of Administration
- Mechanism of Action

HCP Feedback on Donidalorsen Expected TPP[2,3]:

"Impressive"

"Appealing"

"Looks Really Good"

"Increased Freedom"

1. Ionis primary qualitative market research N = 50 Physicians; 2. Donidalorsen TPP took into consideration Phase 2 data. 3. Ionis primary qualitative market research 1Q2021, Allergist / Immunologist respondents

Efficient and Targeted Approach to Reach Patients and HCPs

Concentrated Prescriber Base

Majority of HAE Patients in the US are Treated by Allergists

~1,000 Allergist/Immunologists Manage >70% of HAE Patients[1]

Efficient Field Team

Targeting <100 Customer-Facing Team:

Field Sales Reps Focused on Top Allergist & Immunologist Prescribers

Patient Education Managers Supporting Donidalorsen Patients

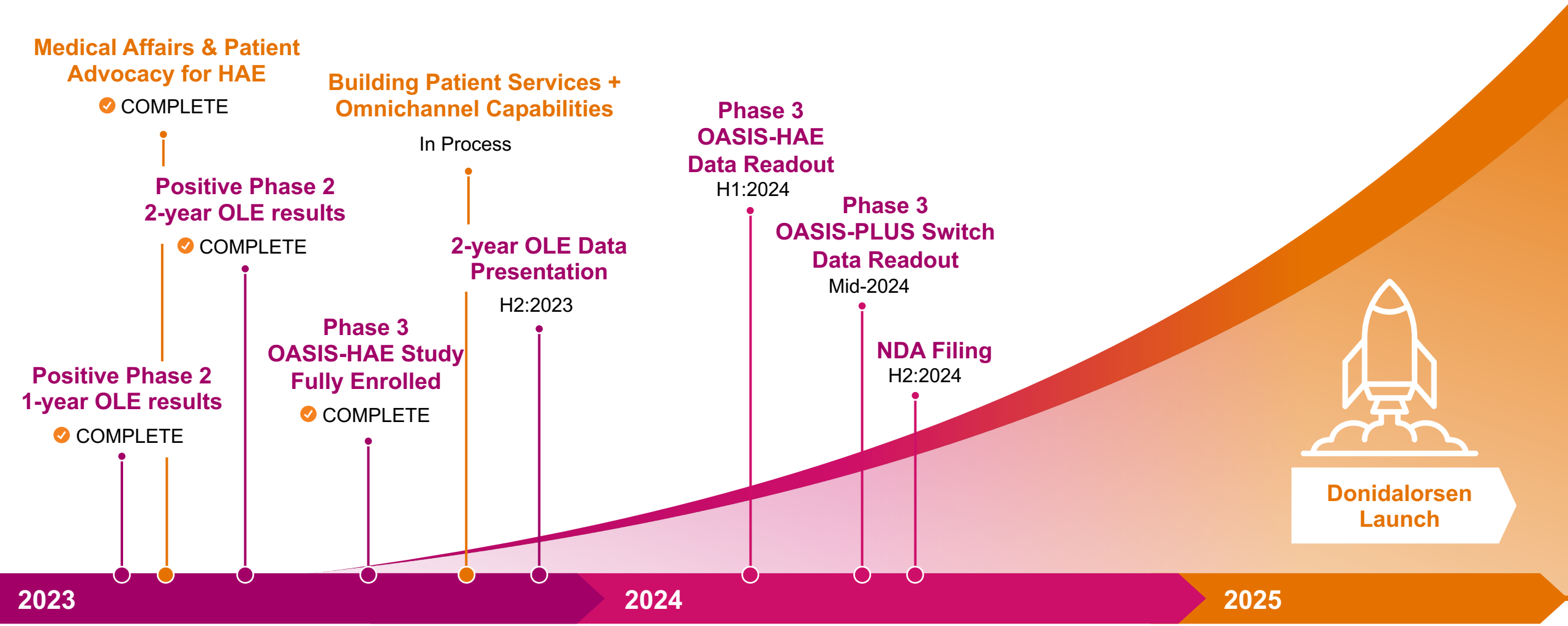
Direct-to-Patient Engagement

Dedicated High-Touch Patient Services

Continued Engagement and Adherence Through Integrated Omnichannel Solutions

1. Ionis secondary market research (2021).

Next Steps to Bring Donidalorsen to Patients[1,2]



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

Driving Donidalorsen Success in a Dynamic Market

Strong Product Profile

QoL & Switch Studies

Access & Patient Support Hub

Patient Engagement

Key Takeaways for Our Medicines on the Horizon[1]

Eplontersen | Olezarsen | Donidalorsen

Poised to Address Significant Patient Needs

ATTR: Underserved and growing patient population

FCS: No disease modifying treatments currently approved in the US

SHTG: Underserved broad patient population

HAE: Substantial unmet need remains

Ready to Deliver to Patients

Applying our commitment to **Innovation** to bring medicines to patients

Starting **first** with **eplontersen** with AstraZeneca[1]

Followed by independent launches for **olezarsen** and **donidalorsen**[1]

1. Assuming approval.

Technology Advances Power Our Future Medicines

Eric Swayze, Ph.D.

Executive Vice President, Research

Ionis Technology Advances Have Resulted in a Rich History of Transformational RNA-Targeted Medicines

Invented best-in-class chemistry as the basis for all our drugs

Optimized delivery to the CNS via local administration

Pioneered mechanisms to modulate gene expression
- Downregulation (e.g. 'silencing' of toxic genes)
- Upregulation (to replace function of missing or broken genes)

Targeted delivery to the liver

World-Class Research Organization: Advancing Technology for Future Medicines

Ionis' Technology Research is Focused on Achieving 3 Key Objectives:

Enhancing the Profile of New Therapies

Our new molecules entering the pipeline will be even better than the existing ones

Expanding Opportunities in Existing Franchises

Cardiovascular

Neurology

Opening Up Therapeutic Opportunities in New Spaces

Pulmonary

Renal

New Technology Advances are Expected to Enhance and Expand our Future Medicines

MsPA Backbone

Increases duration of effect

Improves therapeutic index

Ionis' siRNA Technology

Adds an additional technology (mechanism and chemical class)

For each new program, we evaluate multiple approaches and advance the best molecule

Targeted Delivery

Target heart and skeletal muscle with Bicycle peptides

Enabling future delivery of neurology drugs across the blood brain barrier (BBB)

MsPA Backbone

- Increases duration of effect
- Improves therapeutic index
- Broadly useful in new drugs in both existing and new therapeutic areas

Objectives in Designing the Next Generation Backbone

Maintain or improve potency

Improve duration of effect relative to existing designs

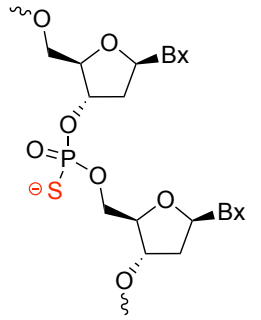
- Comparable to benchmark siRNA designs
- Phosphorothioate (PS) DNA limits metabolic stability (Splicing ASOs with no DNA have year long duration)

Reduce non-specific protein binding

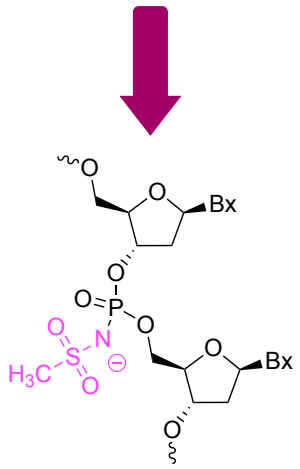
- Expected to improve safety and tolerability profile

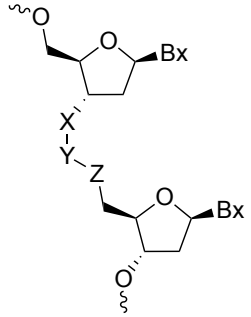
Retain other important attributes

- Binding affinity for RNA target
- Support enzymatic mechanisms (RNaseH1 and Ago2 activity)
- Chemical stability
- Ease and cost of manufacturing



Phosphorothioate (PS)

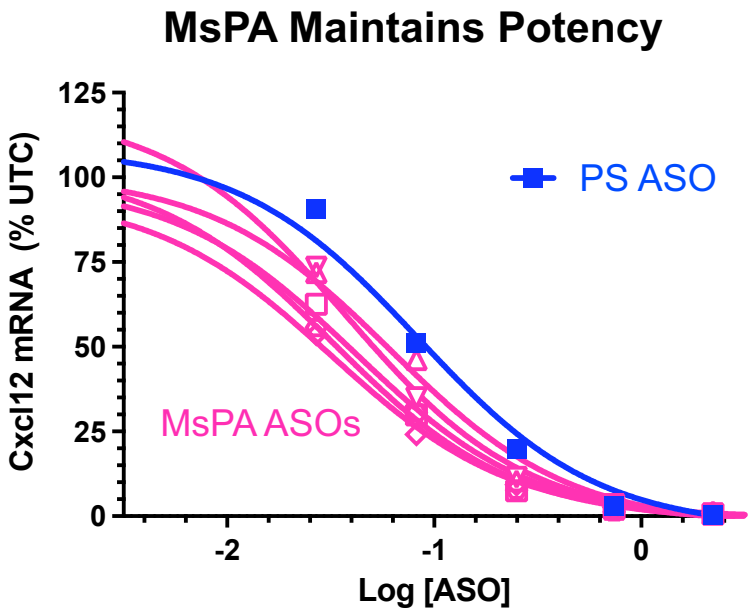


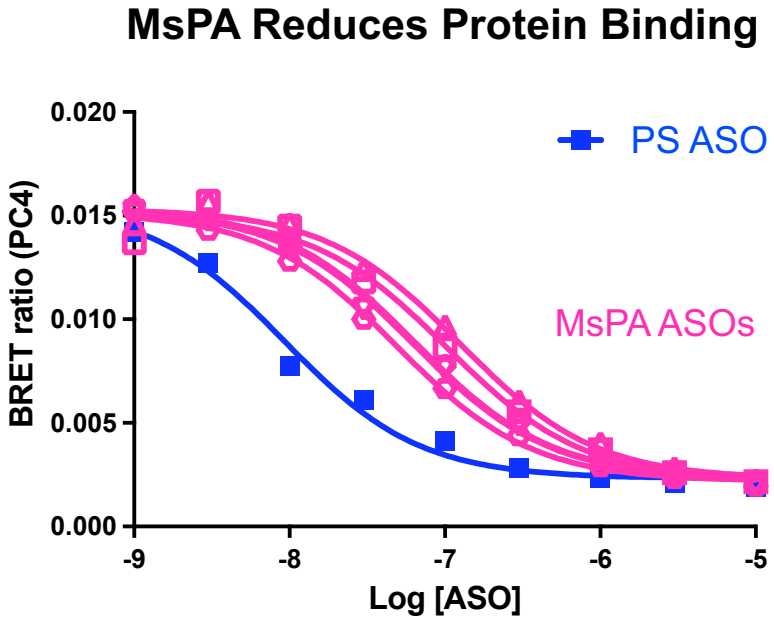


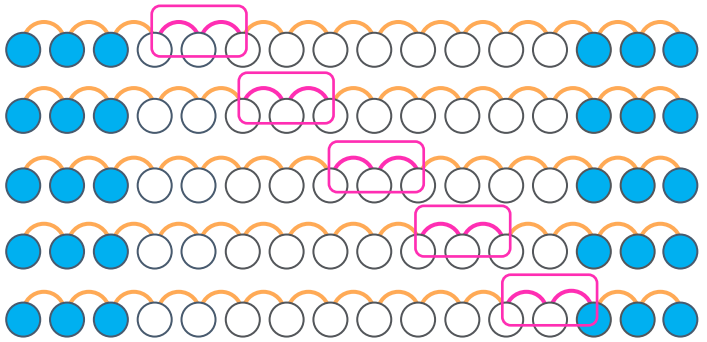
- Hundreds of backbones explored
- None had the desired features

Mesyl Phosphoramidate (MsPA) meets these key objectives

Minimal MsPA Content Can Reduce Protein Binding While Maintaining Potency



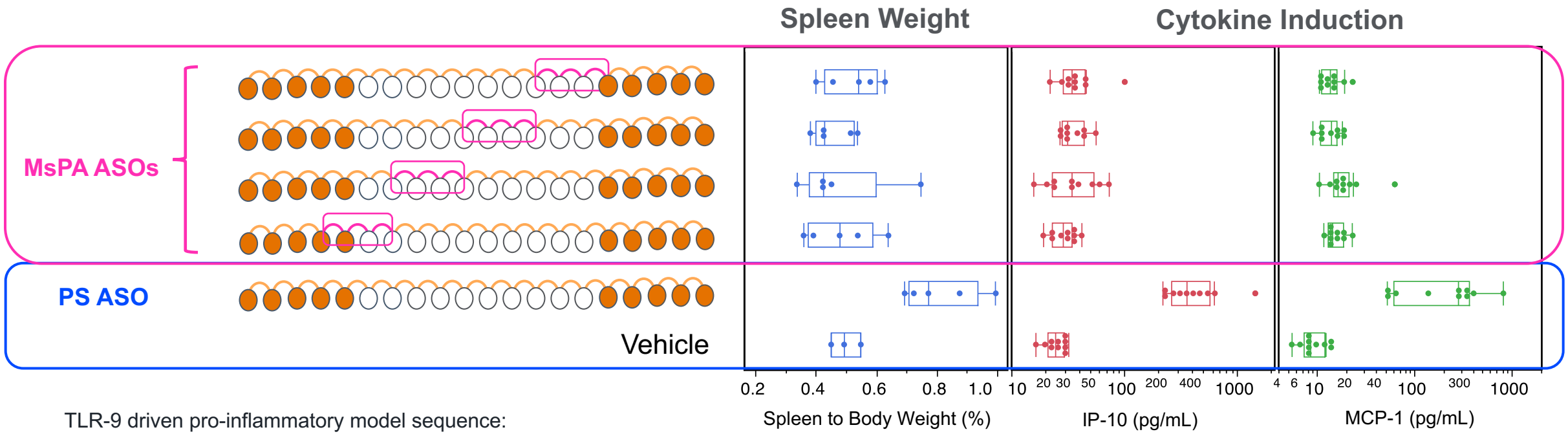




Sequence: G^{m}CATGTT^{m}CT^{m}CA^{m}CATTA; cEt, DNA, MsPA, PS

MsPA Decreases Immune Stimulation

Using a Known Proinflammatory Sequence, MsPA Reduced Immune Response in a Mouse Model

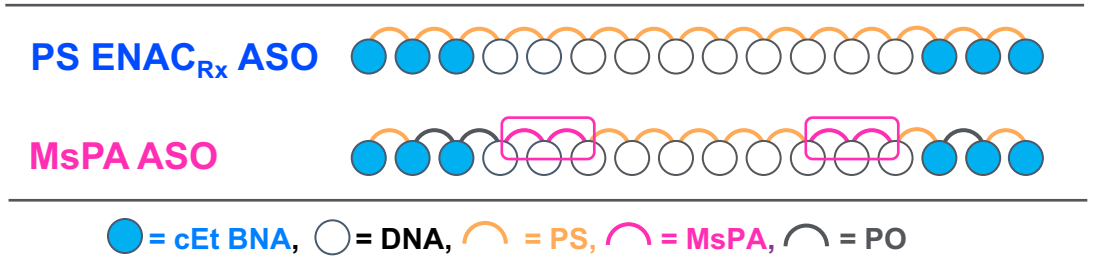


TLR-9 driven pro-inflammatory model sequence:
A^{m}CT^{m}CA^{m}CATTGA^{m}CA^{m}CTGAGGA
MOE, DNA, MsPA, PS

150 mg/kg ASO 6 hr post single dose in C57/BL6 mice

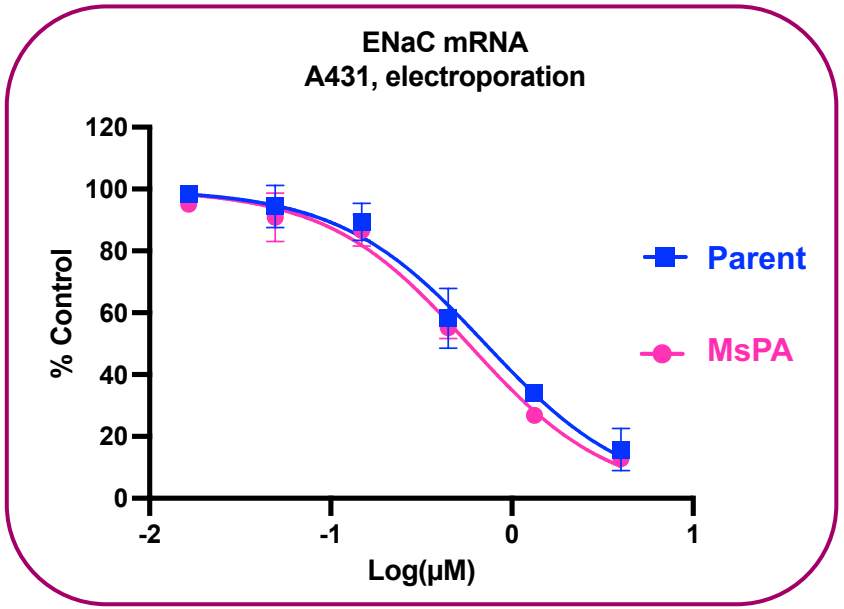
MsPA Substitutions in DNA Region of ASO Reduced the Immune Stimulatory Response

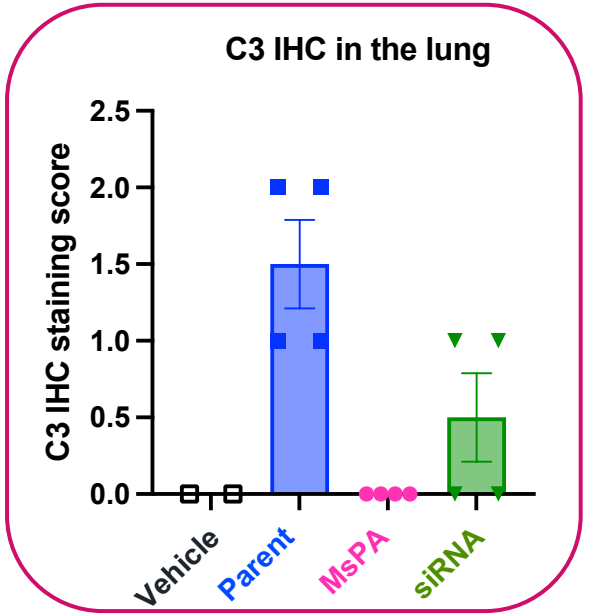
MsPA Improves the Profile of IONIS-ENAC$_{Rx}$ ASO in NHP Lung

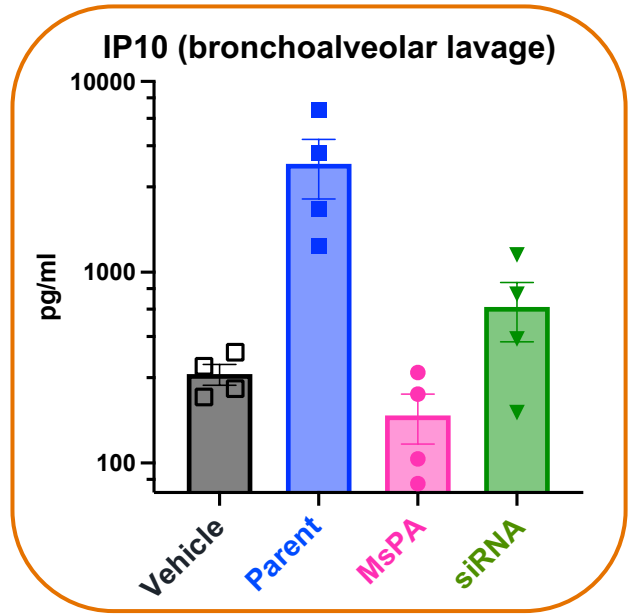


Sequence: $^{m}C^{m}C^{m}C$GATAG^{m}CTGGTTGT
15 mg/kg/week aerosol administration for13 weeks

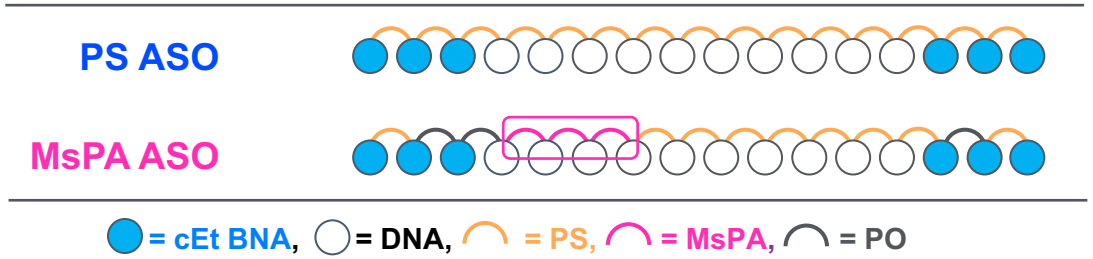
Objectives for MsPA Backbone	
✓	**Similar activity to parent drug**
✓	**No complement activation in NHP**
✓	**Improved profile in NHP** • Lower cytokines/chemokines and cell recruitment • Improved histopathology • No inflammation





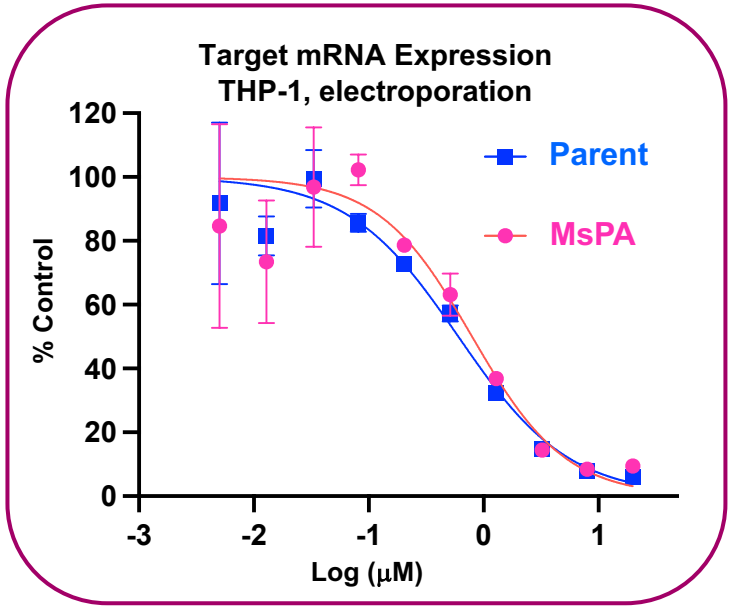


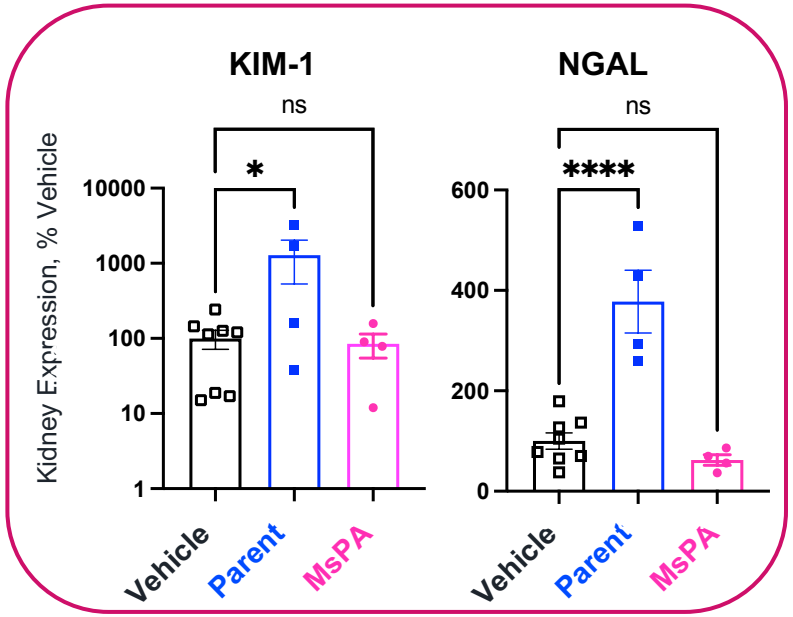
MsPA Improves the Profile of a Renal Target ASO in NHP



Sequence: AA^{m}CTATTAAG^{m}CAA^{m}CGG
30 mg/kg/week subcutaneous administration for 13 weeks

Objectives for MsPA Backbone	
✓	**Similar activity to parent drug**
✓	**No induction of kidney injury markers in NHP**
✓	**Improved profile in NHP** • No inflammation and/or chemokine/cytokine elevation • No platelet reductions • No significant histopathology observations





Histopathological Pro-Inflammatory Response

Inflammatory Infiltrates	Vehicle	Parent	MsPA
Kidney	-	++	-
Injection site	-	+++	+/-
Spleen	-	++	-

MsPA Increases Stability –

Can This Improve Duration?

