Ionis Pharmaceuticals

Investor Day

December 7, 2018

IONIS™ PHARMACEUTICALS

Forward Looking Language Statement

This presentation includes forward-looking statements regarding our business, financial guidance and the therapeutic and commercial potential of SPINRAZA, TEGSEDI™ (inotersen), WAYLIVRA™ (volanesorsen) and Ionis' technologies and products in development, including the business of Akcea Therapeutics, Inc., Ionis' majority owned affiliate. 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, 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, 2017, and its most recent quarterly report on Form 10-Q, which are on file with the SEC. Copies of this 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.

Ionis Today: Successful and Positioned for Greater Value Creation

Key Takeaways

Commercial Programs Transforming the Treatment of Patients with Fatal, Genetic Diseases

- SPINRAZA global access growing; standard-of-care treatment for all patients with SMA
- TEGSEDI approved and launched in U.S., EU and Canada
- WAYLIVRA regulatory reviews ongoing

Ionis is Sustainably Profitable* and Positioned for Growth

- Commercial revenue growing; now 45% of total revenue**
- More than three-fold increase in R&D revenue since 2011
- ~$2 billion in cash***

*Pro forma operating profit; **In the 1st nine months of 2018; ***As of Q3 2018

10+ Programs with the Potential to Deliver Commercial Value Within the Next 5 Years

Advances in our Technology Continue to Enhance the Performance of Ionis Medicines to Expand Commercial Potential

Ionis Today: Continuing Innovation Creating Transformational Medicines

Leading the Discovery and Development of Innovative RNA-targeted Medicines

Growing and Advancing Pipeline of Diverse First/Best-in-Class Medicines

Achieving Sustained Profitability While Increasing Investment in Products, Pipeline and Technology

Delivering Significant Value to Patients and Shareholders

Ionis Today: Transformational Medicines with Potential to Deliver Significant Value to Patients and Shareholders

SPINRAZA (nusinersen)

A life-changing medicine approved globally for the treatment of spinal muscular atrophy

TEGSEDI (inotersen)

A transformative medicine for adult patients with polyneuropathy from hATTR approved in the U.S., EU and Canada

WAYLIVRA (volanesorsen)

A potentially transformative medicine under regulatory review for the treatment of patients with FCS