Current Platform Delivers Attractive Profiles with Infrequent Dosing and Consistent Target Suppression

$MAPT_{Rx}$ data suggest CNS durability to support > every 6-month dosing

Liver targeted delivery supports monthly dosing regimens

Splicing ASOs with no DNA have >1 year duration of effect in mouse

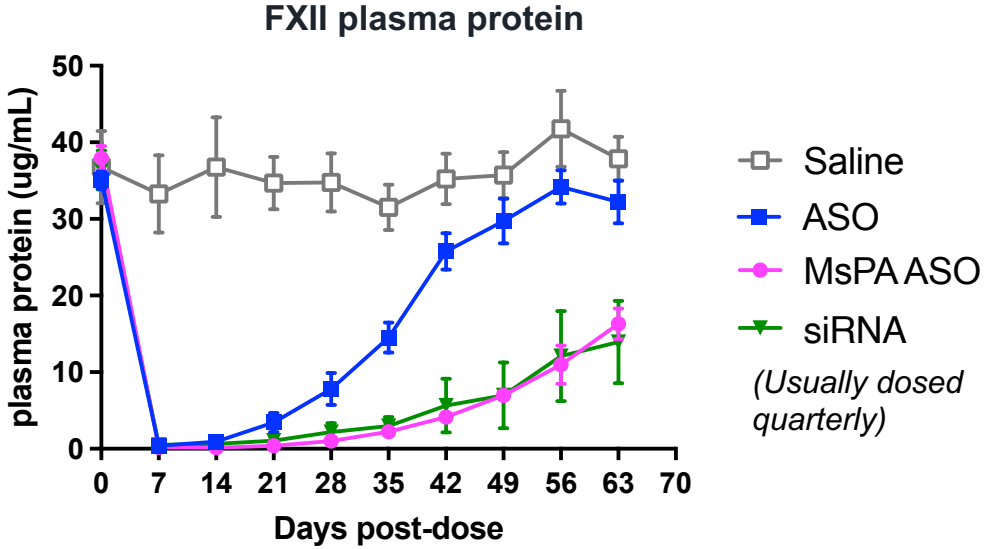
HYPOTHESIS

Substitution of MsPA at metabolized points in an ASO (the PS DNA) should Improve Durability due to Increased Stability

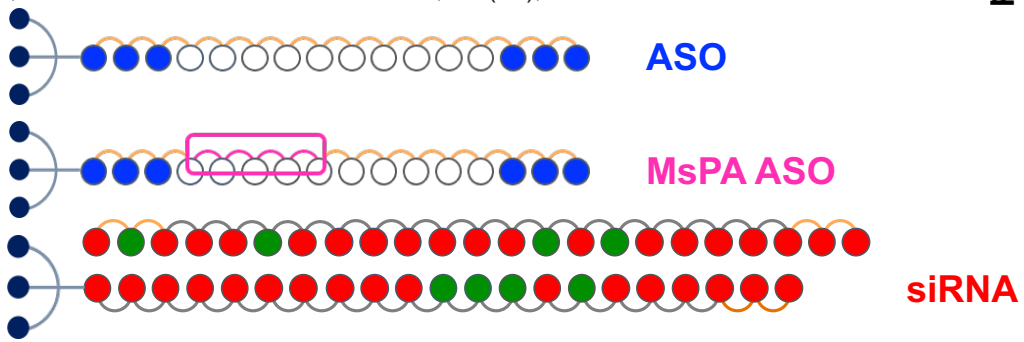
MsPA Designs Increase Duration of Action in Mouse and Monkey

Potential for Quarterly or Longer Dosing Interval

Mouse Single Dose Study

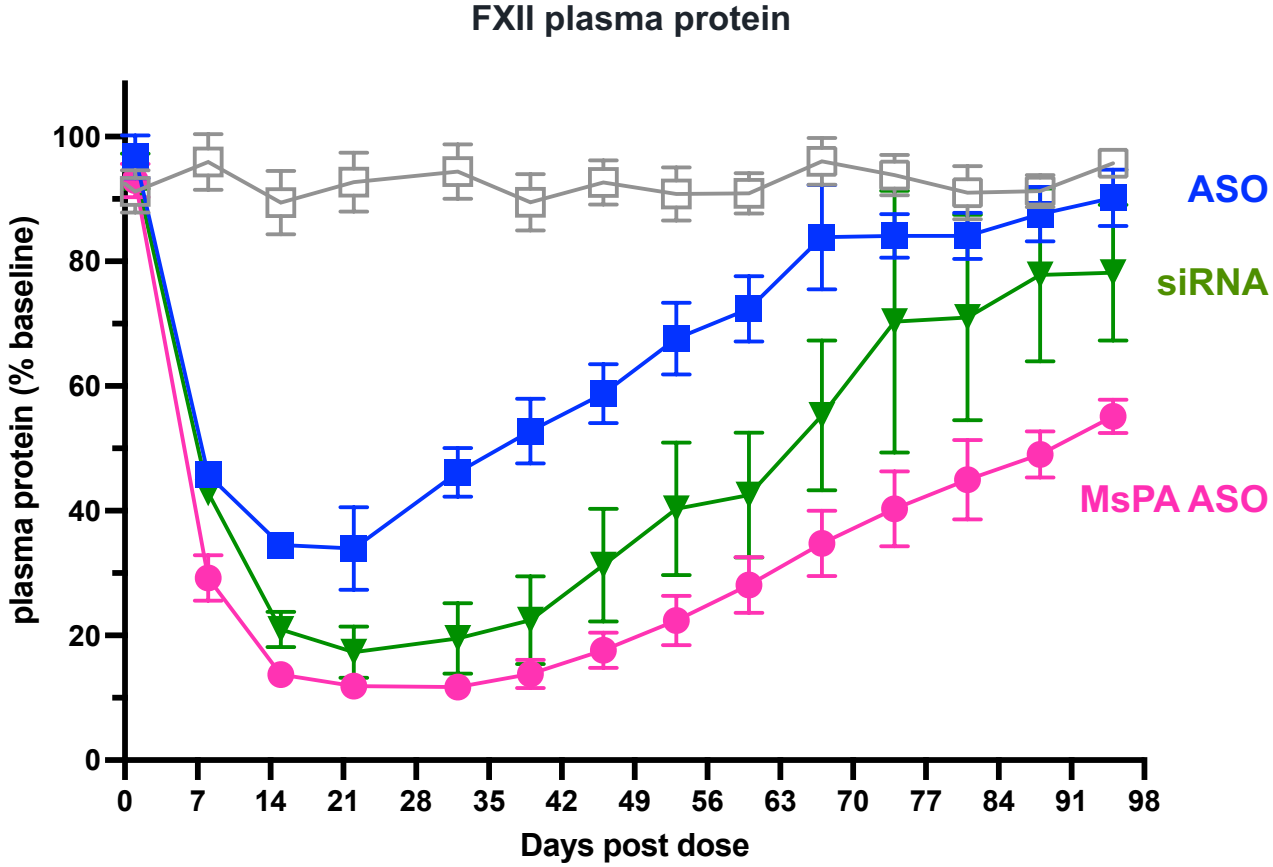


ASO dose 8mg/kg, siRNA dose 5 mg/kg by subcutaneous injection on day 1
Anderson, et al. *Nucleic Acids Research* **2021**, *49* (16), 9026–9041



cEt, DNA, MsPA, OMe, F, PO, PS

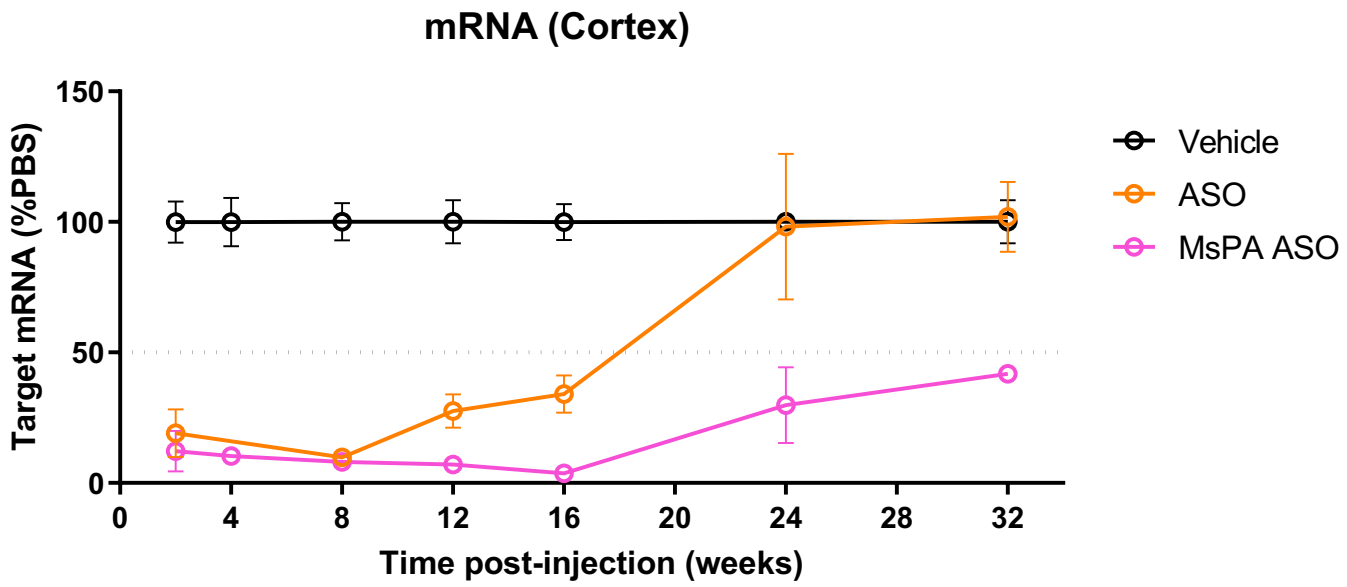
NHP Single Dose Study (Cynomolgus Monkey)

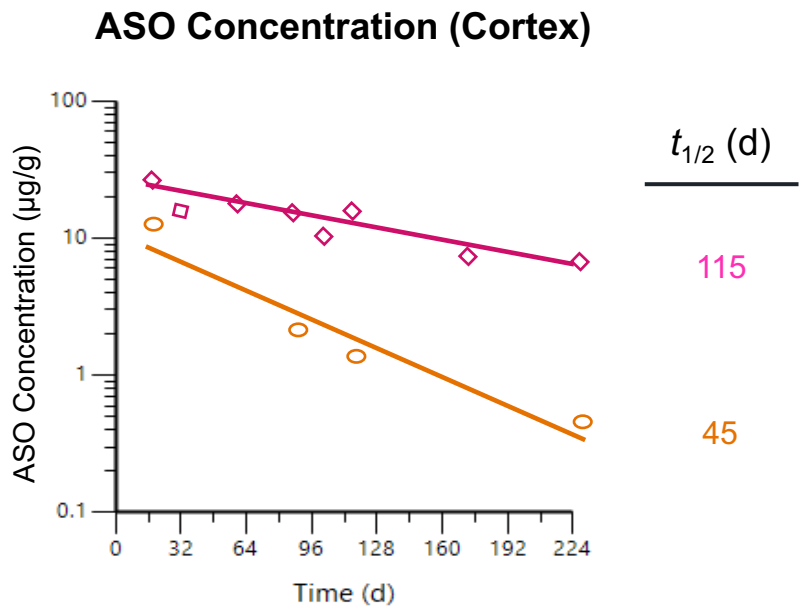


ASO dose 2mg/kg, siRNA dose 1 mg/kg by subcutaneous injection on day 1
ASO sequence: AG^{m}CA^{m}CTTTATTGAGTT
siRNA guide sequence: UAAAGCACUUUAUUGAGUUUCUG

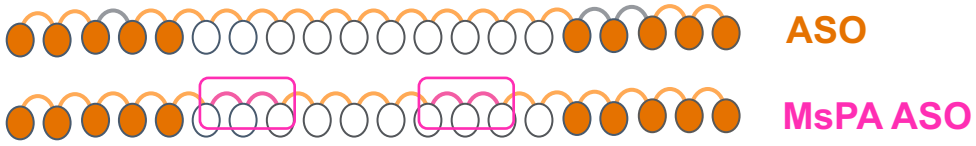
MsPA Designs Increase Duration of Action in the CNS

Potential for Semiannual or Longer Dosing Interval





ASO dose 300 µg by ICV injection on day 1 to 6-10 wks human transgenic mice
PD and drug levels: 28, 56, 84, 112, 168, 224 days days, N=3-4/group
Cortex data shown, but similar data obtained in other brain and spinal cord regions.
ASO sequence: ACAGATATTTTTGTTCTGCC



MOE, DNA, MsPA, PO, PS

Parent ASO is a **quarterly dosed drug** in clinical trials

*MsPA backbone **stabilizes molecule** to metabolism and **increases duration***

MsPA Backbone: Key Takeaways and Next Steps

MsPA Backbone

- Maintains and sometimes increases potency
- Reduces non-specific protein binding relative to PS linkage
- Increases stability over both PO and PS backbone

MsPA has Potential to

- Reduce dose frequency (≥ semiannual in CNS and ≥ quarterly in liver)
- Reduce side effects such as pro-inflammatory effects
- Expand therapeutic opportunities in new tissues (e.g. lung and kidney)

Next Steps

- Evaluate investigational medicines containing MsPA in human clinical studies
- Broadly utilize MsPA in all our candidate identification programs

siRNA

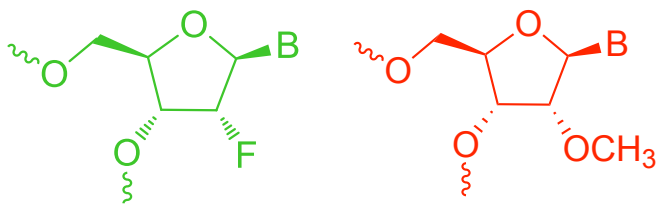
- Expands technology base with an additional mechanism and chemical class
- For each program, we evaluate multiple approaches and advance the best molecule

Ionis Has A History of Technology Development in the RNAi Space

Beginning in ~2000, Ionis had an **extensive program** focused on the siRNA mechanism

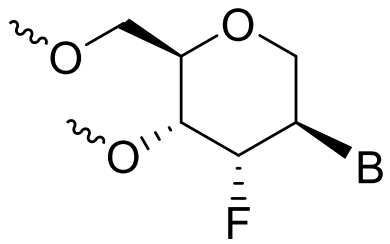
This effort led to the **invention** of several key chemistries that are **crucial to the success** of modern siRNAs

‘RNA Free’ siRNA



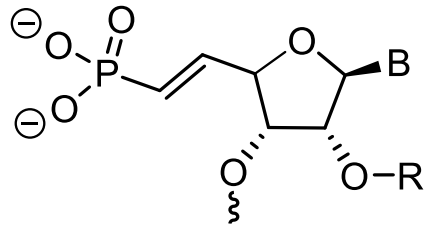
Achieved using exclusively 2’-F and 2’-OMe chemistry

FHNA



A stable 2’-F mimic

5’-Vinyl phosphonate

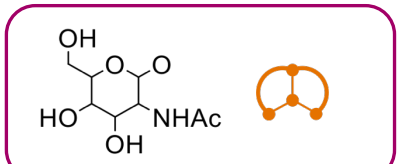


A stable phosphate mimic which is required for optimal duration and potency (especially in non-hepatic tissues)

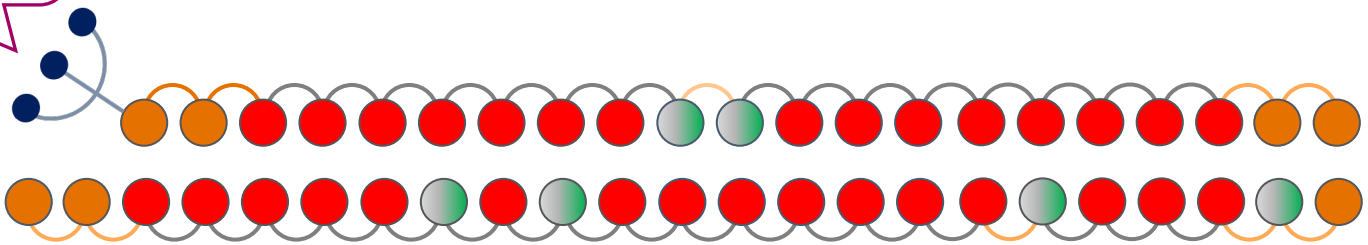
Allerson et al. J. Med. Chem. 2005, 48, 901-904; Schirle, et al. J. Am. Chem. Soc. 2016, 138, 8694-8697; Lima, et al. Cell 2012, 150, 883-894.

Ionis siRNA Optimization Strategy

Maximize Potency, Increase Stability and Reduce 2'-F Nucleoside Content

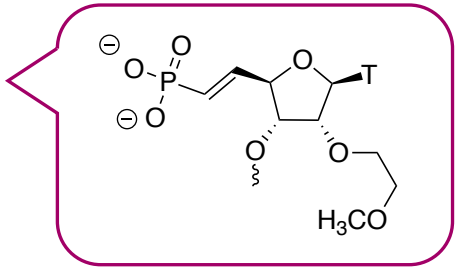


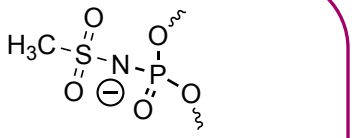
A delivery strategy is usually required



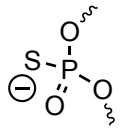
Antisense 3'-

Use Ionis MOE Vinyl Phosphonate for maximal potency



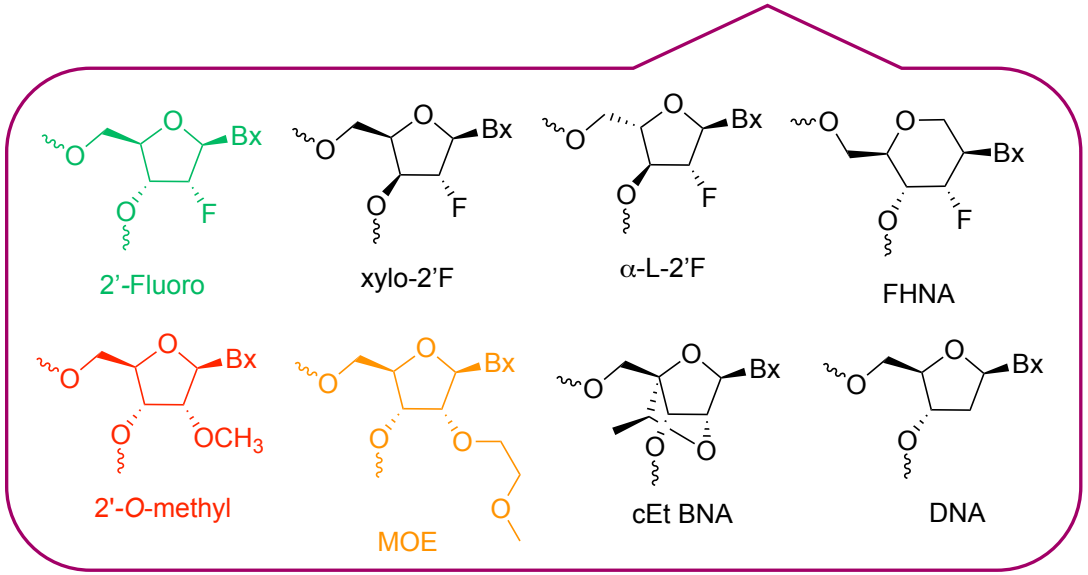


mesyl phosphoramidate (MsPA)



phosphorothioate (PS)

Stable backbones at terminal ends



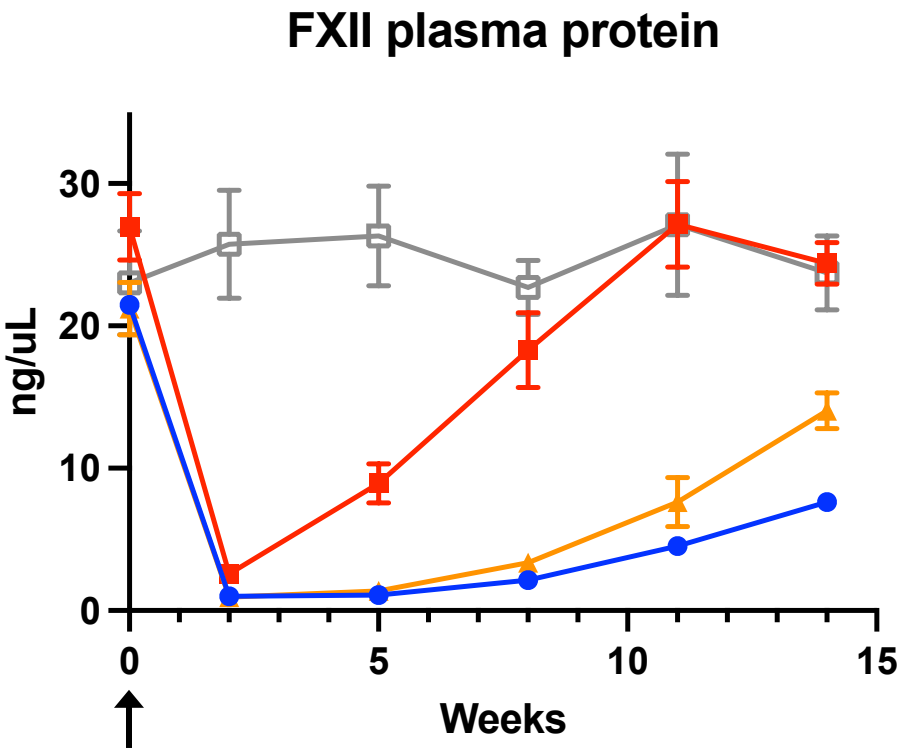
Substitute 2'-Fluoro with stereoisomer analogs, FHNA, and DNA

Add MOE and cEt for stability as tolerated

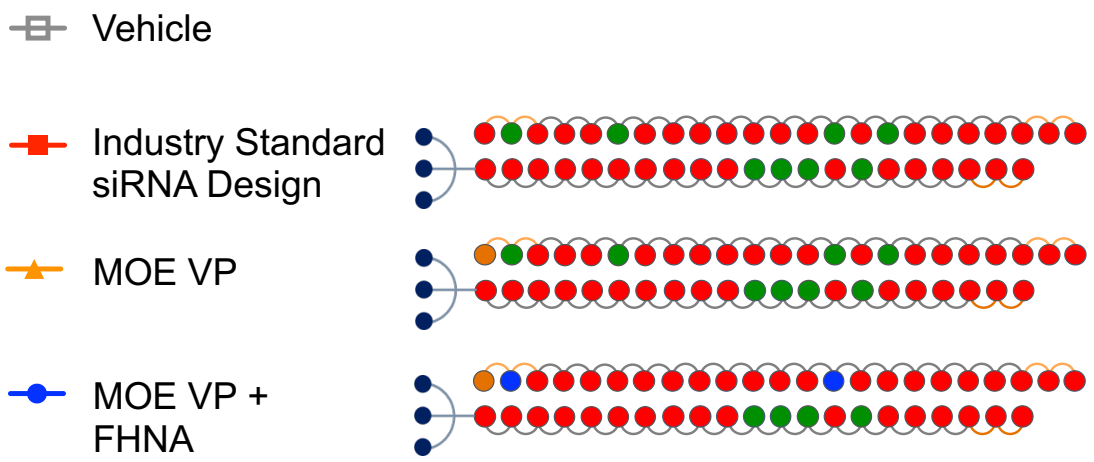
Chemistry Key: DNA, PO, PS, MsPA, OMe, F, MOE

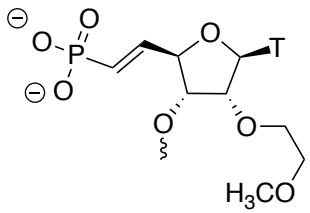
Improving siRNA Duration of Effect – An Example Optimization

Vinyl Phosphonate and FHNA Can Improve Duration Relative to 'Industry Standard' siRNA Design

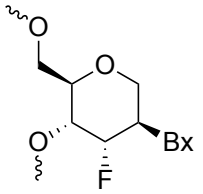


Mice dosed at day 0
with 1 mg/kg siRNA





MOE VP



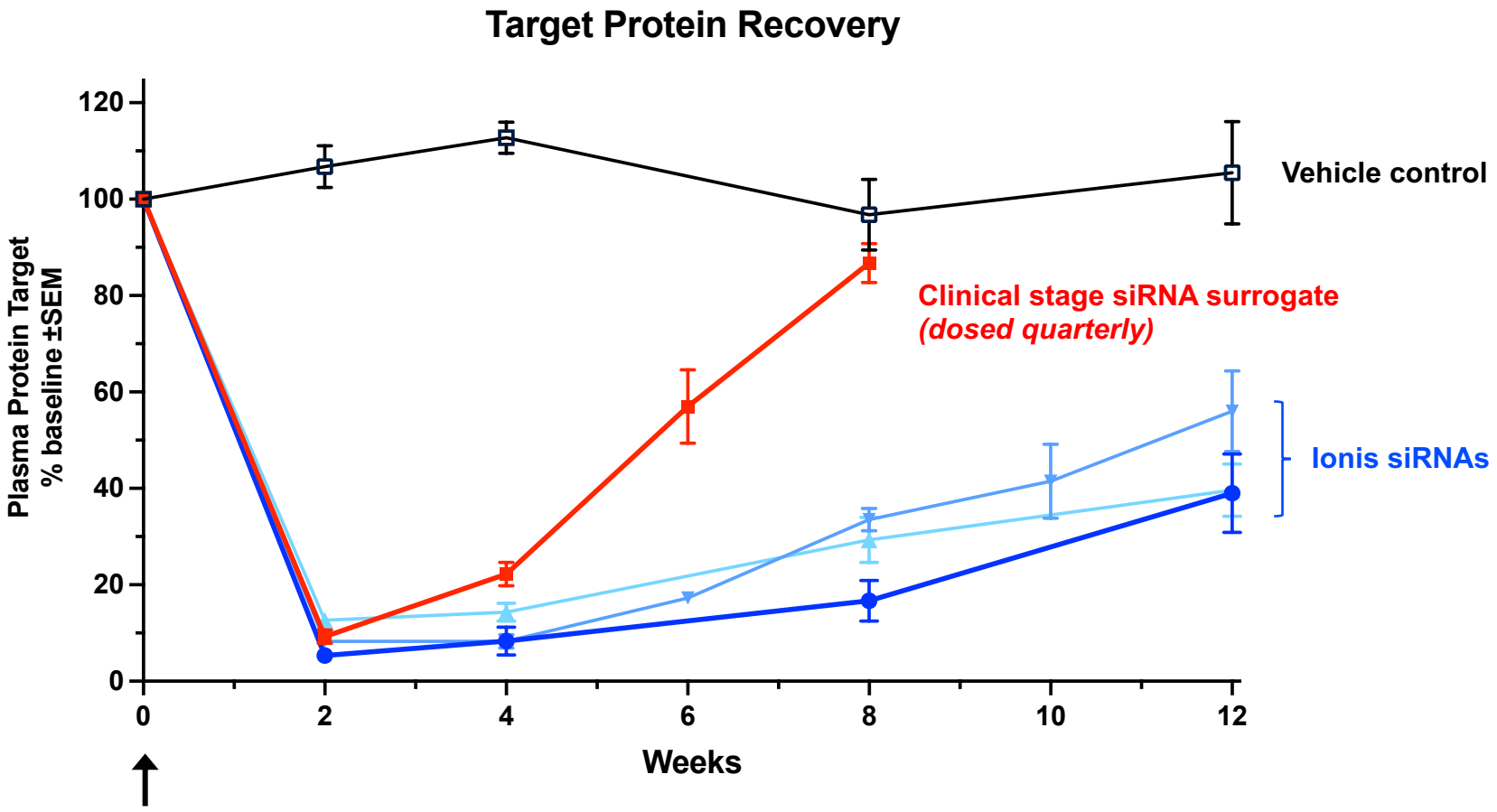
FHNA

Chemistry Key: s = PS, MOE VP T, 2'-F, 2'-OMe, FHNA
siRNA guide sequence: UAAAGCACUUUAUUGAGUUUCUG

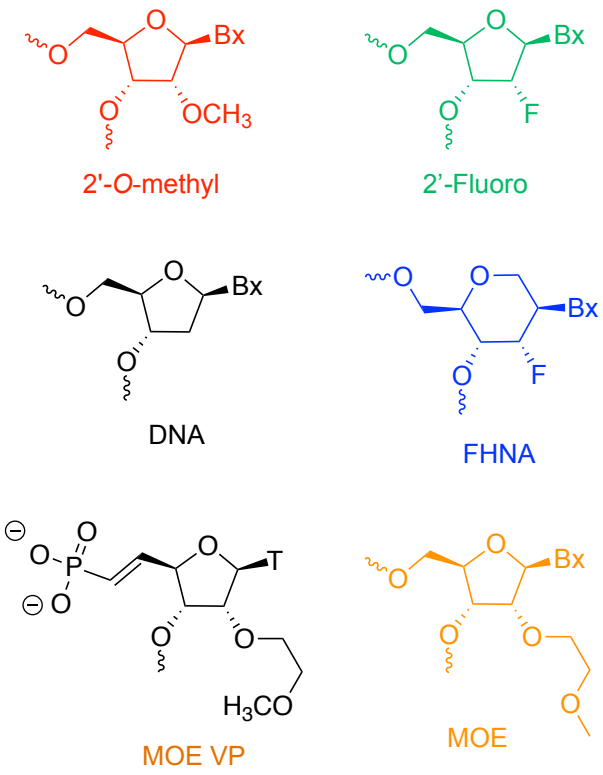
The 'industry standard' siRNA designs are usually dosed quarterly in humans. This improvement suggests semiannual or longer dosing intervals are possible.

Ionis siRNA Designs Improve Duration of Effect

Success in a Follow-on Program For a Liver Target – Goal is Semiannual or Longer Dosing Interval



Human Transgenic mice dosed at day 0 with 1 mg/kg siRNA



Ionis siRNA designs contain MOE VP, and mixtures of 2'-F, 2'-OMe, MOE, DNA and/or FHNA

siRNA: Key Takeaways and Next Steps

Ionis Chemistries are Beneficial for siRNA Designs

Ionis-Optimized siRNA has Potential to

- Reduce dosing frequency (target is ≥ semiannual in liver)
- Enhance potency for specific targets *(such as primarily cytoplasmic RNAs)*
- Expand beyond the liver (e.g. with Bicycle targeted delivery)

Next Steps

- Evaluate Ionis siRNA investigational medicines in human clinical studies
- Internally compete with other mechanisms for all new candidate programs

Targeted Delivery

- Bicycle conjugates effectively target heart and skeletal muscle
- Potential for delivery of neurology drugs across the blood brain barrier

We Have Focused Targeted Delivery on Bicycle Peptides

This Creates New Opportunities for Our Cardiovascular and Neurology Franchises

Multiple Tissues

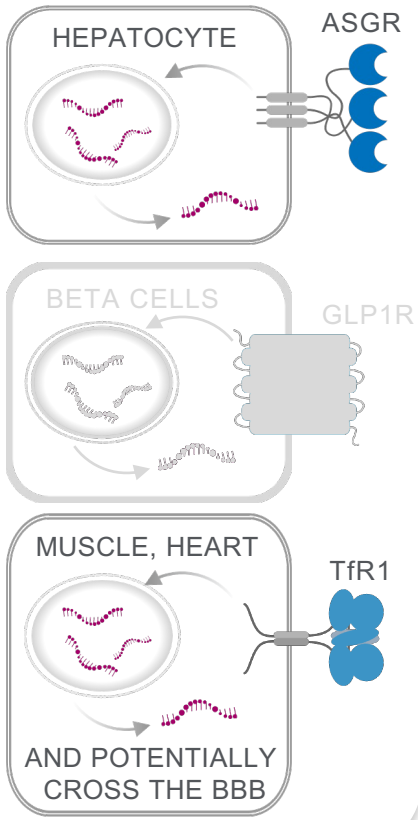
Liver

Pancreas

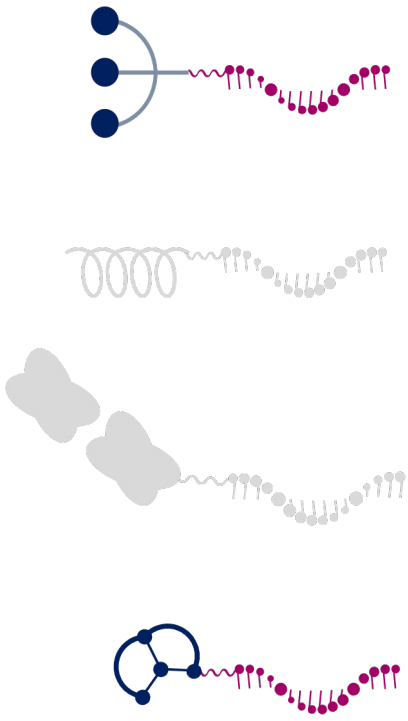
Skeletal and Cardiac Muscle

Crossing the Blood Brain Barrier

Many Others in Research Stage



Multiple Ligands



Carbohydrates

Peptides

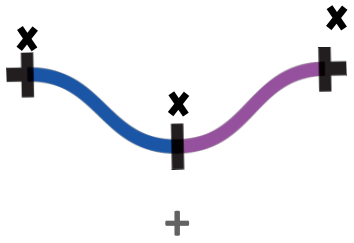
Antibodies and FAB Fragments

Bicycle Peptides

Bicycle® Technology – Constrained Peptides Provide Antibody-like Binding with a Small Drug-like Scaffold

Bicycle®

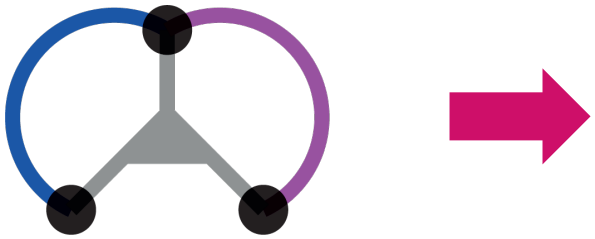
Short linear peptide



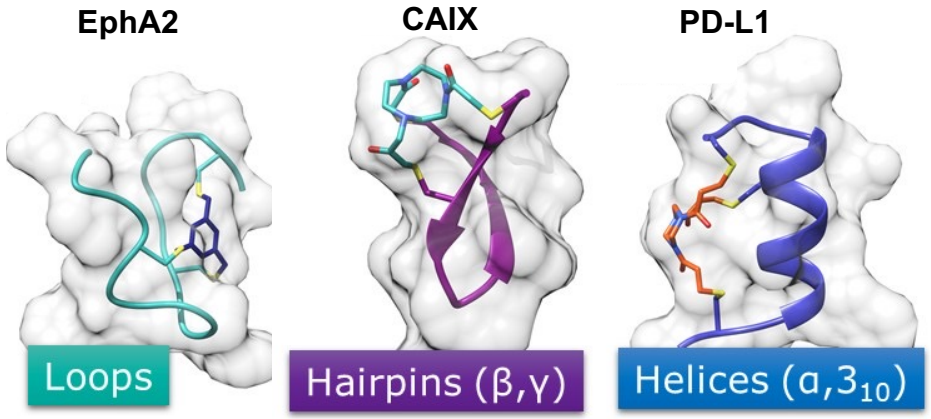
+

Scaffold

Bicycle®

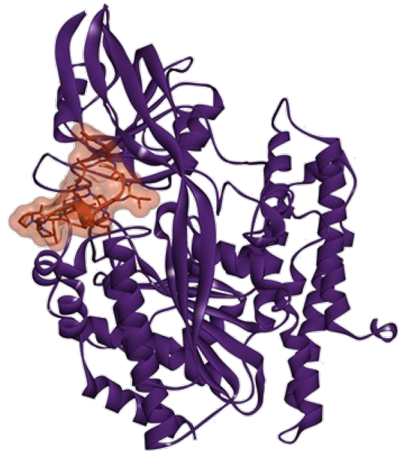


Biologically relevant structures that bind diverse proteins



Favorable Properties

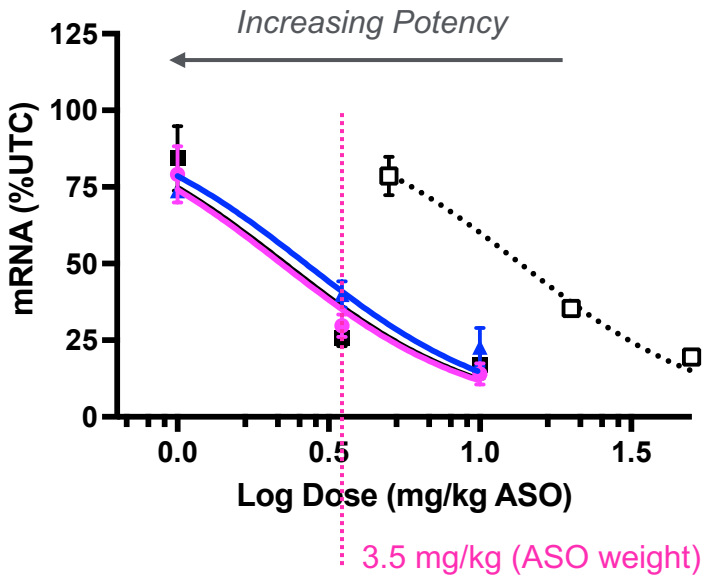
- ✓ Small size (1.5-2 kDa)
- ✓ High specificity
- ✓ Chemical synthesis (NCEs)
- ✓ Complex protein targets druggable
- ✓ Not immunogenic



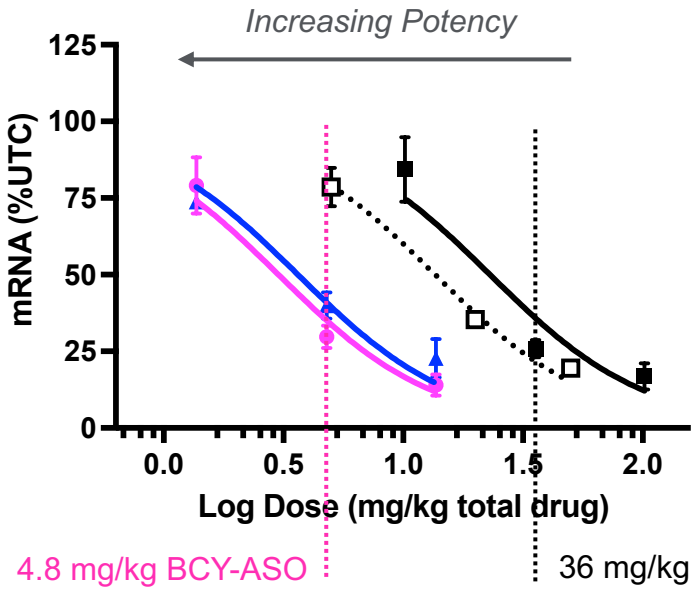
Structure of human TfR1 (purple) bound to a Bicycle lead (red)

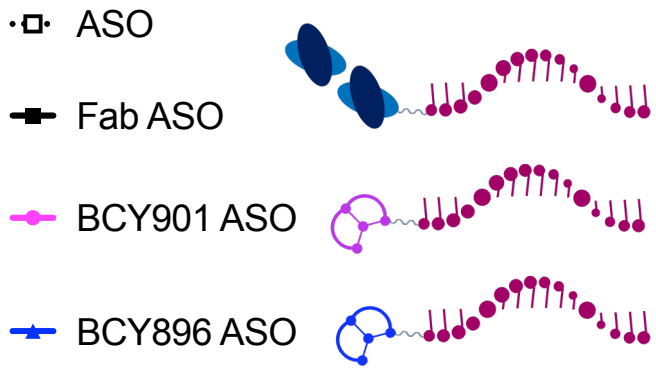
Transferrin Receptor (TfR1) Targeting *Bicycle*-ASO Conjugates Improve Potency Relative to ASO and Fab-ASO Conjugates

Potency Based on Mass of ASO Administered



Potency Based on Mass of Total Drug Administered

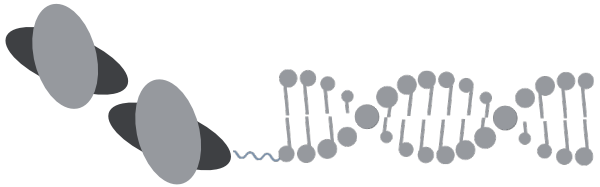




Potency of Bicycle-ASO and Fab-ASO is the **same on a molecular basis**

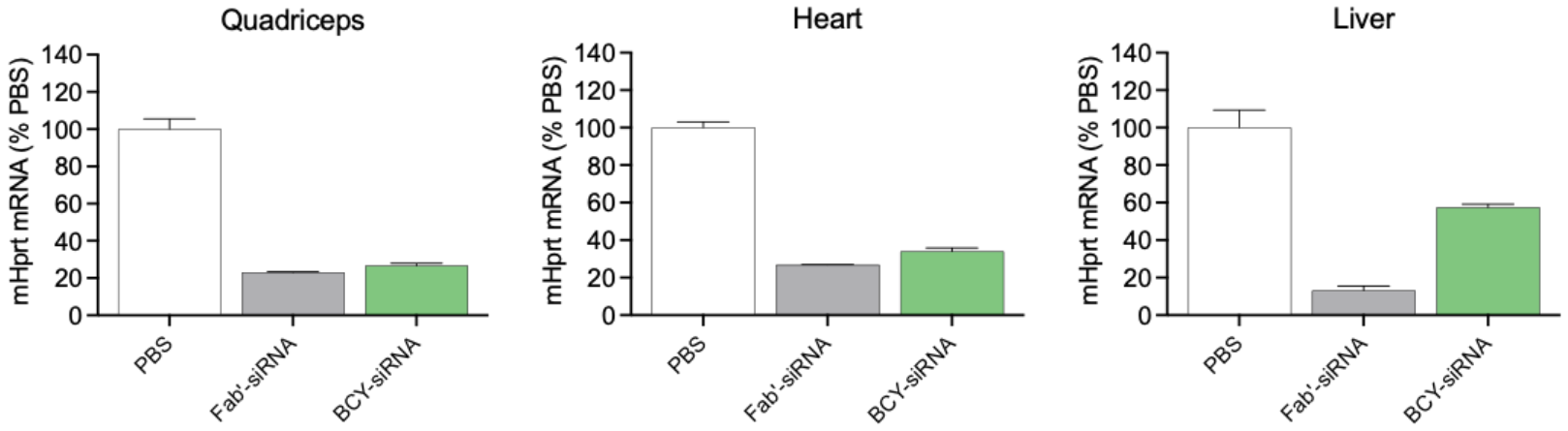
But Fab is large – so based on total drug mass, **Bicycle ASO is more potent**

Bicycle-siRNA Conjugate Targeting TfR1 is Equally Active in Muscle as Fab-siRNA Conjugate (Based on siRNA mass)



FAB'-siRNA (~15mg/kg total dose)

BCY-siRNA (~4mg/kg total dose)

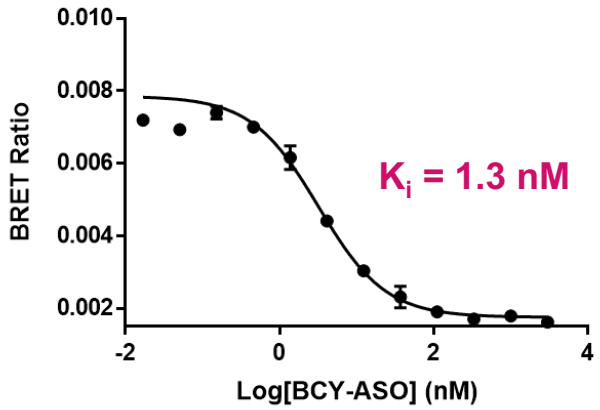


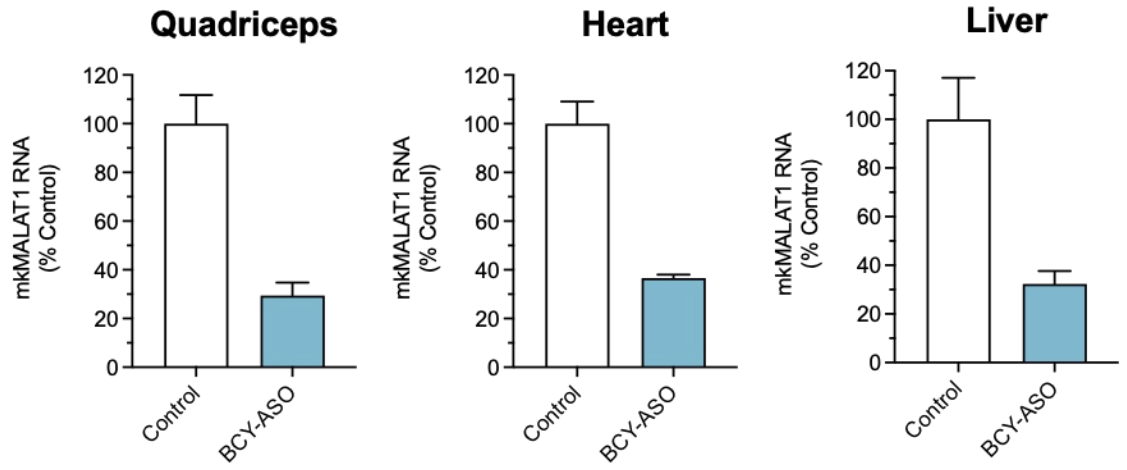
Bicycle conjugate is selective, as it targets muscle well, but has reduced activity in liver

Bicycle-siRNA or Fab-siRNA targeting mouse Hprt mRNA dosed for 3 weeks in hTfR1$^{KI/+}$ mice at a dose of at 3.5mg/kg/week siRNA (4mg/kg siRNA-bicycle, 15mg/kg siRNA-Fab). Target mRNA in quadricep muscle shown, other skeletal muscles have similar reduction.

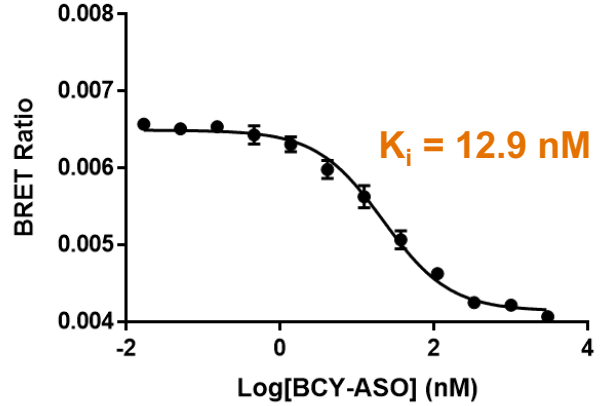
Bicycle-ASO and siRNAs Bind TfR1 and Reduce Target RNAs in NHP Skeletal and Cardiac Muscle

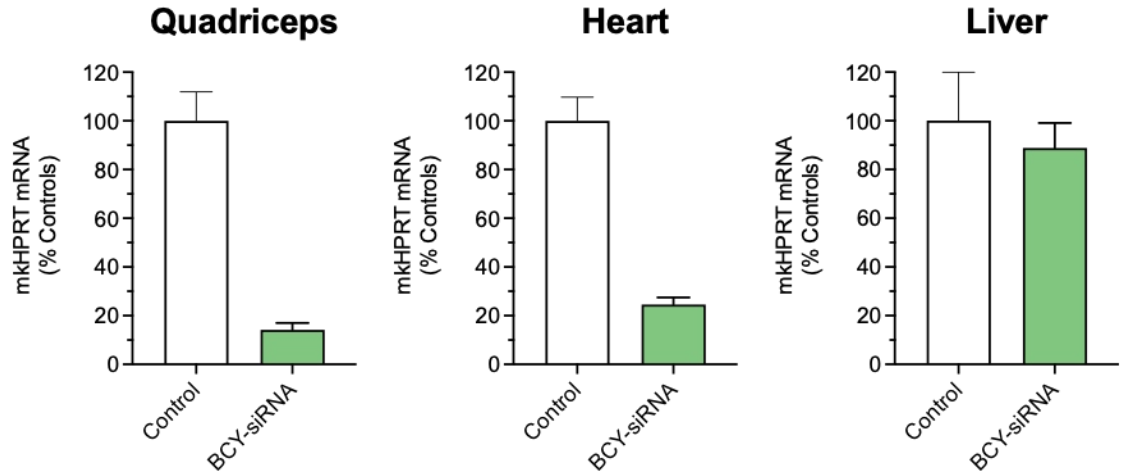
Bicycle-ASO vs. Human TfR1





Bicycle-ASO vs. NHP TfR1



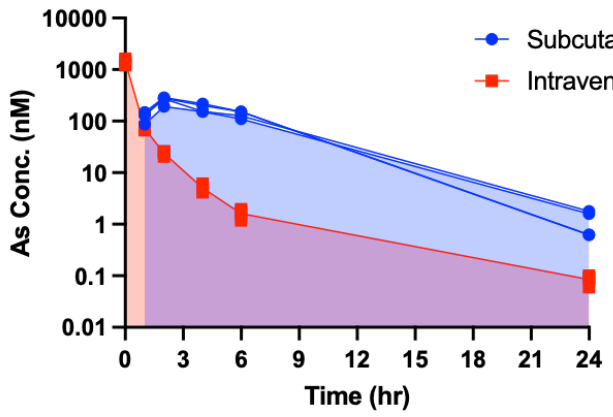


Malat1 Bicycle-ASO or Hprt Bicycle-siRNA dosed for 3 weeks in cynolmolgus monkey at 25 mg/kg/week.