The Next Wave of Important Commercial Opportunities

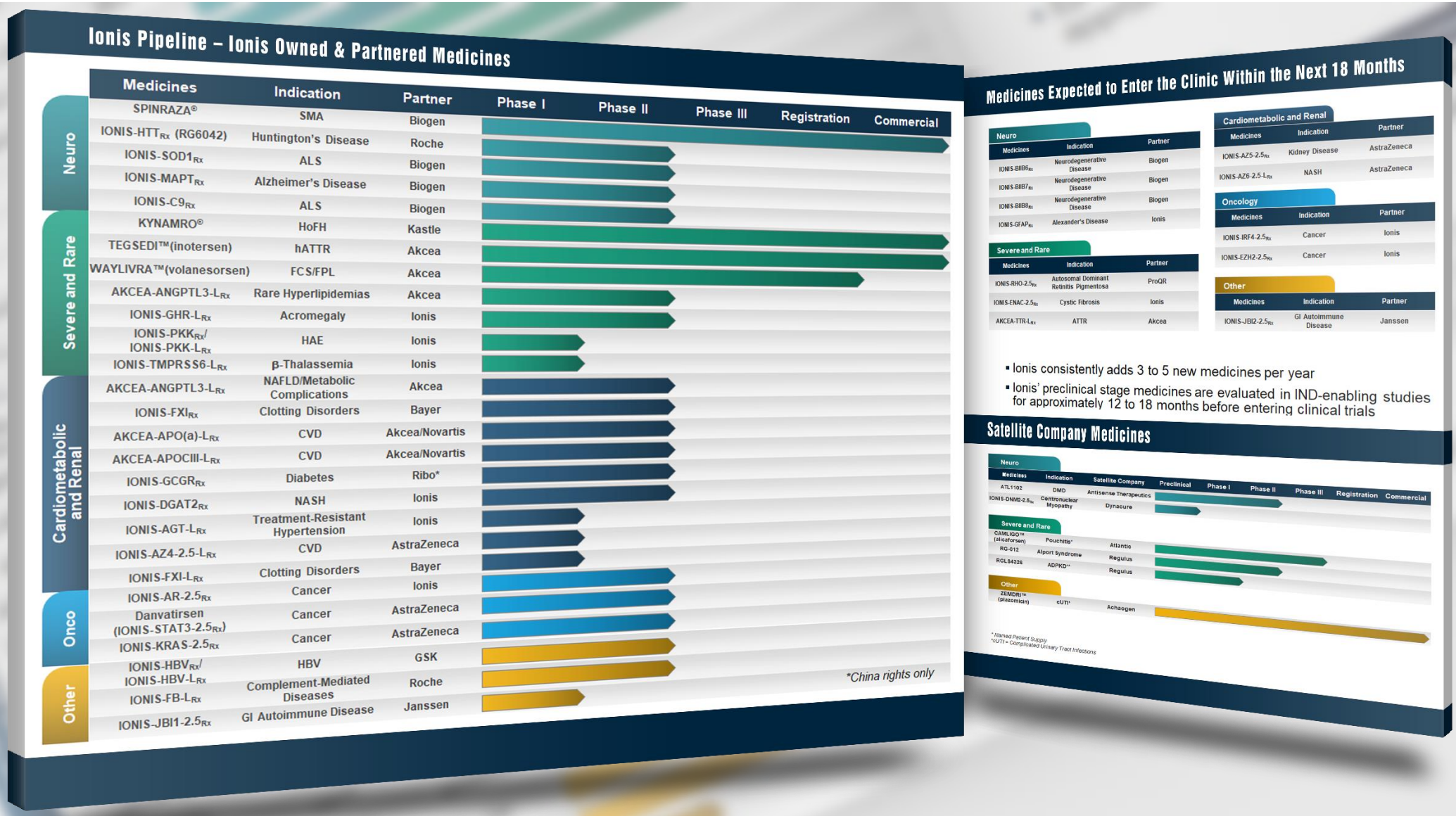
10+ Medicines May Enter Pivotal Programs in the Next 2 Years

Several SPINRAZA-like Quality Breakthrough Product Opportunities

Drug Discovery and Development Strategy: Broadly Addressing Therapeutic Areas that Drive Value For Patients and Shareholders

1. Focus on novel, first or best-in-class medicines that can transform therapy
2. Create and maintain a balanced portfolio of medicines targeting large, moderate and rare disease opportunities
3. Balance opportunity and types of risks across the pipeline
4. Continue to expand the value of antisense technology: More targets, mechanisms, organs and routes of delivery

Ionis Today: Advancing and Growing Pipeline of Over 40 Medicines



Ionis Today: Strong Financial Performance Resulting From Prolific Innovation and Intelligent Business Strategy[1]

~$2 billion in cash

$408 million in revenue

$25 million in operating income[2]