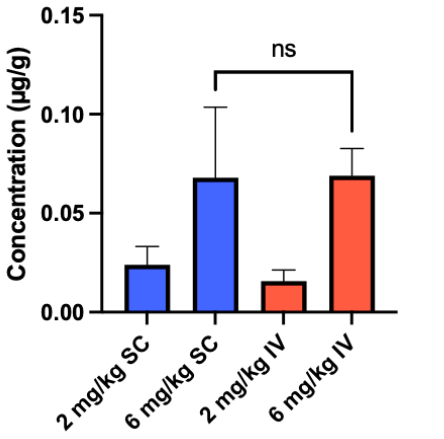
Success in a Candidate Program: Human Optimized Bicycle siRNA

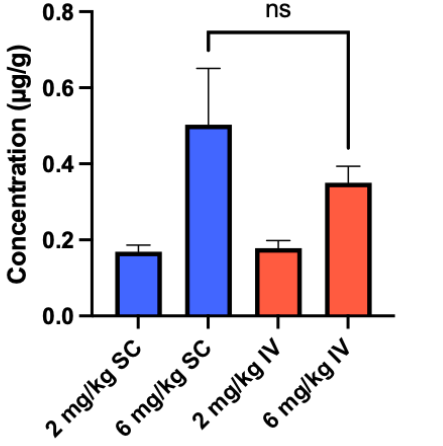
Good Subcutaneous Bioavailability and Target Reduction in NHP Heart and Muscle

NHP PK Study

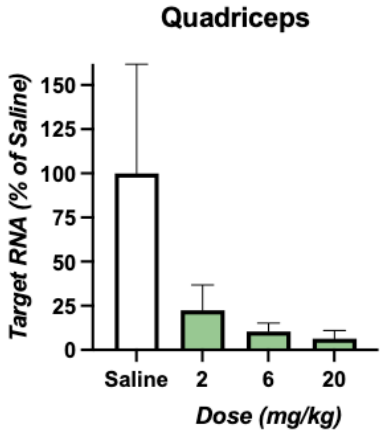


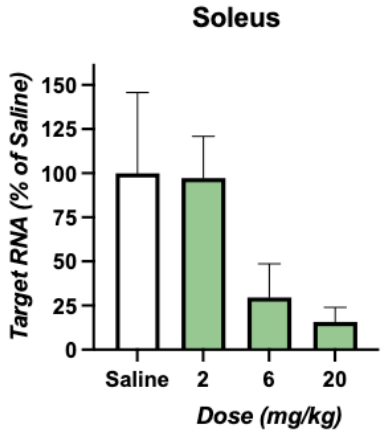
C_{max}	AUC
257	1409
1409	839

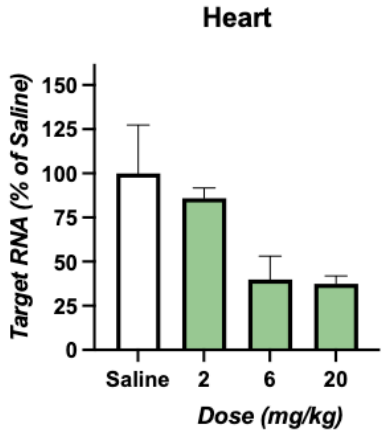




NHP Target Reduction







Bicycle-siRNA dosed weekly for 3 weeks in cynomolgus monkey at the indicated dose.

Bicycle Targeted Delivery: Key Takeaways and Next Steps

Bicycle Conjugates

- Are small, with low molecular weight, simplifying manufacturing
- Deliver both ASOs and siRNAs effectively to skeletal and cardiac muscle
- Have excellent subcutaneous bioavailability

Bicycle Targeted Delivery Has the Potential to

- Reduce total dose (potentially improving therapeutic index)
- Increase dosing flexibility (e.g., low volume sc)
- Create new therapeutic opportunities in the skeletal and heart muscle, furthering our neurology and cardiovascular franchises

Next Steps

- Evaluate Bicycle siRNA investigational medicines in IND-tox studies and human clinical studies
- Advance new medicines for skeletal and cardiac muscle

Technology Advancements in Neurology

Leading and Growing Neurology Pipeline

- **Proven innovation** with:
  - 2 approved breakthrough medicines,
  - 12 medicines in clinical development, and
  - >10 in lead optimization and preclinical development
- Plan to **grow** our **wholly owned pipeline** into additional disease areas and larger more common indications

Enabled by Multiple Technology Advancements

- Advances in **chemistry**
- **Optimized intrathecal (IT) delivery** provides broad ASO distribution to the CNS
- **Validated** gene upregulation and downregulation mechanisms in CNS
- Established potential for **long dose intervals of ≥ 6 months** with RNA-targeted medicines to treat neurological diseases

Next Hurdle: Systemic Delivery

- **Delivering** oligonucleotides across the **blood brain barrier** would enable **multiple new opportunities** in neurology

Can Transferrin Receptor Mediated Transcytosis Facilitate Oligonucleotides Crossing the Blood Brain Barrier (BBB)?

Key Objectives

- Learn the characteristics of systems that facilitates crossing the BBB
- Identify systems that cross the blood brain barrier without a protein (antibody) component
- Simplify the system, just as our Bicycle muscle targeting strategy has

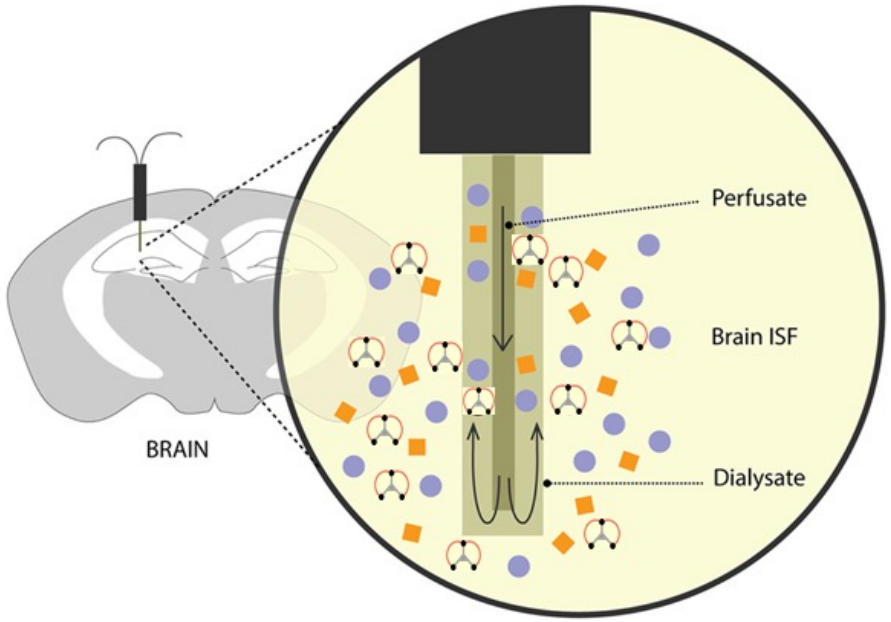
Strategy

- Prepare surrogates of protein (antibody) based ligands in the literature
  - Some have shown early success[1]
  - This serves as a positive control
- Determine key characteristics of successful solutions
- Identify multiple families of Bicycle cyclic peptides that have these key characteristics
- Identify Bicycle conjugates that cross the blood brain barrier and modulate their target in the CNS

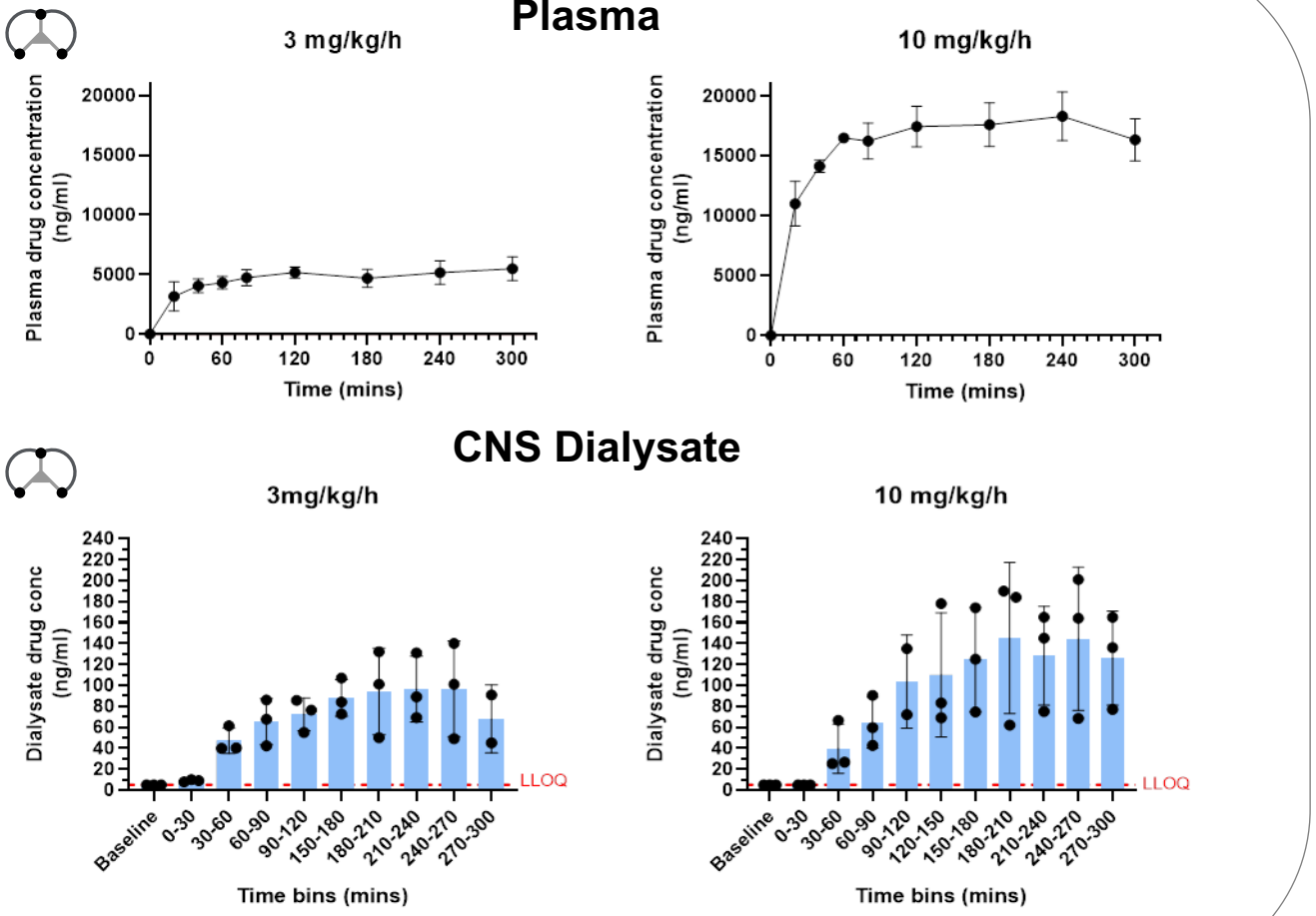
1. Barker, *et al. bioRxiv* 2023.04.25.538145

Transport of a TfR1 *Bicycle*® Across the BBB

Demonstrated in a Non-human Primate Brain Microdialysis Study



- *Bicycle*® to TfR1 infused i.v. (3mg/kg/h & 10mg/kg/h) to steady state.

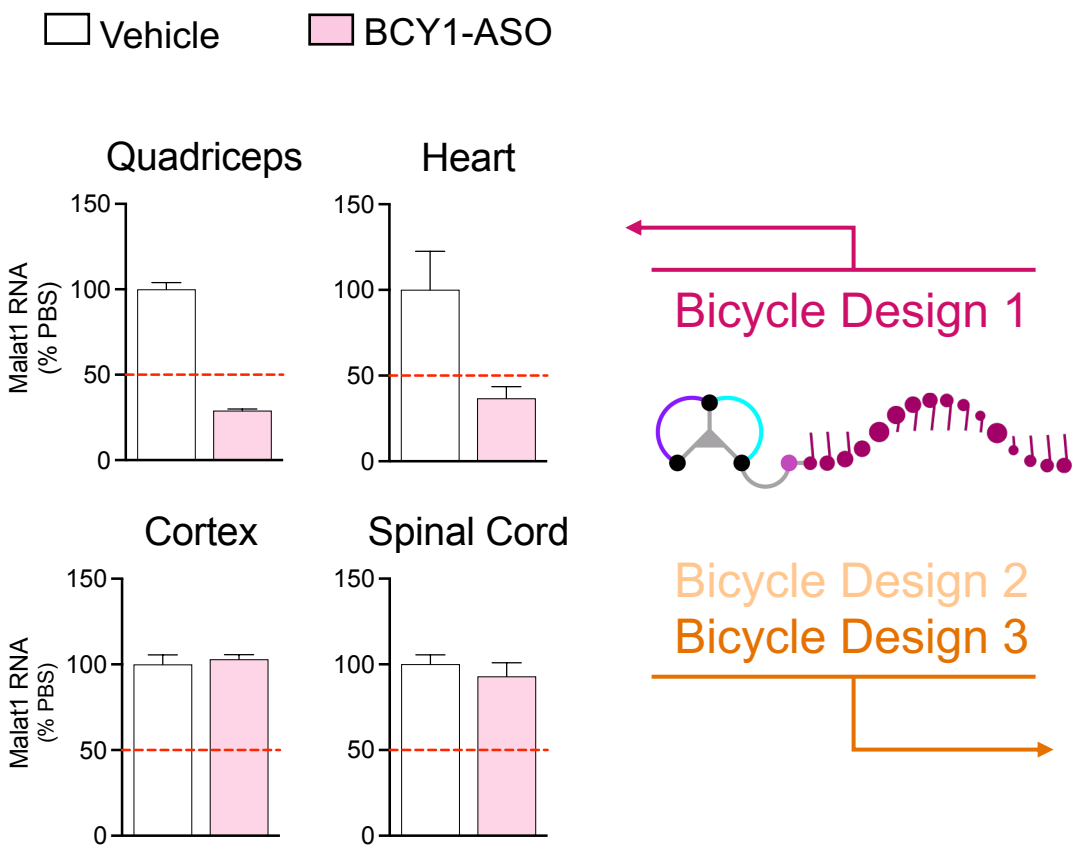


- LLOQ = 5ng/mL.

Bicycle®

A Bicycle ASO Conjugate Can Effectively Cross the BBB

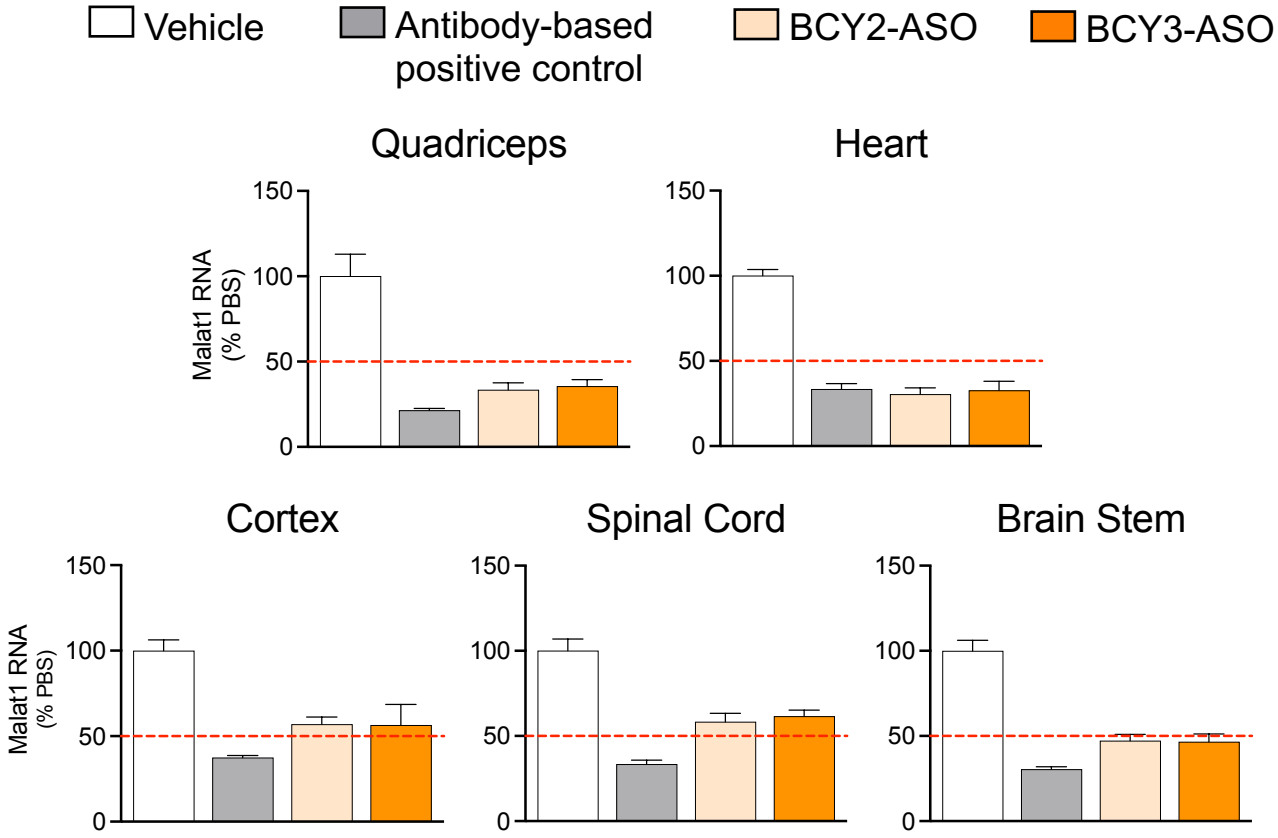
Muscle targeted Bicycle design does not cross the BBB



hTfR^{KI} mice dosed IV at 3 mg/kg ASO eq. on d1, 8, 15; sac d22

Other Bicycle designs can cross the BBB

Small structure with no antibody/protein



hTfR^{KI} mice dosed IV at 3.5 mg/kg ASO eq. on d1, 8, 15, 22; sac d36

Ionis' New Technology Advancements Continuously Improve the Platform

MsPA Backbone

Increases stability – can reduce dosing frequency

Reduces non-specific protein binding – improves therapeutic index

Enables expansion into new tissues – such as kidney and lung

Ionis' siRNA Technology

Ionis chemistries can increase stability – potential for reduced dosing frequency

Adds a new mechanism and chemical class – optimal for some targets and applications

Targeted Delivery *via* Bicycles

Delivers cargo to skeletal and cardiac muscle – enables expansion of opportunities in neurology and cardiovascular franchises

Small size – simplifies structure

Can cross the blood brain barrier – potential for systemic delivery to the CNS

Ionis Technology Advancements are Positioned to Enhance and Expand the Value of our Future Medicines

Advances in:

MsPA backbone | Ionis' siRNA technology | Targeted delivery strategies

Positioned to:

- **Enhance the profile of new therapies entering the pipeline**
- **Expand Opportunities in Existing Franchises**
- **Open up Therapeutic Opportunities in New Spaces**

Ionis is the RNA-targeted therapeutics company with expertise in multiple modalities, which enables us to make the best drug for a given indication – agnostic to drug modality

Morning Wrap Up

Brett Monia, Ph.D.

Chief Executive Officer

Increasing Value for Patients and All Stakeholders

Morning Session

Ionis Evolution

Fully Integrated and focused

On the Horizon

Eplontersen | Olezarsen | Donidalorsen

Technology Advances Power our Future Medicines

Coming Up After Lunch

Beyond the Horizon

Next Wave of Wholly Owned Medicines

Clear Path to Unlocking Next-Level Value

Focused and Ready to Deliver Next-Level Value to Patients and Stakeholders

Beyond the Horizon: Next Wave of Wholly Owned Medicines

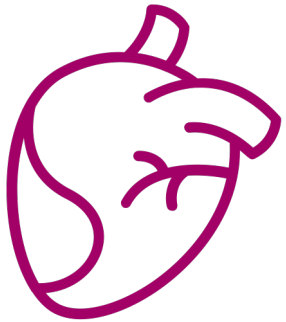
Robust Pipeline of Potentially Transformational Investigational Medicines

Ionis' Proven Neurology Leadership and Platform

Holly Kordasiewicz, Ph.D.

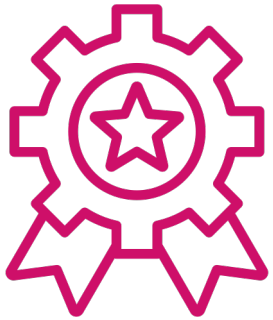
Senior Vice President, Neurology

Our Two Leading Franchises + Attractive Specialty Medicines Provide a Rich Portfolio of Opportunities



Cardiovascular

Neurology



Specialty

Why Neurology?

Neurology

Many patients without any approved treatments

Proven track record of first-in-class disease modifying medicines

Over a decade of experience discovering and developing CNS medicines

Opportunity for an evergreen pipeline

Significant transformational potential

Ionis Discovered First-in-Class Disease-Modifying Neurology Medicines[1]

Leading the Field with Many Years of Experience and Real-Time Learnings

1. SPINRAZA: www.spinraza.com; QALSODY: www.qalsody.com; Biogen is responsible for commercializing SPINRAZA and QALSODY.

Leading and Validated Neurology Franchise

2

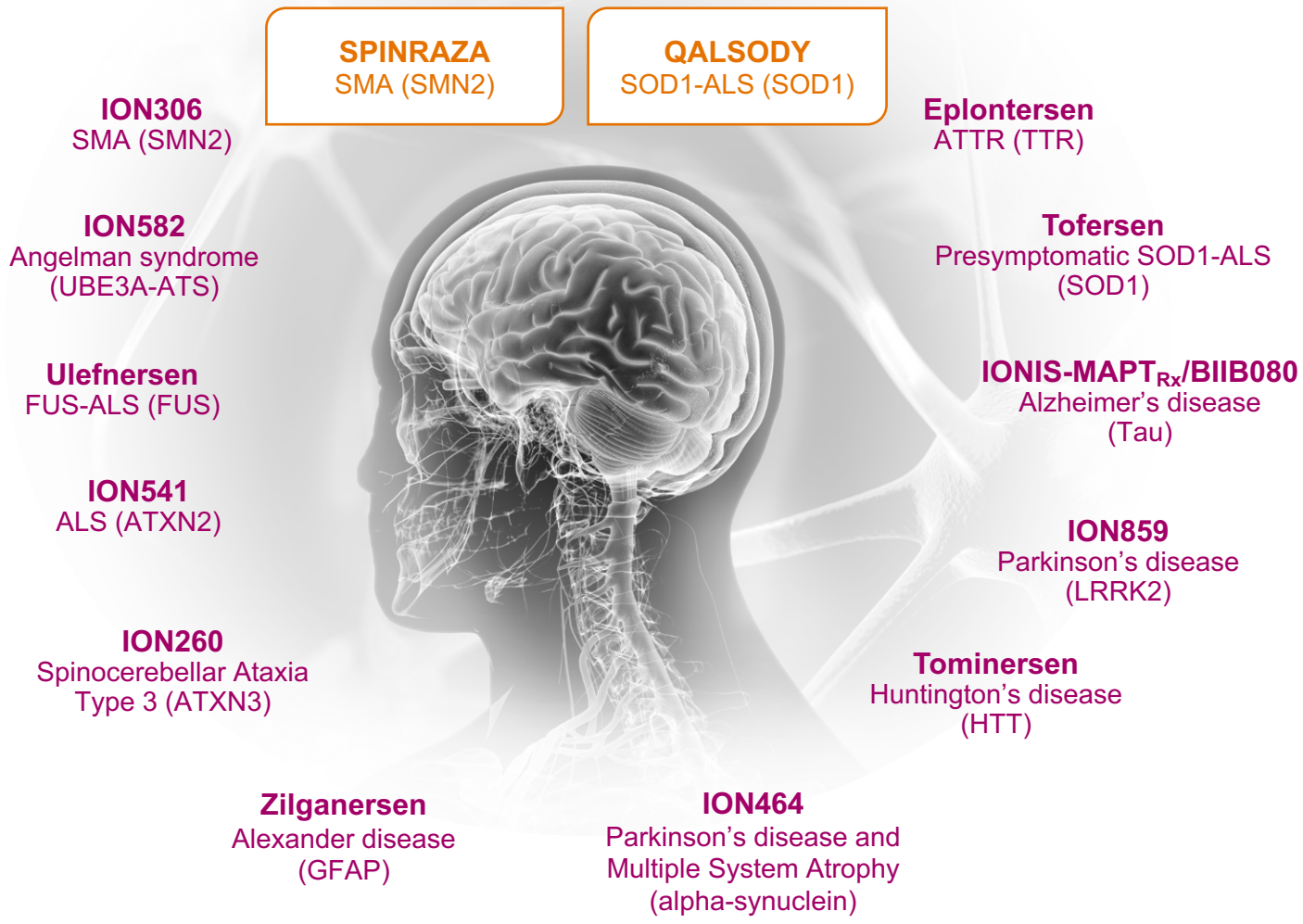
Approved Medicines[1]

12

Medicines in Clinical Development

>10

Medicines in Lead Optimization and Preclinical Development



1. SPINRAZA: www.spinraza.com; QALSODY: www.qalsody.com; Biogen is responsible for commercializing SPINRAZA and QALSODY.

Key Neurology Advancements Made and Lessons Learned

Technology

Pioneered **transformative advances** in delivery and chemistry

Optimized intrathecal (IT) delivery provides broad ASO distribution to the CNS

Validated both splicing and RNase H mechanisms in the CNS in patients

Established potential for long dose intervals of ≥ 6 months with RNA-targeted medicines to treat neurological diseases

Clinical Development

Disease reversal is possible

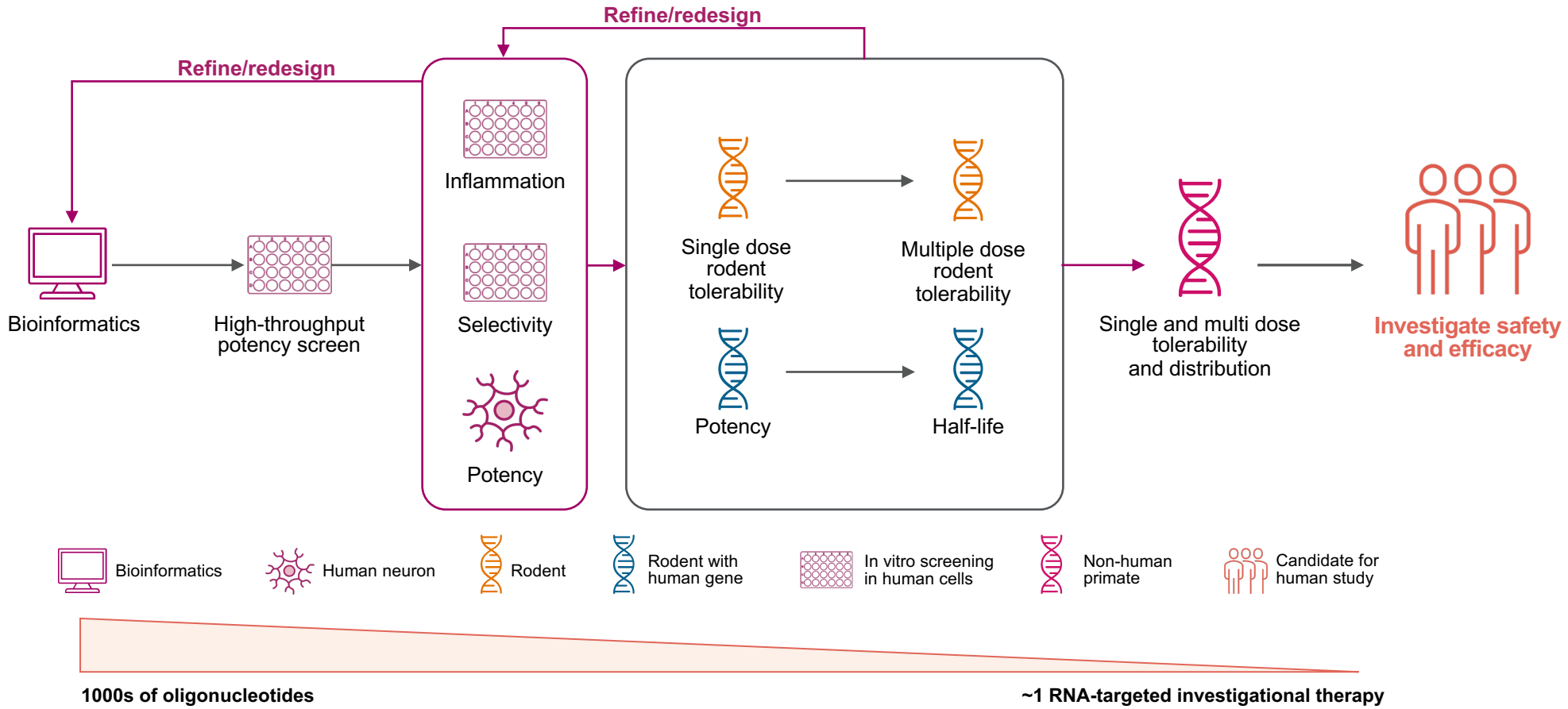
Early treatment can **provide robust benefit** with disease modifying medicines

In adult-onset neurodegenerative diseases, disease **modifying effects can take time**

Creative trial design can **address many of the challenges** of disease-modifying trials

Our Extensive CNS Experience Helps Us Design First- or Best-in-Class RNA-Targeted Therapeutics for CNS Diseases

We Are Continually Advancing the Design, Screening, and Development of Our Investigational Neurology Franchise RNA-targeted Therapeutics



Optimized ASOs Provide Long Duration of Action with Potential for Dosing Intervals of ≥ 6 Months

Long Duration of Action

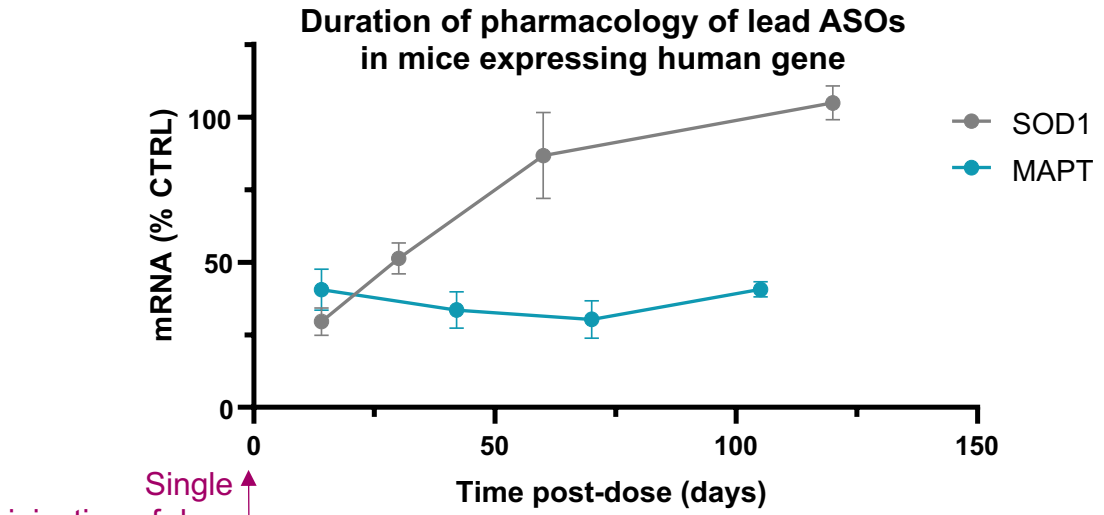
Optimized screening paradigms to identify highly potent ASOs with a long duration of action

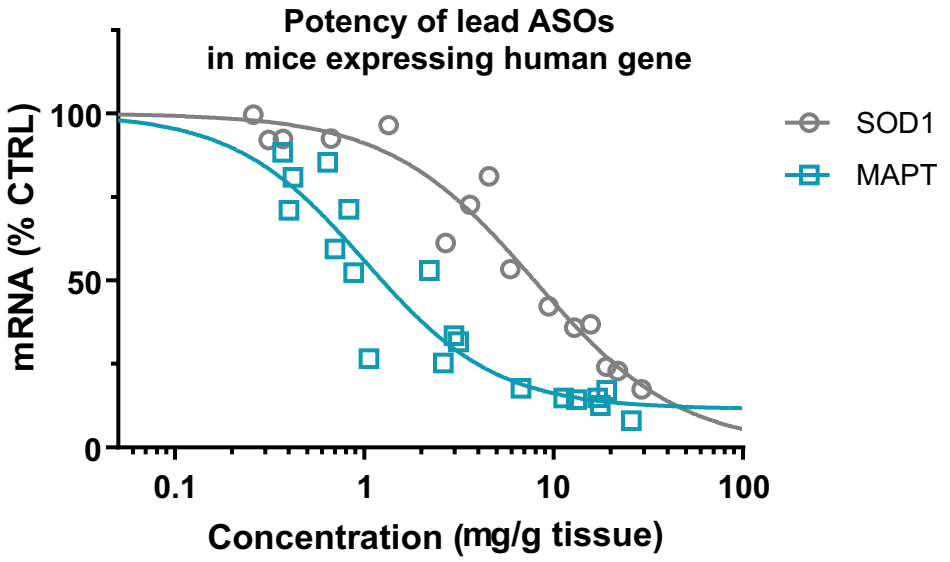
IONIS-MAPT$_{Rx}$ (BIIB080) is the most advanced example of a highly potent ASO with a long duration of action

- MAPT$_{Rx}$ has improved potency and duration of action compared to tofersen (SOD1) in preclinical studies[1,2]

This improved duration of action **translated from preclinical models to patients**

- MAPT$_{Rx}$ is currently in a **Phase 2 study** evaluating three- and six-monthly dosing





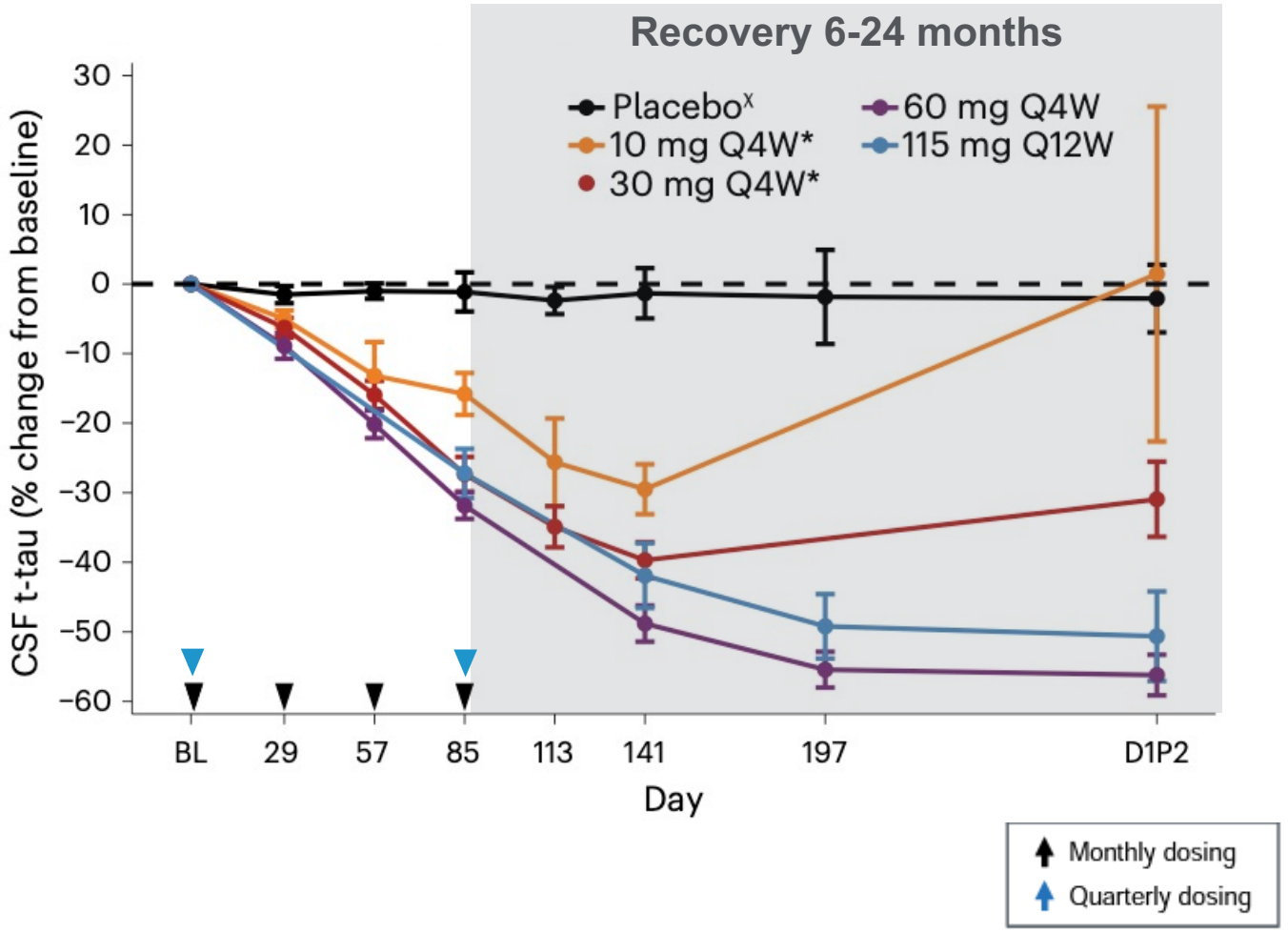
1. McCampbell et al., JCI, 2018; 2. Mummery et al., Nat Med, 2023

IONIS-MAPT$_{Rx}$: Rapid, Substantial and Sustained Reduction in Tau in CSF in Phase 1b Study

MAPT$_{Rx}$ (BIIB80) is designed to **reduce production and thus aggregation of tau protein** associated with disease in Alzheimer's disease

Total tau in the CSF **continued to decline 16 weeks post-last dose** of BIIB080 in 4-and 12-week cohorts

Favorable tolerability and safety profile



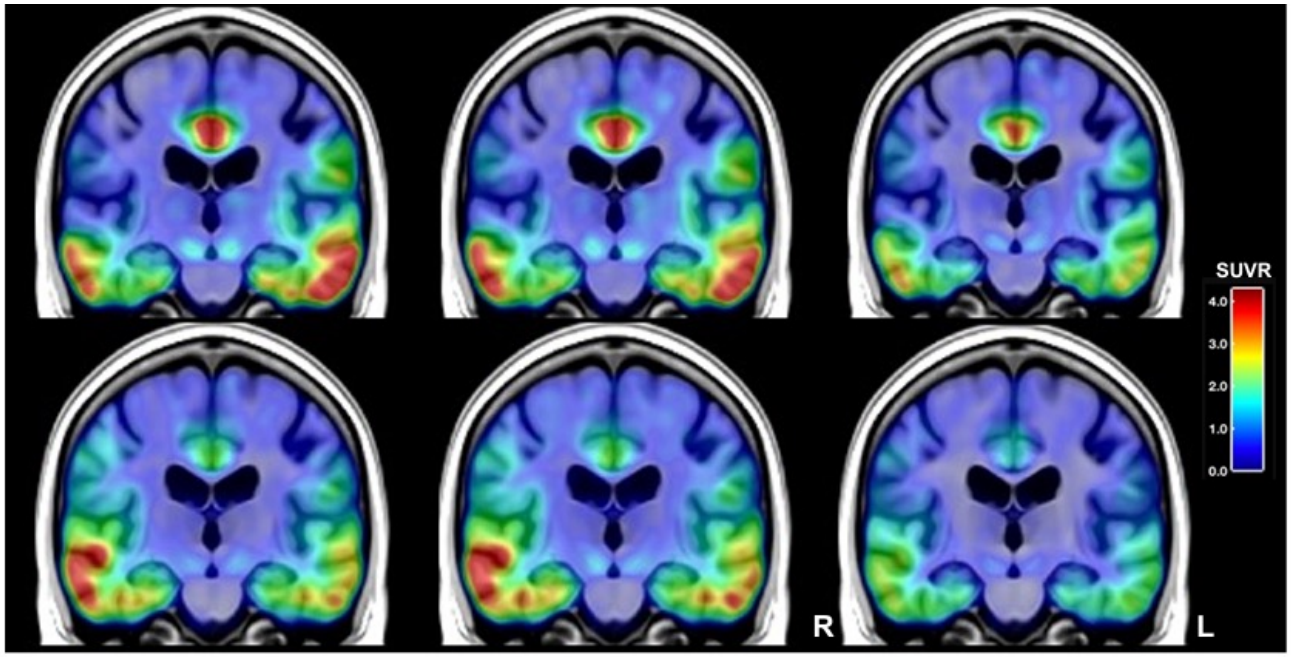
Mummery et al., Nat Med, 2023; AD = Alzheimer's disease; CSF = cerebrospinal fluid; Q4W = every 4-week dosing; Q12W = every 12-week dosing; t-tau = total tau

IONIS-MAPT$_{Rx}$: Consistent Reduction in Tau Burden Across All Brain Regions

Screening —Placebo→ **Week 25** —115mg Q12W→ **Week 100**

2380-4011
67 y/o
Male
CDR= 0.5
MMSE= 26

2176-4009
71 y/o
Male
CDR= 0.5
MMSE= 26



CELIA Phase 2 Study underway in patients with early AD

Phase 1b Tau PET Results

Patients initially on placebo then MAPT$_{Rx}$ (BIIB080) showed **reduced tau burden following treatment**

Reduced tau burden at all doses and dose frequencies in the long-term extension study

Generally **well-tolerated at all doses and dose frequencies**

Collins et al., AD/PD 2023 CDR Clinical Dementia Rating scale; MMSE Mini Mental State Examination; SUVR standard uptake value ratio;
CELIA Study (Biogen conducting): Clinialtrials.gov/NCT05399888

Our Leading Neurology Franchise Today

Extensive experience in CNS with **>15,000** patients treated across **>10 diseases**, including:

- Spinal muscular atrophy (SMA)
- Huntington's disease
- Parkinson's disease
- Amyotrophic Lateral Sclerosis (ALS) / Lou Gehrig's disease
- Alzheimer's disease

2 Approved **breakthrough medicines**

12 **Medicines in clinical development**

>10 **Medicines in lead optimization and preclinical development**

Deep Institutional Knowledge

Identify First- or Best-in-Class CNS Medicines

Robust Pipeline Addressing Serious Neurological Diseases

The Next Wave of Ionis' Wholly Owned Potentially Transformative Medicines

Evolution of Ionis' Prolific Neurology Pipeline

Neurology Drug Discovery

Biogen

Key long-term neurology partner (7 programs in development)

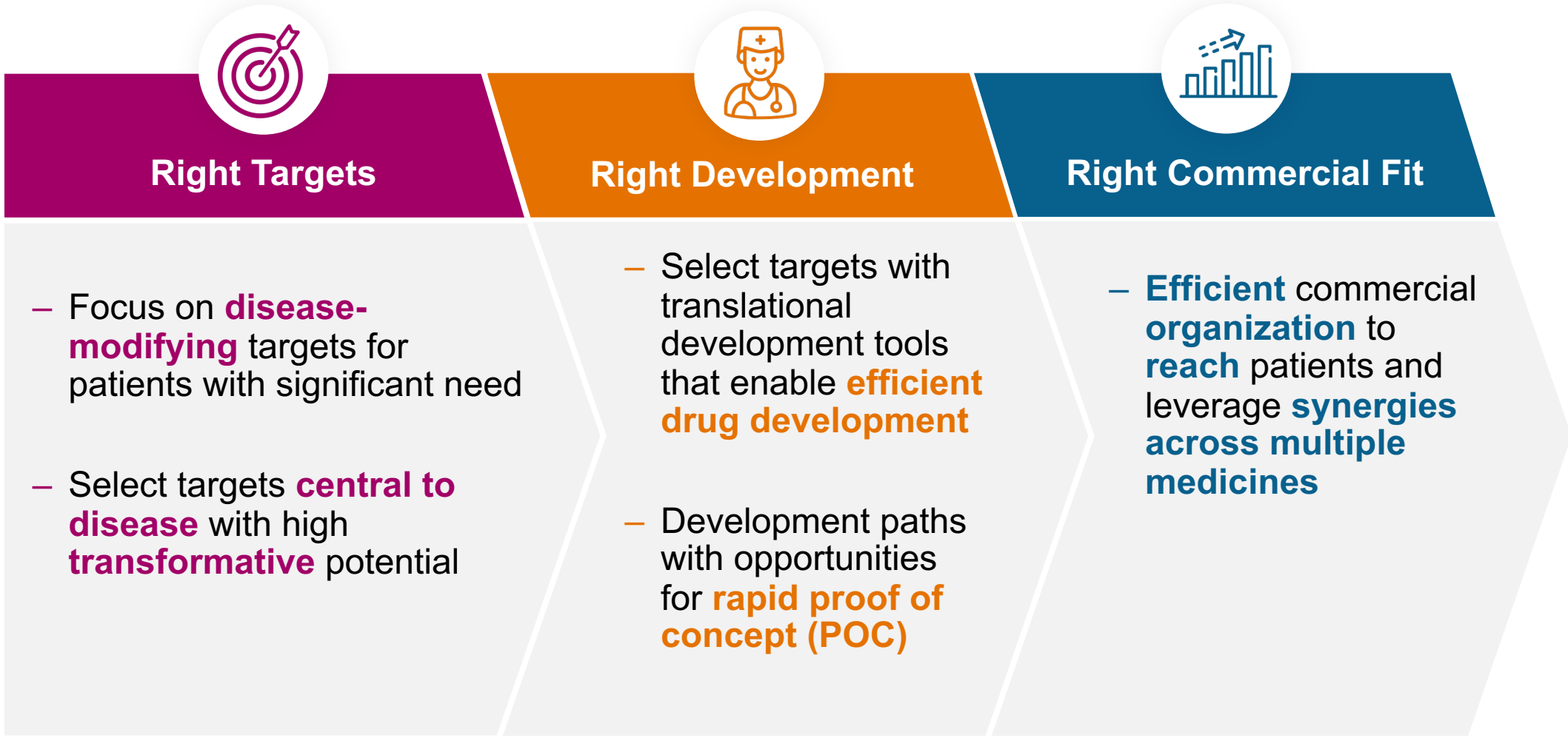
Ionis Wholly Owned Neurology Franchise

Other Partnerships

Programs best suited for partner development

Targeted Expansion of Wholly Owned Neurology Franchise

Focused on advancing potentially transformative medicines



Prioritized Four Pillars Balancing Research, Development and Commercial Criteria

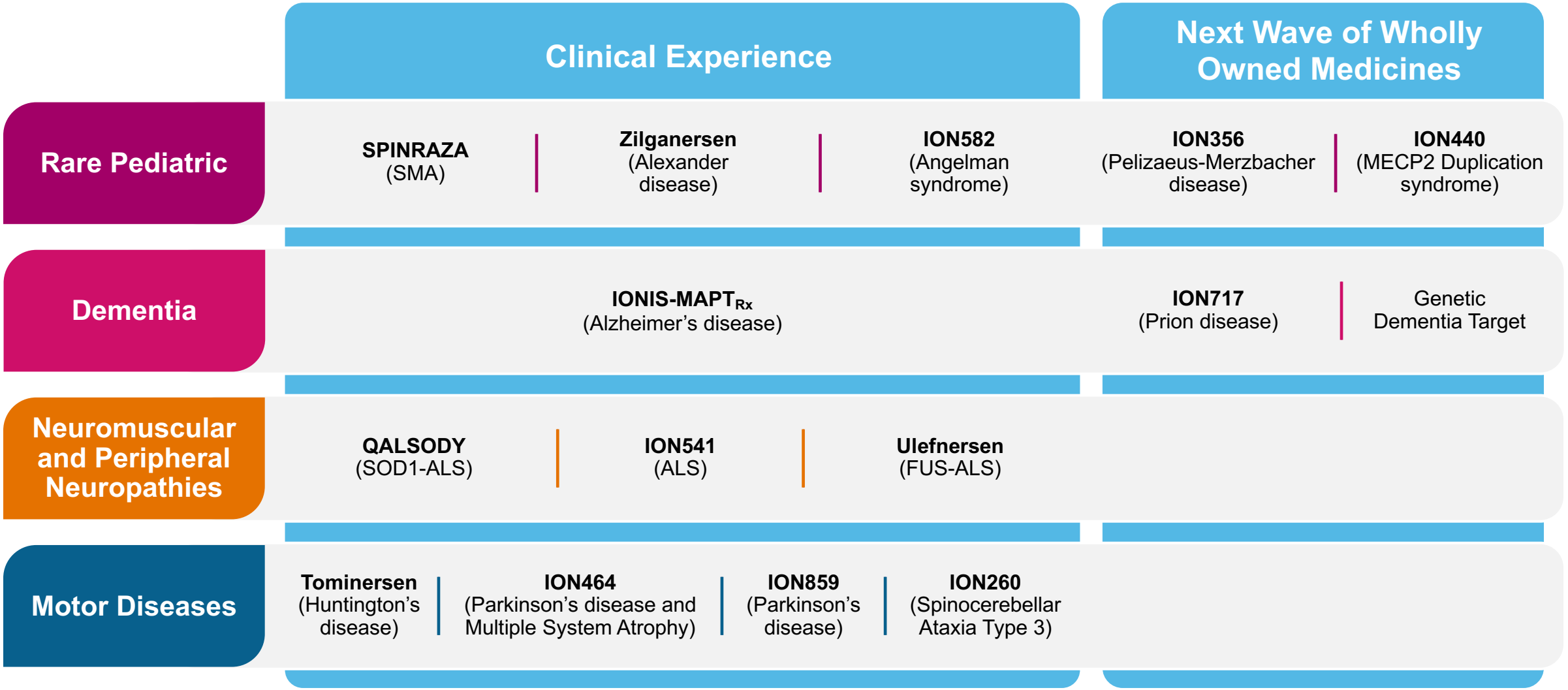
Rare Pediatric Neurology

Dementia

Neuromuscular and Peripheral Neuropathies

Motor Diseases

Clinical Experience with Ionis' Medicines and Potential for Growth in Each Pillar



Wholly Owned Neurology Franchise First Focused on Rare Pediatric Neurology and Dementia

Rare Pediatric Neurology

Zilganersen
Alexander Disease
Pivotal study underway

ION356
Pelizaeus-Merzbacher Disease (PLP1)
First in patient study to start in 2024[1]

ION440
MECP2 Duplication Syndrome
First in patient study to start in 2024[1]

Dementia

ION717
Prion Disease (PRNP)
First in patient study to start in 2023[1]

Genetic Dementia Target
Preclinical development
First in patient study to start in 2024[1]

1. Timing based on current estimates, subject to change.

Rare Pediatric Neurology

- **Epilepsies**
- **Intellectual Disability**
- **Leukodystrophies**
- **Neurodevelopmental Disorders**

Significant need for transformative therapies

1 in 6 children are affected by a neurological disorder[1]

Many diseases in children are caused by a **mutation or change in a single gene**

Young developing brains have a tremendous **capacity for growth and repair**

Opportunities for **efficient, rapid clinical development**

1. St. Jude; Neurological Disorders: A New Direction, Spring 2021

Zilganersen: Targeting GFAP for the Treatment of Alexander Disease

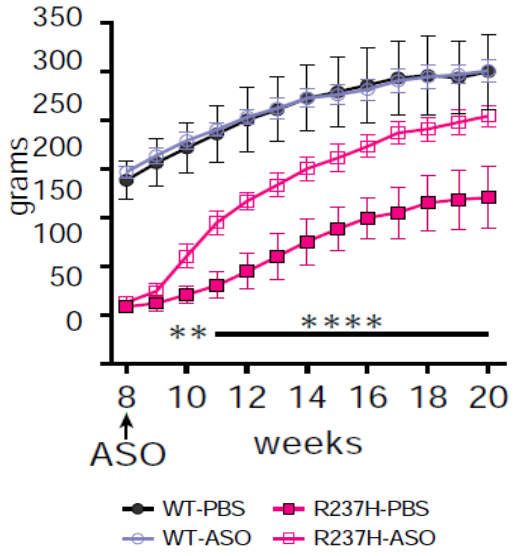
Alexander disease (AxD) is fatal, and patients experience **many symptoms**, the most burdensome often being gross and fine **motor** deficits, **speech** difficulties, **cognitive** impairment, **ataxia** and **seizures**

AxD is caused by autosomal dominant gain-of-function mutations in glial fibrillary acidic protein (GFAP)[1,2] and Zilganersen targets GFAP RNA.