Driven by a more than 15% increase in revenue over 2017

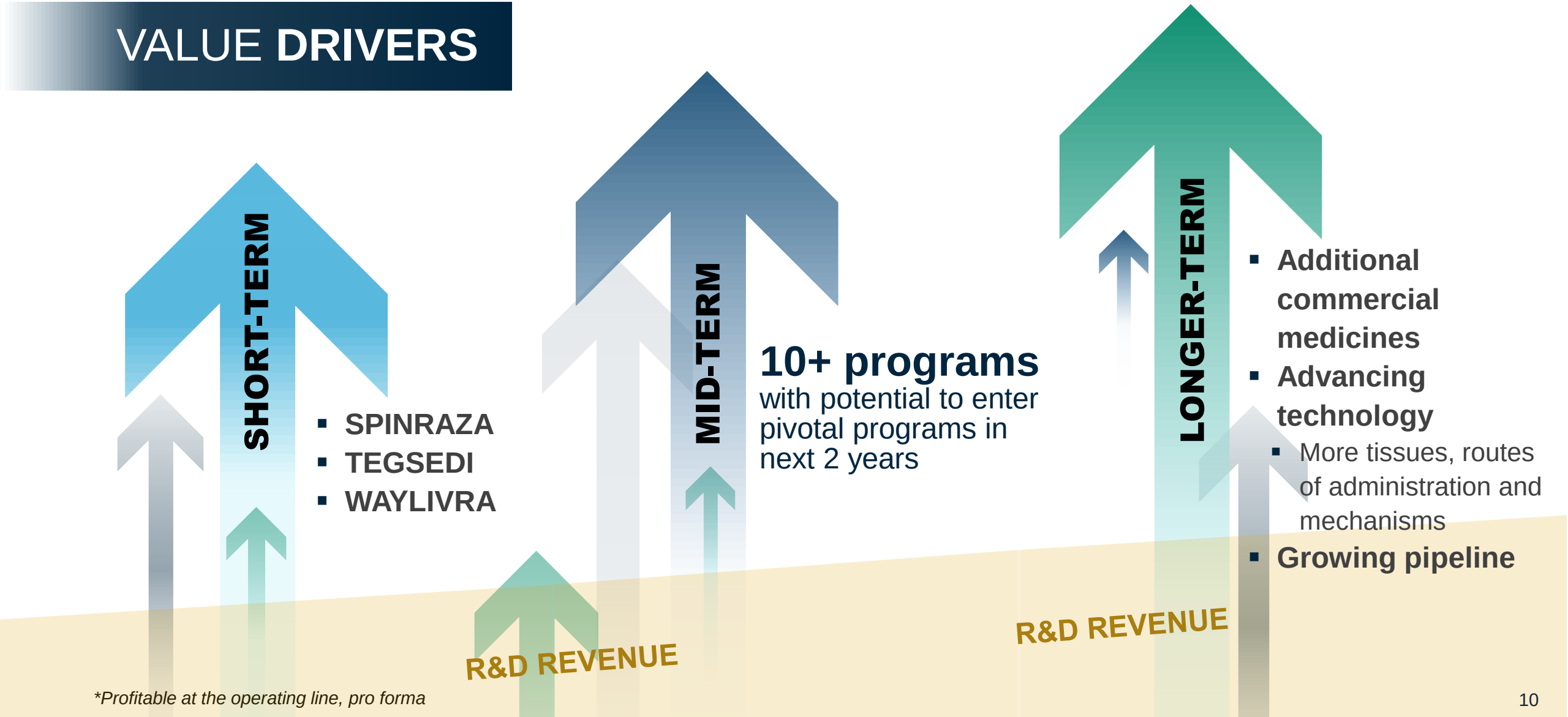
IONIS™ PHARMACEUTICALS

[1]*As of end of Q3 2018*
[2]*Pro forma*

Ionis: Delivering Value Today and Into the Future

Sustained Profitability* and Substantial Cash Enables Increased Innovation to Drive Value

VALUE **DRIVERS**



SHORT-TERM

- **SPINRAZA**
- **TEGSEDI**
- **WAYLIVRA**

MID-TERM

10+ programs
with potential to enter pivotal programs in next 2 years

LONGER-TERM

- **Additional commercial medicines**
- **Advancing technology**
  - More tissues, routes of administration and mechanisms
- **Growing pipeline**