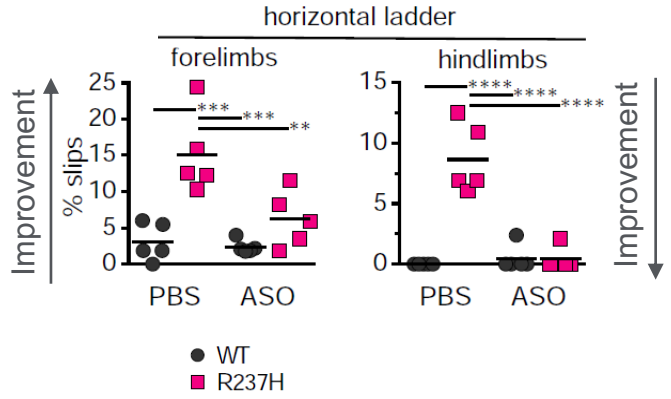
Mutations in **GFAP** cause spontaneous **overexpression** of GFAP that **accumulates** in the brain, leading to extensive white matter **damage**[3]

Pivotal Study Underway

Improved body weight



Improved motor function



R237H:AxD Mutant Rat
WT: Wildtype littermate

- **Motor deficits**
- **Limb strength**
- **Body weight**
- **Pathology**

Were all **prevented/restored** with both early and late intervention in preclinical models[3,4]

1. Brenner et al., Nat Genet, 2001; 2. Messing et al., J Neurosci, 2012;
3. Rosenthal, Beitr Pathol Anat, 1898; 4. Hagemann et al., STM, 2021.

Pivotal Study for Zilganersen

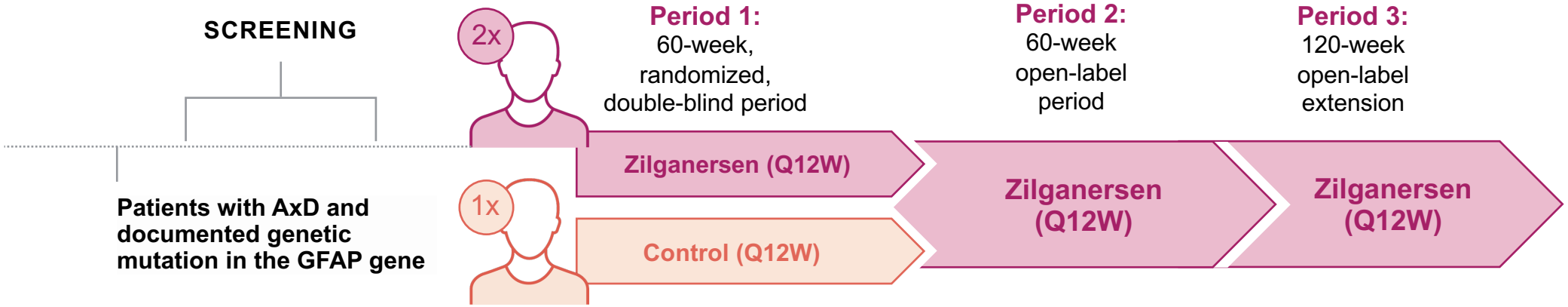
DESIGN

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 of age will be conducted at select trial sites

PRIMARY ENDPOINT

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



Data Planned for 2025[1]

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

ION356: Potentially Transformational Wholly Owned Pediatric Neurology Medicine for the Treatment of Pelizaeus-Merzbacher Disease

ION356 (PLP1 targeting ASO) Pelizaeus-Merzbacher Disease (PMD)

PMD is a severe leukodystrophy and patients can experience many symptoms including, movement and cognitive impairment[1]

PMD is caused by gain-of-function mutations or duplications in PLP1[2,3]

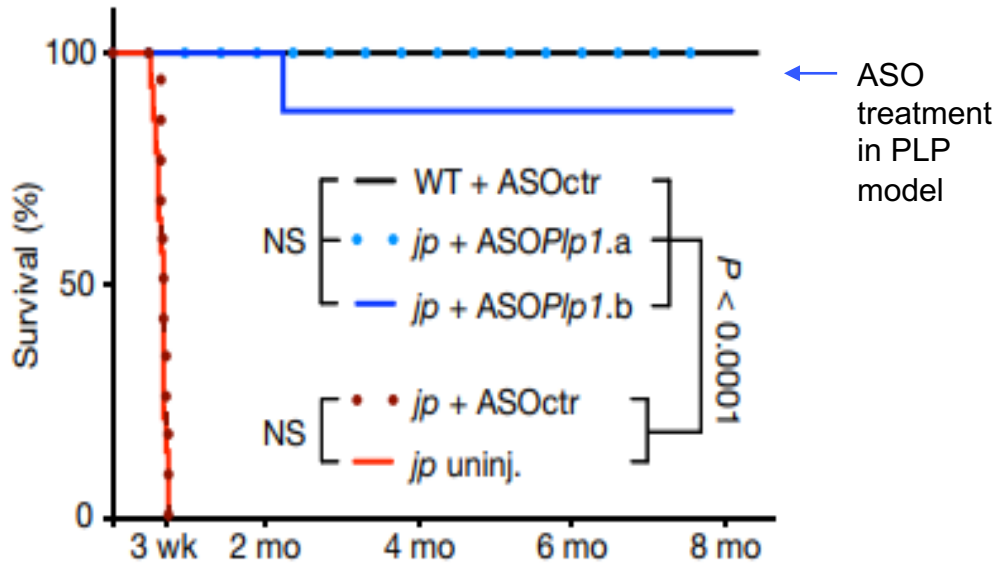
Suppression of PLP1 restored oligodendrocyte numbers and extended lifespan in PMD models[4]

Natural history study ongoing (NCT05659901)

Granted Orphan Drug Designation by FDA

First in patient study to start in 2024[5]

Extended survival after treatment

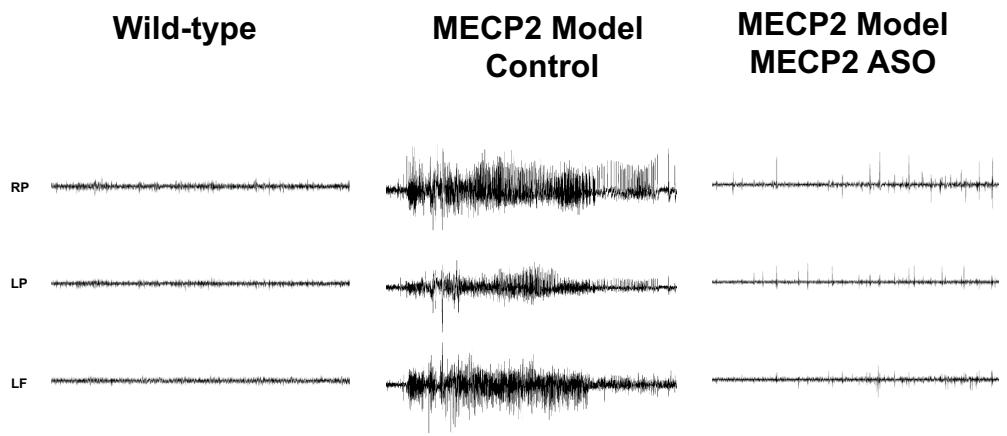


Elitt et al. 2020 *Nature*

1. Osório MJ, Goldman SA, Handb Clin Neurol, 2018; 2. Inoue et al., Am J Hum Genet, 1996; 3. Mimault et al., Am J Hum Genet, 1999; 4. Elitt et al., Nature, 2020; 5. Timing based on current estimates, subject to change.

ION440: Potentially Transformational Wholly Owned Pediatric Neurology Medicine for the Treatment of MECP2 Duplication Syndrome

Prevention of EEG deficit after treatment



Stainberg et al. 2016 *Nature*

ION440 (MECP2 targeting ASO) *MECP2 Duplication Syndrome (MDS)*

MDS is a severe developmental disease where children often experience intellectual disability, speech, motor delay and seizures[1,2]

MDS is caused by duplication, triplication, or translocation of the MECP2 gene[3,4]

MeCP2 protein reduction restores function, including EEG, in mouse models[5]

Natural history study ongoing (NCT06014541)

First in patient study to start in 2024[6]

1. Gaudio et al., Genetics in Med, 2006; 2. Lugtenberg Europ J of Hum Gen, 2009; 3. Ramocki et al., Ann of Neurol, 2009; 4. Ramocki et al., Am J of Med Gen Part A, 2010; 5. Stainberg et al., Nature, 2006; 6. Timing based on current estimates, subject to change.

RESEARCH ARTICLE

Science Translational Medicine

DRUG DISCOVERY

Antisense Oligonucleotides Delivered to the Mouse CNS Ameliorate Symptoms of Severe Spinal Muscular Atrophy

LETTER

nature

Towards a therapy for Angelman syndrome by targeting a long non-coding RNA

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

LEUKODYSTROPHY

Antisense therapy in a rat model of Alexander disease reverses GFAP pathology, white matter deficits, and motor impairment

LETTER

nature

Reversal of phenotypes in *MECP2* duplication mice using genetic rescue or antisense oligonucleotides

Yehezkel Sztainberg[1,2], Hong-mei Chen[3,4,5], John W. Swann[3,4,5], Shuang Hao[2,5], Bin Tang[2,5], Zhenyu Wu[2,5], Jianrong Tang[2,5], Ying-Wooi Wan[2,6], Zhandong Liu[2,5], Frank Rigo[7] & Huda Y. Zoghbi[1,2,5,8]

JCI insight

RESEARCH ARTICLE

Antisense oligonucleotide therapy for *KCNT1* encephalopathy

LETTERS

https://doi.org/10.1038/s41591-019-0608-y

nature medicine

Therapeutic inhibition of mTORC2 rescues the behavioral and neurophysiological abnormalities associated with *Pten*-deficiency

Clear Benefits Observed in Preclinical Models Across a Range of Serious Pediatric Neurology Diseases with Ionis' Drugs

ANNALS OF NEUROLOGY

RESEARCH ARTICLE

***Scn8a* Antisense Oligonucleotide Is Protective in Mouse Models of *SCN8A* Encephalopathy and Dravet Syndrome**

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

DRUG DEVELOPMENT

Antisense oligonucleotide therapy in a humanized mouse model of *MECP2* duplication syndrome

Article

nature

Suppression of proteolipid protein rescues Pelizaeus–Merzbacher disease

JCI The Journal of Clinical Investigation

Antisense oligonucleotide therapy reduces seizures and extends life span in an *SCN2A* gain-of-function epilepsy model

Dementias

General

- Over 50 million people worldwide are living with dementia[1]
- Dementia is a significant burden for those diagnosed, their families and caregivers
- Dementia affects how someone thinks, remembers and reasons:
  - Symptoms include difficulty with everyday tasks, confusion, memory loss and changes in mood and behavior

Focus Area

Focused first on dementias with known genetic causes and risk factors

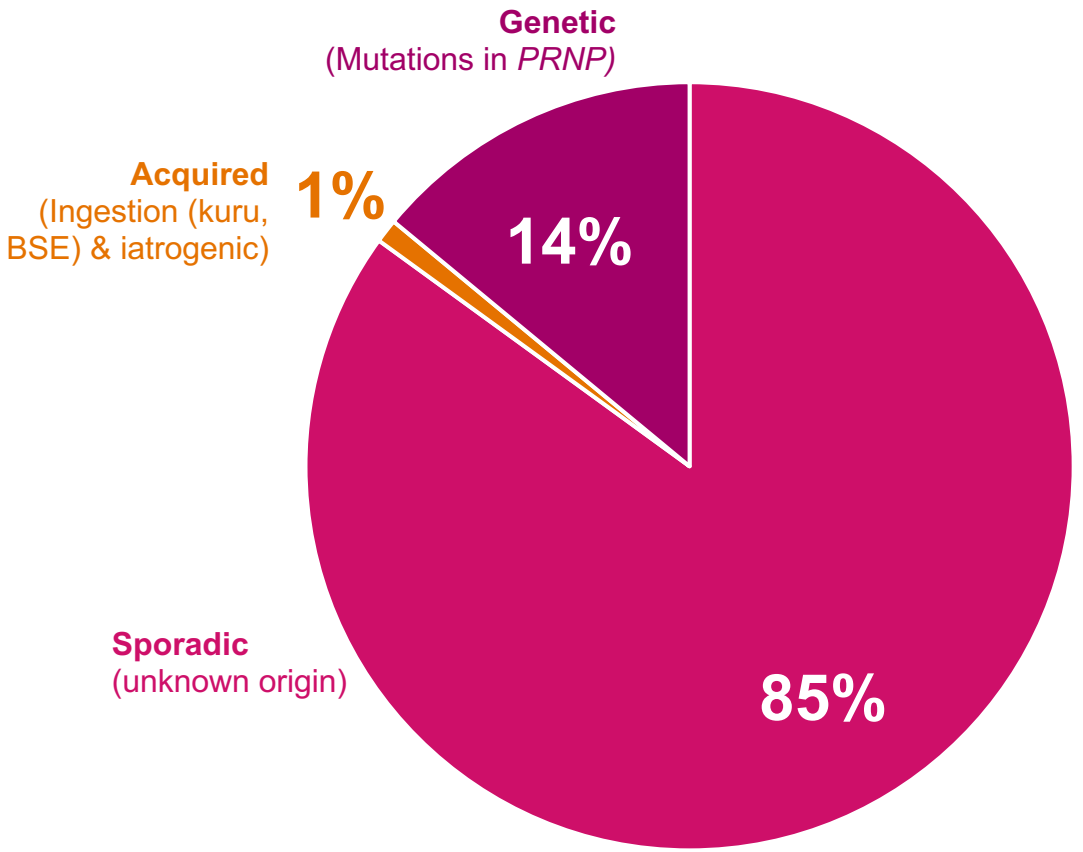
Advancing programs for targeted populations with high need and rapid development paths

Potential to expand into broader populations over time

1. WHO Key Facts, 2023.

ION717: Targeting PRNP for the Treatment of Prion Disease

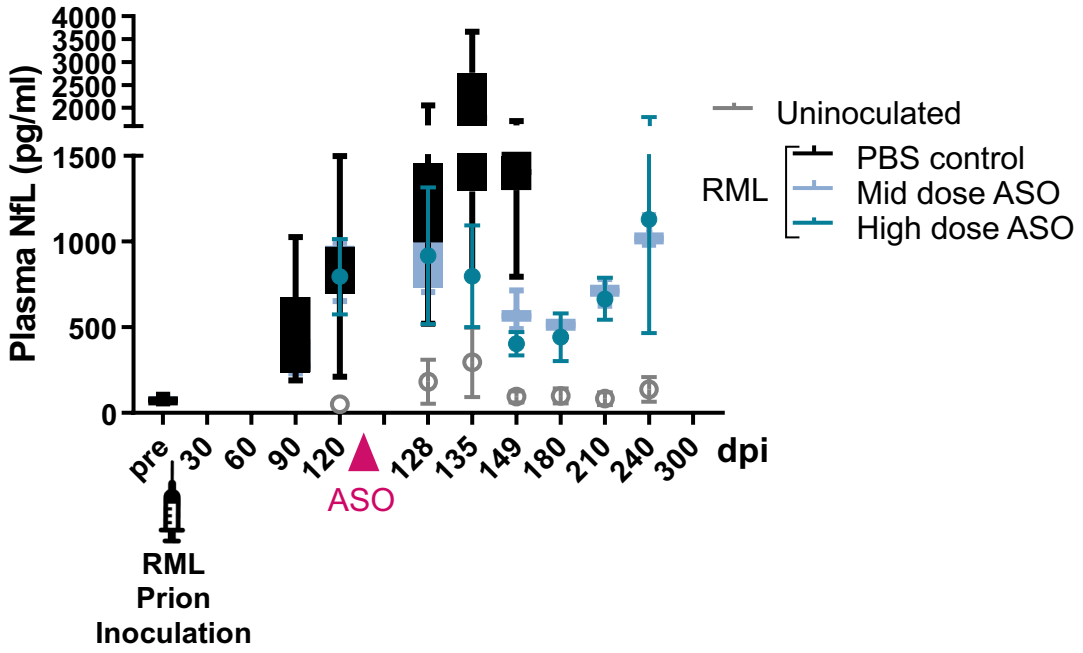
- Prion disease is a **fatal dementia** caused by misfolding of prion protein (PrP)[1,2]
- Patients experience a precipitous decline often with cognitive, motor and psychiatric deficits, usually **succumbing** to disease **within 12 months**[3,4]
- ION717 targets the PRNP RNA, encoding PrP. PrP is the **root cause** of all **forms of prion disease.**[5,6,7]
- PRNP suppression in animal models **extends survival**[8,9]
- **PrProfile Phase 1/2a study** of ION717 planned to start in 2023[10]



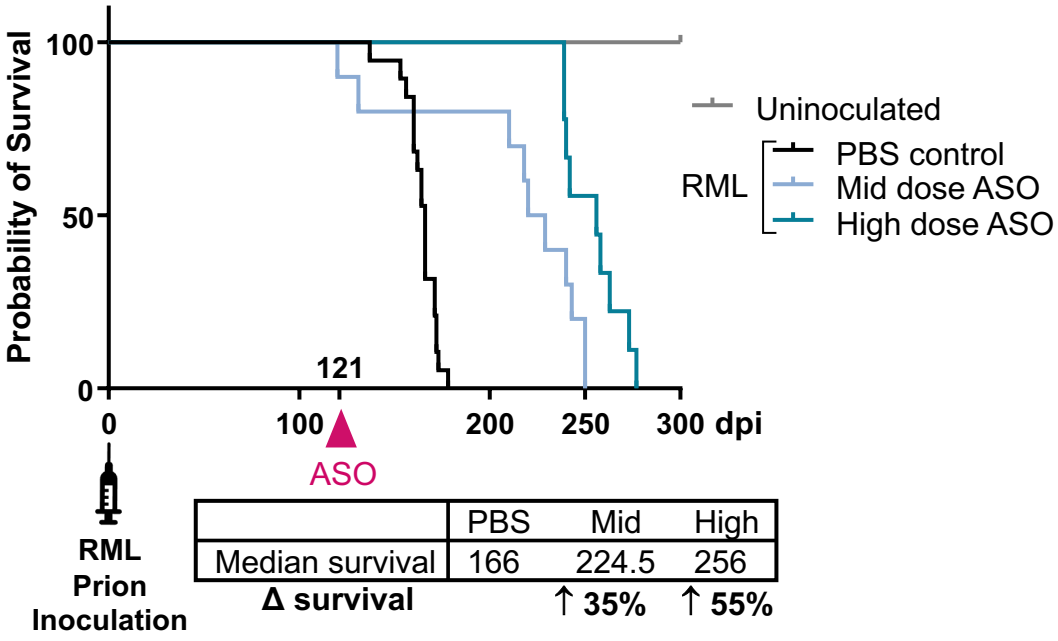
1. Prusiner, Sci Am, 1984; 2. Prusiner, Cell, 1990; 3. Parchi et al., Annal Neurol, 1999; 4. Geschwind 2015. "Prion Diseases." Continuum (6, Neuroinfectious Disease); 5. Jones et al., Lancet Neurol, 2020; 6. Mead et al. Eur J Hum Genet, 2006; 7. Palmer et al., Nature, 1991; 8. Raymond et al., JCII, 2019; 9. Minikel et al. NAR, 2020. 10. Timing based on current estimates, subject to change.