**Profitable at the operating line, pro forma*

Today's Presenters

Stanley Crooke, M.D., Ph.D.
Chief Executive Officer and Chairman

Brett Monia, Ph.D.
Chief Operating Officer

Richard Geary, Ph.D.
SVP Development

Damien McDevitt, Ph.D.
Chief Business Officer

Beth Hougen
Chief Financial Officer

Today's Agenda

8:00 AM	**Welcome and Introductions**	*Stanley Crooke, M.D., Ph.D.*
	SPINRAZA, TEGSEDI and WAYLIVRA	*Damien McDevitt, Ph.D.*
	The Next Wave of Commercial Opportunities	*Brett Monia, Ph.D.*
	Q&A	
9:45 AM	Break (15 minutes)	
	Key Value Drivers From Mid-stage Pipeline	*Richard Geary, Ph.D.*
	Financial Strength Today and Beyond	*Beth Hougen*
	Ionis Delivering Value Today and in the Future	*Stanley Crooke, M.D., Ph.D.*
11:30 AM	***Final Q&A***	

Agenda for Planned Webcast in Q2 2019

Research Strategy

Early Stage Pipeline

Converting Advances in Ionis' Technology to Commercial Value

SPINRAZA, TEGSEDI & WAYLIVRA

Commercial Update

Damien McDevitt, Ph.D.
Chief Business Officer

Breakthrough Medicines Bringing Significant Value to Patients Today

Key Takeaways

SPINRAZA® (nusinersen) injection 12 mg/5 mL

- The standard-of-care for all patients with SMA
- Recognized by the medical and scientific communities with the Prix Galien awards and prestigious Breakthrough Prize
- Blockbuster medicine, commercialized through Biogen, positioned for continued worldwide growth

Tegsedi™ (inotersen) injection 284 mg/1.5 mL

- Multi-country launch is underway through commercial affiliate, Akcea
- Preparing to expand into new jurisdictions, including Latin America, with partner PTC Therapeutics
- Positioned to add growth in commercial revenue

waylivra™ (volanesorsen sodium) Injection 300mg in 1.5mL

- First-in-class therapy for the treatment of people with FCS
- Potential to transform the treatment of this severe, rare disease with no therapeutic options

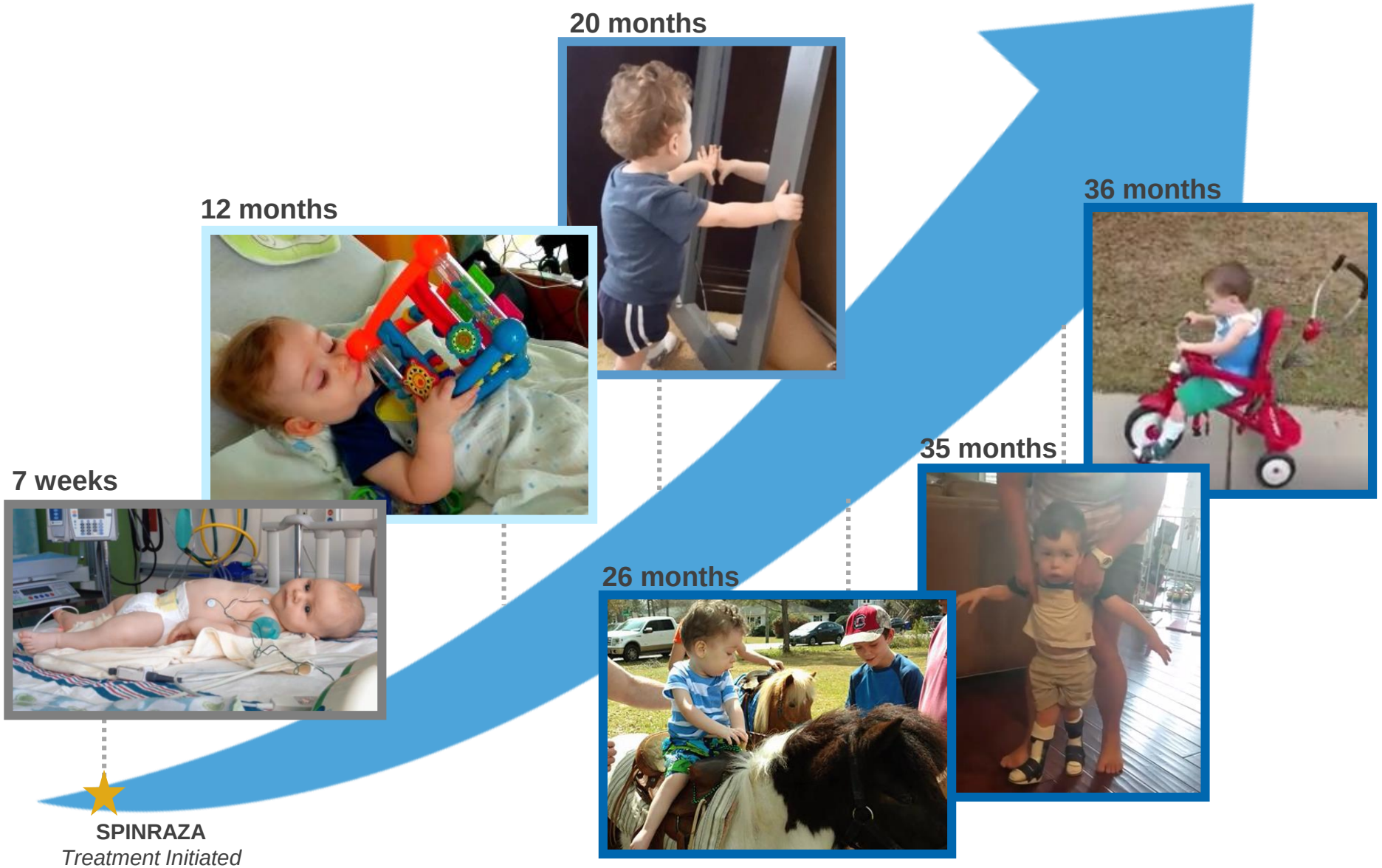
SPINRAZA® (nusinersen) injection 12 mg/5 mL