Dose-Dependent Reversal of Plasma NfL Levels and Extended Survival with ASO Treatment Initiated in Late-Stage Disease in Prion Model

Plasma NfL Reversal in Model of Prion Disease



Extended Survival in Model of Prion Disease

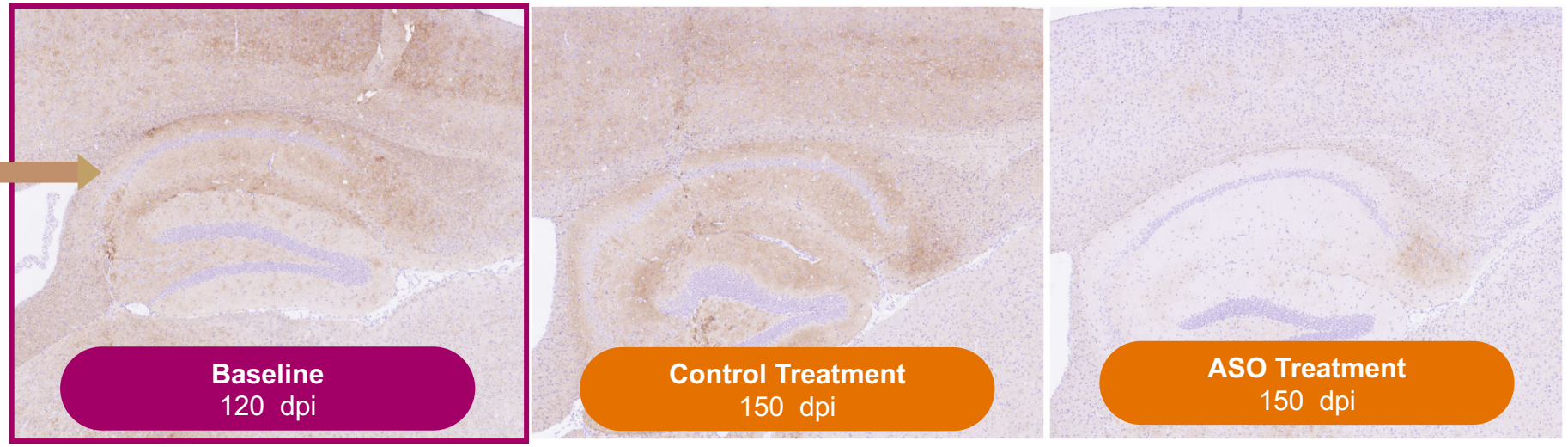


	PBS	Mid	High
Median survival	166	224.5	256
Δ survival		↑ 35%	↑ 55%

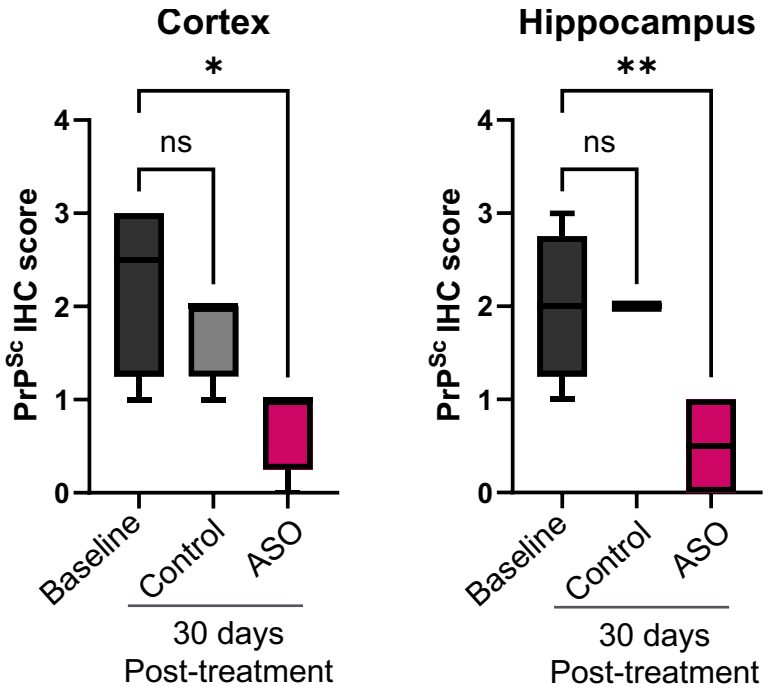
Minikel et al. NAR, 2020; Ionis, unpublished

Reversal of PrP Deposits After ASO Treatment Initiated in Late-Stage Disease Model

PrP deposits (PrP^{SC}) as determined by PrP Immunohistochemistry following proteinase K treatment



RML Injected Mice
with PrP ASO at 120 Days Post-RML prion inoculation (dpi), pathology performed at 150 dpi



Raymond et al., JCII, 2019; Ionis, unpublished

ION717: Phase 1/2a Study Planned to Start Before the End of 2023

PrPROFILE

Uniquely Positioned to Bring a Steady Flow of Innovative Neurology Medicines to Patients

Ionis is leading the field in advancing transformative RNA-targeted medicines for neurological diseases

Proven innovation with **2 approved breakthrough medicines** and **12 medicines in clinical development**

There is a **significant need** for transformative disease-modifying medicines and we are positioned to **continually bring** these medicines to **patients**

Focus on our wholly owned programs with highest likelihood of **transformative benefits** and modest development paths

Plan to **grow** our **wholly owned pipeline** into additional disease areas and larger more **common indications**

Poised to Deliver Innovative Neurology Medicines to Patients

Rachel Carnes

Senior Vice President, New Product Strategy

Creating a Focused, High-Value Portfolio with Long-term Potential

Assess Strategic Fit for Ionis

- Prioritize medicines aligned to our strategic therapeutic areas
- Prioritize medicines that have an enhanced product profile
- Balance risk and investment

Advance the Most Attractive Opportunities

- Prioritize medicines with significant transformational potential

Integrate Commercial Assessments

- Throughout the process as medicines advance in research and development

Patients' Lives can be Significantly Impacted by Neurological Disorders

A Diagnosis of a Neurological Disease Can Strike with Devastating Impact on Patients and their Families Throughout the Life Journey

Lilas, Alexander Disease Patient, and her brother[1]

Patients with Alexander Disease may Experience:

- Cognitive delay or decline
- Speech difficulties
- Gross motor decline or delay
- Failure to thrive
- Seizures

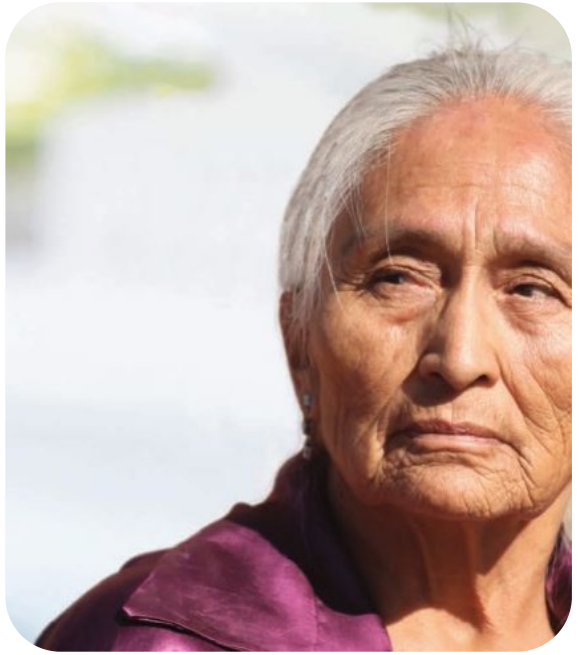


Image from Alzheimer's Association website[2]

Patients with Dementia Develop a Loss of Cognitive Abilities that Leads to:

- Impaired memory and thinking
- Personality changes
- Insomnia
- An eventual loss of independence

Lilas, https://www.endaxd.org/patients/lilas
'Alzheimer's Disease Facts and Figures' Annual Report https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf

Executing on our Strategy to Bring our Potentially Transformational Neurology Medicines to Patients

Ionis is leading the field in advancing important RNA-targeted medicines for neurological diseases

Broad range of medicines in our portfolio for **rare** and **common** diseases

Strategy to bring **the most impactful medicines** to patients in an efficient way over time

We Started with a Vision and Purpose

Vision

Optimize **patient access** to our wholly owned neurology medicines by building resources and expertise in **targeted neurology spaces** enabling us to **realize synergies** increasing our **competitive advantage** and driving **increased value**

Purpose

Identify and advance wholly owned neurology medicines that:

Have first- or best-in-class potential

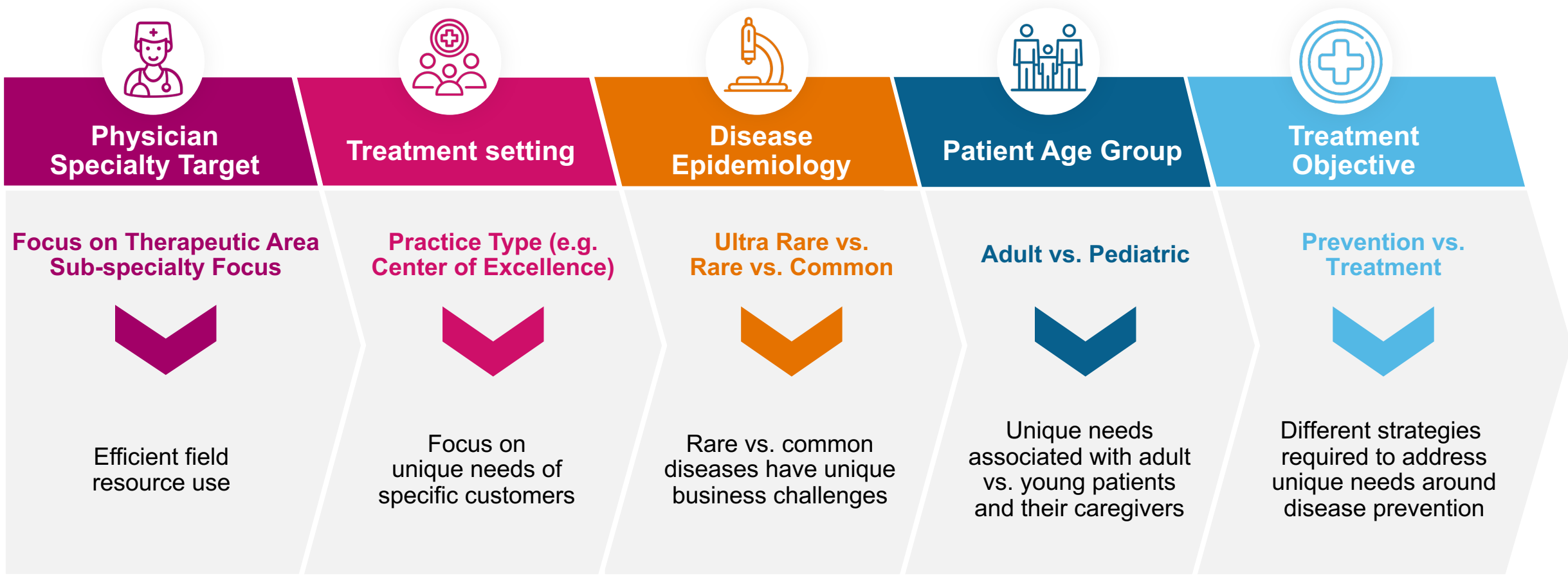
Create efficiencies / synergies

Enable us to focus our resources and expertise

Targeted Expansion of Wholly Owned Neurology Franchise

Focused on Advancing Potentially Transformative Medicines

Optimizing Synergies Across Our Neurology Pipeline



Near-Term Focus in Rare Pediatric and Dementia Pillars with Potential for Paradigm-Changing Treatments

Near-Term Focus

Next Wave of Wholly Owned Medicines

Rare Pediatric

Zilganersen
(Alexander Disease)

ION356
(Pelizaeus-Merzbacher Disease)

ION440
(MECP2 Duplication Syndrome)

Dementia

ION717
(Prion Disease)

Genetic Dementia
Target

Future Pillars

Neuromuscular and Peripheral Neuropathies

Motor Diseases

As Wholly Owned Medicines Advance from Research into Clinical Development

Concentrated Footprint Enables Innovative and Focused Commercialization Strategy

Lean

- Single field team per pillar focused on centers of excellence where the patients are
- Patient services leveraged across medicines
- Launches become ‘plug and play’ as new medicines are approved within each pillar

Medical Focused

- Disease education focused on patient identification genetic testing, guidelines and administration
- Emphasis on field medical support

Digital Minded

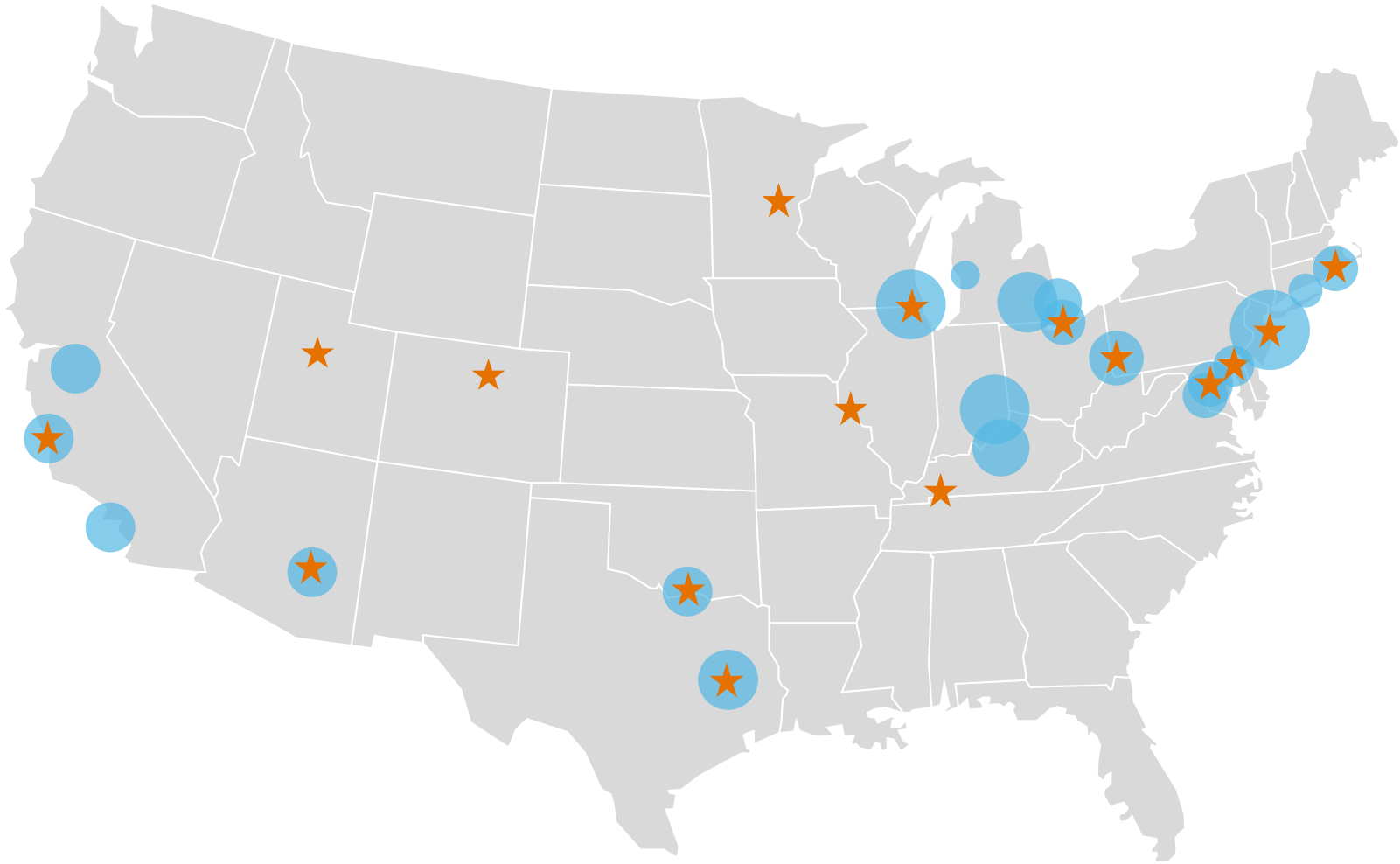
Omnichannel activation enables:

- increased reach and frequency to targeted HCPs and patient community
- a broad range of tools and multichannel content (social media, webinars, customer relationship management, etc.)

Many core activities overlap given similarities between disease areas

Opportunities for synergies within pillars

Pediatric Neurology: Concentrated Footprint



Pediatric Leukodystrophy Patient Clusters by Claims Analysis

Top Pediatric Leukodystrophy KOL Location

Zilganersen Opportunity: No Disease Modifying Medicines for Alexander Disease Today

Patients have a median survival of between **14 and 25 years**[1,2]

~65%
Of cases occur in children[3]

Prevalence of **1 in 1-3 million**[4]

Accounts for between **2-8% of leukodystrophies** and may be underreported[5]

Key Areas of Focus:

Increasing awareness and recognition of Alexander disease

Educating regarding the clinical program

Ensuring access to all appropriate patients

Steelman Family, Alexander Disease Patients

1. Messing, Albee. Alexander Disease: A Guide for Patients and Families. Colloquium Series on Neuroglia in Biology and Medicine: From Physiology to Disease. Vol. 4. No. 1. Morgan & Claypool Life Sciences, 2017; 2. Prust M, et al. GFAP mutations, age at onset, and clinical subtypes in Alexander disease. Neurology. 2011;77(13):1287-1294. 3. Srivastava et al., 1993; 4. 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; 5. Heim et al., Am J Med Genet 1997; 71:475-478 and Cohen et al., Ann Hum Genet 2020; 84:11–28;

ION717 Opportunity: No Disease Modifying Medicines for Prion Disease Today

Fatal with rapid, progressive **decline of cognitive ability** (thinking and memory), **personal independence**, **speech** and **communication**[1,2,3,4]

~500 patients die in the US each year of Prion disease[5]

Key Areas of Focus:

Increase the awareness of Prion disease

Support expedited diagnosis

Ensure patients have timely access to ION717

Sonia, Genetically at risk for developing prion disease and her husband, Eric[6]

1. Kortazar-Zubizarreta, I., H. Erana, A. Pereda, et al. Analysis of a large case series of fatal familial insomnia to determine tests with the highest diagnostic value. J Neuropathol Exp Neurol. 2023;82(2):169-79; 2. Safadi, D., O. S. Cohen, J. Chapman, et al. The epidemiological and clinical characteristics of patients with young-onset genetic Creutzfeldt-Jakob disease. Neurol Res. 2023:1-4; 3. Shir, D., E. B. Lazar, J. Graff-Radford, et al. Analysis of Clinical Features, Diagnostic Tests, and Biomarkers in Patients With Suspected Creutzfeldt-Jakob Disease, 2014-2021. JAMA Netw Open. 2022;5(8):e2225098; 4. Nakatani, E., Y. Kanatani, H. Kaneda, et al. Specific clinical signs and symptoms are predictive of clinical course in sporadic Creutzfeldt-Jakob disease. Eur J Neurol. 2016;23(9):1455-62. 5. Maddox, R. A., M. K. Person, J. E. Blevins, et al. Prion disease incidence in the United States: 2003-2015. Neurology. 2020;94(2):e153-e57; Centers for Disease Control and Prevention 2022 available at: https://www.cdc.gov/prions/cjd/occurrence-transmission.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fprions%2Fcjd%2Foccurance-transmisison.html. 6. Image from CJD Foundation website.

Growing our Leading Neurology Franchise Over Time

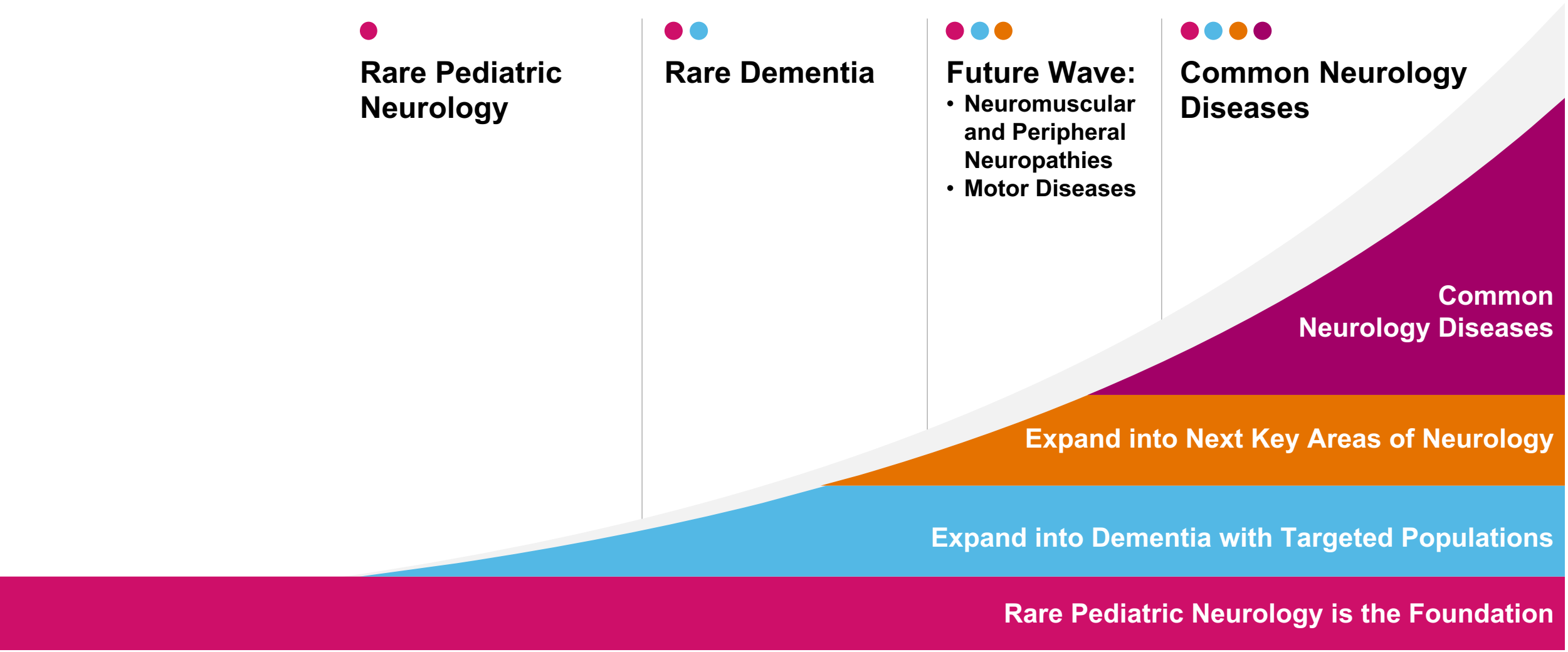
On track to Add 1-2 Neurology Programs to Our Wholly Owned Pipeline Per Year With Potential to Move into Larger Indications Over Time

Rare Pediatric Neurology

Rare Dementia

Future Wave:
- **Neuromuscular and Peripheral Neuropathies**
- **Motor Diseases**

Common Neurology Diseases

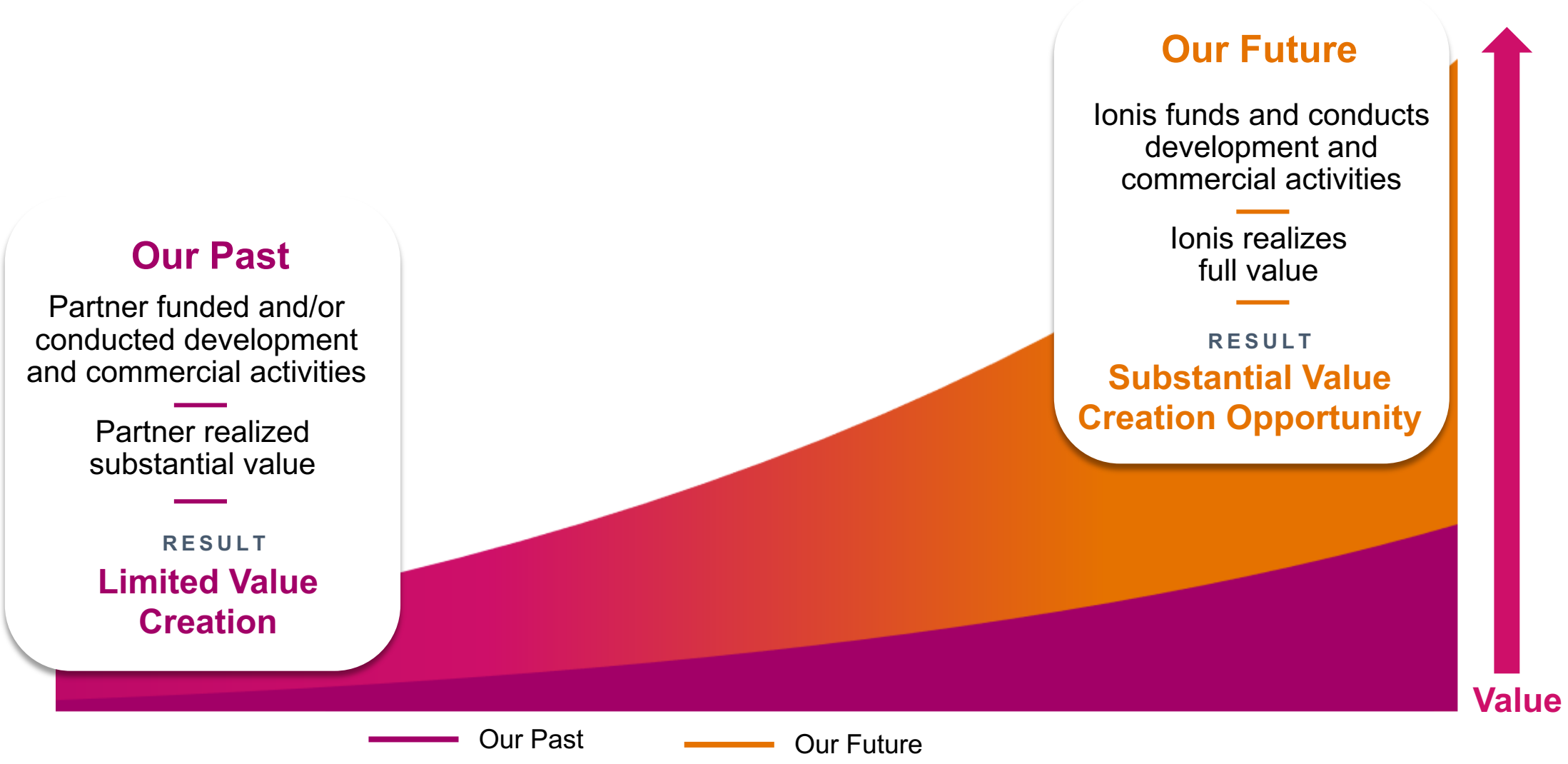


Clear Path to Unlocking Next-Level Value

Beth Hougen

Chief Financial Officer

Positioned for Next-Level Growth



Clear Path to Drive Value Creation

Foundation

Strong
Financial Foundation
and
Robust Innovative
Pipeline Position Ionis
to Drive Value

Invest

Invest to Bring Important
Medicines to Patients

—

Advancing Pipeline
and Technology
to Drive Steady Cadence
of New Medicines

Growth

Positive Cash Flow
Powered by
Substantial Revenue
Growth

Uniquely Positioned with Strong Financial Foundation to Bring Medicines to Patients

>$2B of cash and short-term investments[1]

Significant royalty revenue with SPINRAZA as the cornerstone

Substantial and sustained R&D revenue from multiple sources

1. As of June 30, 2023.

Investing Efficiently to Drive Positive Cash Flow

Late-Stage Medicines	Ionis' large Phase 3 studies are at or near full enrollment
Go-to-Market Activities	Integrated commercial capabilities in place; right-sizing and scaling for successful launches
Next Wave of Medicines	Investing in advancing our growing wholly owned pipeline
Cutting-Edge Technologies	Continued innovation for future medicines

Modest Expense Growth over the Short- and Mid-Term

R&D Expenses Approaching Steady State

SG&A Expenses Ramp In-line with Planned Launches

Clear Path to Growing Revenue

Combined multi-billion-dollar revenue potential

R&D Revenue from Partners

Strong foundation of substantial recurring revenue from multiple sources

New sources to add to R&D revenue

Royalties

Multiple approved medicines today generating royalty revenue

4 partnered medicines positioned to add significant royalty revenue in the short- and mid-term[1]

Product Revenue

Olezarsen and donidalorsen on the horizon to be our first wholly owned products[1]

Additional wholly owned medicines just beyond the horizon[1]

1. Assuming approval.

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R&D Revenue from Partnered Programs: Important Source of Funding Powering Ionis' Medicines to the Market

Existing Partnership Programs Advance

New Medicines from Existing Partnerships

New Partnerships

Strong Foundation of Substantial Recurring Revenue

Upfront Payments | License Fees | Milestone Payments

Up to >$15 Billion in Potential Future R&D Payments from Partners[1]

1. Does not include commercial milestone payments under collaboration agreements of >$7 billion.

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Our Royalty Revenue Today and Into the Future

Royalty Revenue Today[1]

SPINRAZA

QALSODY

Majority Driven by SPINRAZA

Global leader for treatment of SMA

Earned >$1.5B
in royalty revenue to date

Our Next Potential Medicine

Eplontersen

Co-Developing and Commercializing in the US with AstraZeneca

AstraZeneca responsible for majority of US and all OUS commercial and medical affairs costs

Attractive royalty rates up to mid-20%

Potential to amplify royalties with up to $2.9B of sales milestone payments

Other Late-Stage Medicines

Pelacarsen
Bepirovirsen
IONIS-FB-L_{Rx}

Potential to benefit millions of patients worldwide

Partner responsible for development, commercial and medical affairs costs[2]

Attractive royalty rates up to the low 20%

Significant sales milestone payments of up to >$1.2B

1. SPINRAZA: www.spinraza.com; QALSODY: www.qalsody.com; Biogen is responsible for commercializing SPINRAZA and QALSODY. 2. We are responsible for completing the Phase 2 study of IONIS-FB-L_{RX}.

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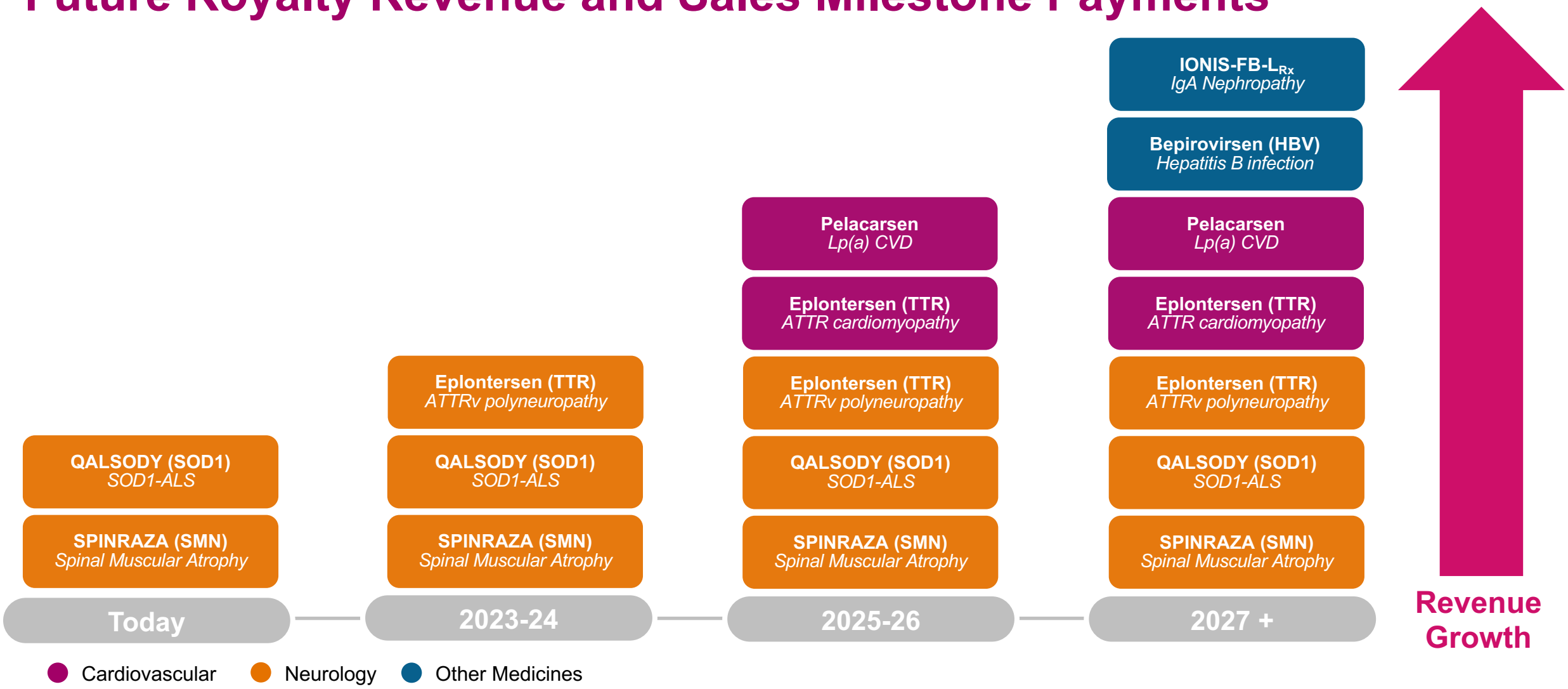
Partnered Programs: Substantial Opportunity for Future Royalty Revenue and Sales Milestone Payments[1]



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Important Medicines Unlock Significant Revenue Potential[1]

Olezarsen

Large Patient Population[2]

Broad Phase 3 program progressing well

Building on eplontersen infrastructure

>$1B peak product revenue potential[3]

Donidalorsen

High-Value Opportunity

Phase 3 program designed to support switch market dynamic

Efficient commercial model

>$500M product revenue potential[3]

Next Wave

High Patient Need Areas

Starting first with rare pediatric neurology and dementia

Aiming for first- or best-in-class

Anticipated synergies to drive efficiency

Start in rare, with ability to expand into broader indications

1. Assuming approval, including olezarsen for SHTG. 2. Planned to begin in FCS, a rare indication and move to SHTG, a broad indication. 3. Market opportunity and peak sales estimates are based on current assumptions and are subject to change. Olezarsen peak sales potential based on modest penetration into total addressable market.

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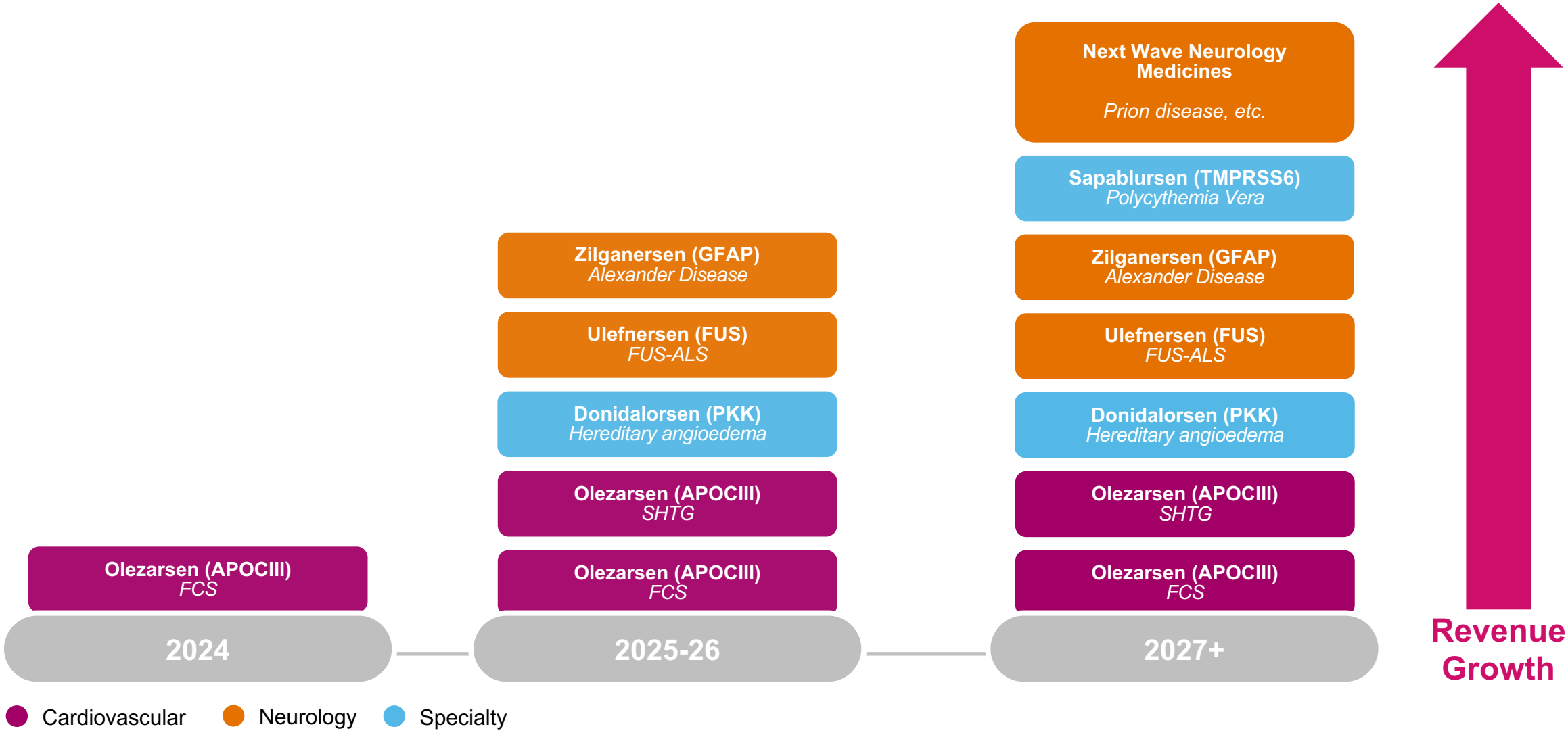
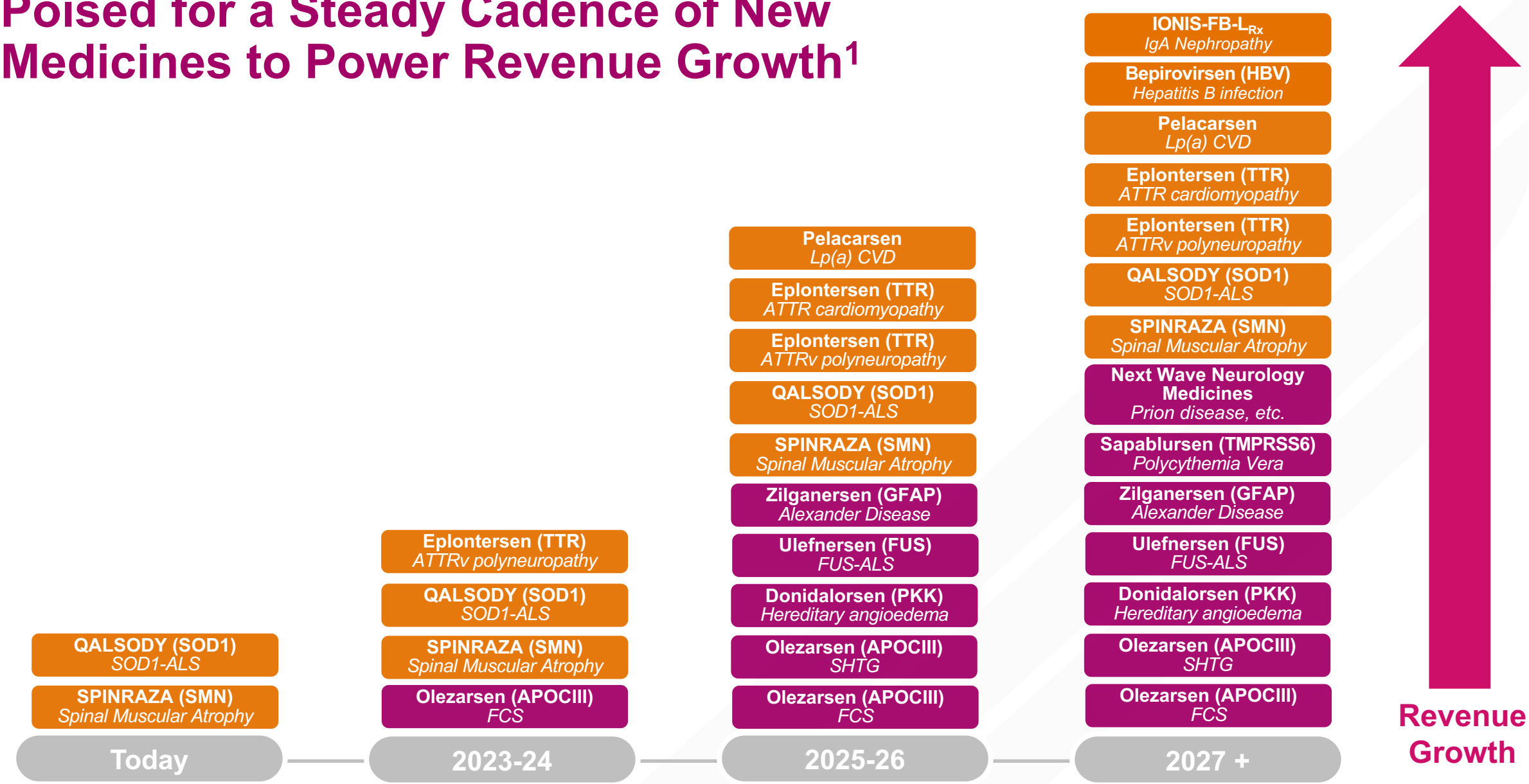
Significant Product Revenue Potential[1]



1. Estimated timing of potential US approval based on current assumptions and are subject to change.

Poised for a Steady Cadence of New Medicines to Power Revenue Growth[1]



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Key Takeaways:

Executing Strategy to Unlock Next-Level Value

Strong Financial Foundation

>$2B of **cash** and short-term **investments**[1]

Substantial and **sustained recurring revenue** from multiple sources

Enables **continued investment** to drive **increasing value**

Investing for Revenue Growth

Executing **go-to-market activities** for **multiple near-term launches**

Advancing pipeline **to deliver steady cadence of new medicines to patients**

Advancing **next-generation technologies** for **future transformational medicines**

Path to Positive Cash Flow

Growing revenue from **new product launches**

Growing royalty revenue from multiple marketed medicines today + additional medicines poised to reach market in the short- and mid-term

Strong foundation of substantial recurring R&D revenue from multiple sources

1. As of June 30, 2023.

Focused and Ready to Deliver Next-Level Value to Patients and Stakeholders

Brett Monia, Ph.D.

Chief Executive Officer

Executing on a Clear Vision

Driving Substantial Value for Patients and All Stakeholders

Delivering a Steady and Growing Cadence of Potentially Transformational Medicines

- **Technology Leadership**
- **Prioritizing and Expanding the Ionis Wholly Owned Pipeline**
- **Delivering Ionis Medicines Directly to Patients**

Financial Strength and Responsibility

Positioned to Bring Potentially Transformational New Medicines to Patients

Steady Cadence of Launches – Starting in 2024

Eplontersen

ATTRv-Polyneuropathy	ATTR-Cardiomyopathy

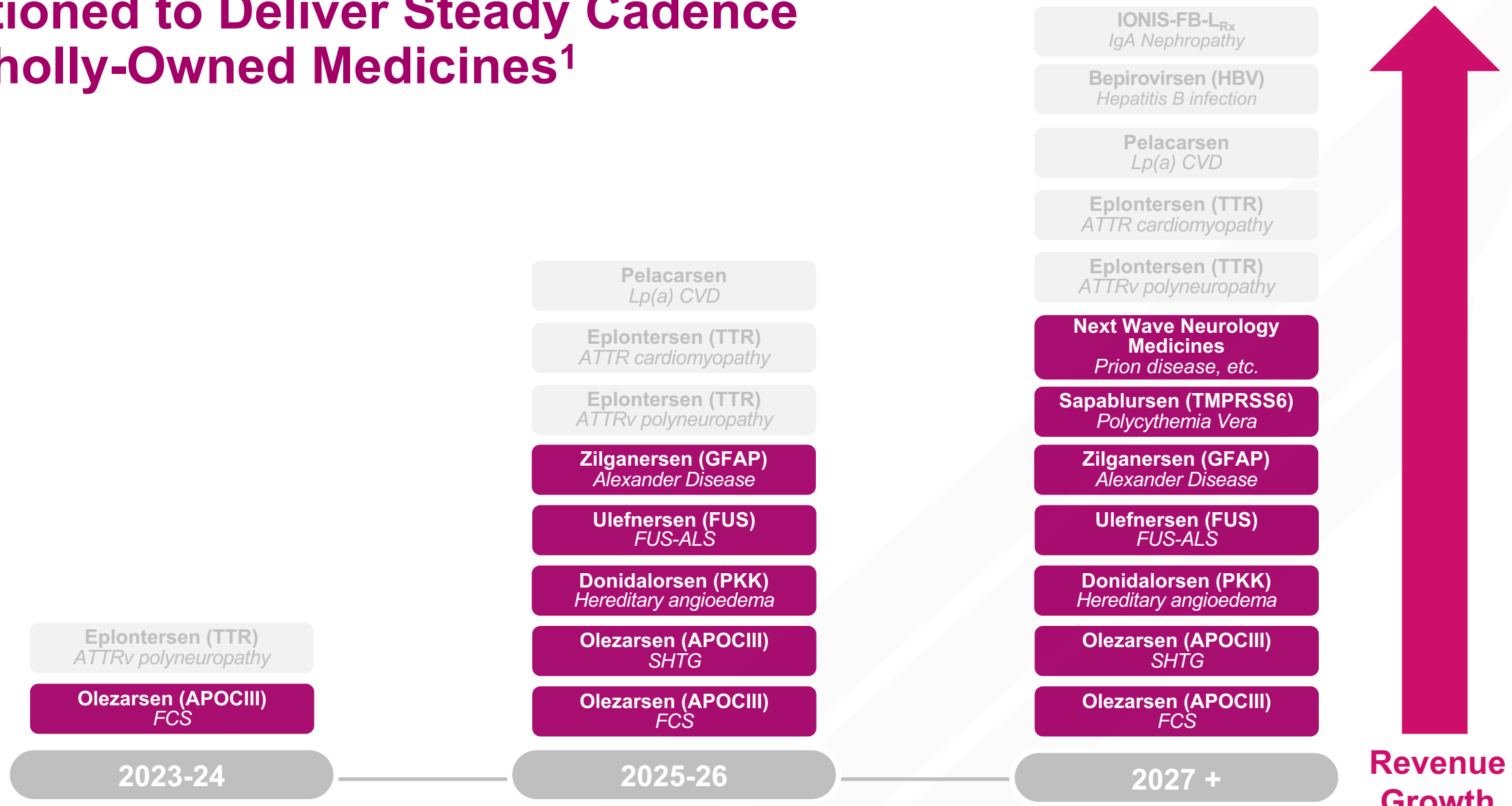
Olezarsen

Familial Chylomicronemia Syndrome (FCS)	Severe Hypertriglyceridemia (SHTG)

Donidalorsen

Hereditary Angioedema (HAE) Prophylaxis

Positioned to Deliver Steady Cadence of Wholly-Owned Medicines[1]



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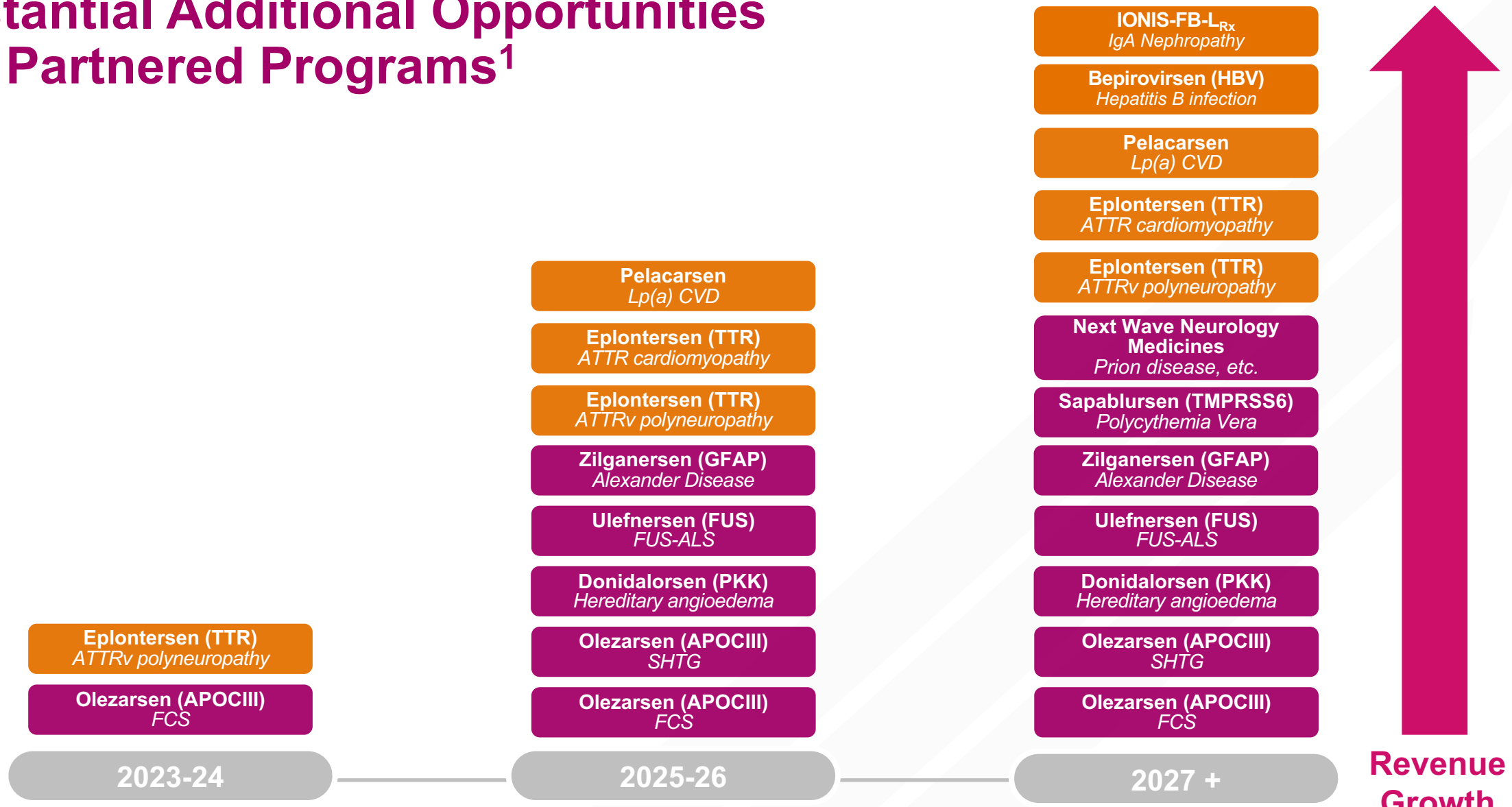
Substantial Additional Opportunities from Partnered Programs[1]



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Ionis Innovation Day: Key Takeaways

Drive Next-Level Value for Patients and All Ionis Stakeholders

01

Established Wholly Owned Pipeline

Advancing and growing our wholly owned pipeline in focused therapeutic areas, including neurology

02

Integrated Commercial Capabilities in Place

Steady cadence of new potentially **transformational medicines** to the **market**

03

Leading Technology

Advancing technology to:

- **Expand existing franchises**
- **Address new therapeutic areas**

04

Strong Financial Foundation Poised for Growth

Multi-billion-dollar revenue opportunity will enable **positive cash flow**

Jackson,
Angelman Syndrome Patient

IONIS® Innovation Day

Discovering, Developing and Delivering Transformational Medicines

October 4, 2023 | Nasdaq: IONS