SPINRAZA: Creating a New Future for Patients with SMA and Their Families

SMA BEFORE SPINRAZA	SMA AFTER SPINRAZA The Standard-of-Care
Most common genetic cause of infant death	Babies achieving normal milestones with pre-symptomatic treatment
Progressive degeneration and dependence	Patients gaining strength and improved quality of life
Delayed diagnosis	Newborn screening beginning to provide earlier diagnosis and treatment

SPINRAZA® (nusinersen) injection 12 mg/5 mL

Cameron's Story: A Child's Journey



SPINRAZA® (nusinersen) injection 12 mg/5 mL

Pre-Symptomatic Treatment Enables Infants with SMA to Develop Like Their Healthy Counterparts

Motor milestone	Expected age of attainment in healthy infant[1]	Attainment at last visit among those the expected age of attainment or older[a,b]	
		3 *SMN2* copies	2 *SMN2* copies
 Full head control	5 mo	10/10 (100%) infants	15/15 (100%) infants
 Independent sitting[c]	7 mo	10/10 (100%) infants	14/15 (93%) infants
 Stands with support	8 mo	10/10 (100%) infants	13/15 (87%) infants
 Walking with support (cruising)	11 mo	10/10 (100%) infants	12/15 (80%) infants
 Standing unaided	12 mo	9/10 (90%) infants	7/15 (47%) infants
 Independent walking	15 mo	9/9 (100%) infants	7/13 (54%) infants

HINE motor milestone achievement in NURTURE infants through day 778 HINE = Hammersmith Infant Neurological Examination Hammersmith; NURTURE study interim analysis data cutoff date: May 15, 2018; [a]HINE Section 2 was assessed in NURTURE participants up until the Day 778 study visit; [b]Age and maximal milestone attainment at last study visit before data cutoff. In some infants, the motor milestone was achieved and then not documented at the last visit ; [c]HINE independent sitting is defined as a stable sit or pivots/rotates.

Swaboda, K. (2018, October 6). Nusinersen in Infants Who Initiate Treatment in a Presymptomatic Stage of Spinal Muscular Atrophy (SMA): Interim Efficacy and Safety Results From the Phase 2 NURTURE Study, Mendoza, Argentina.

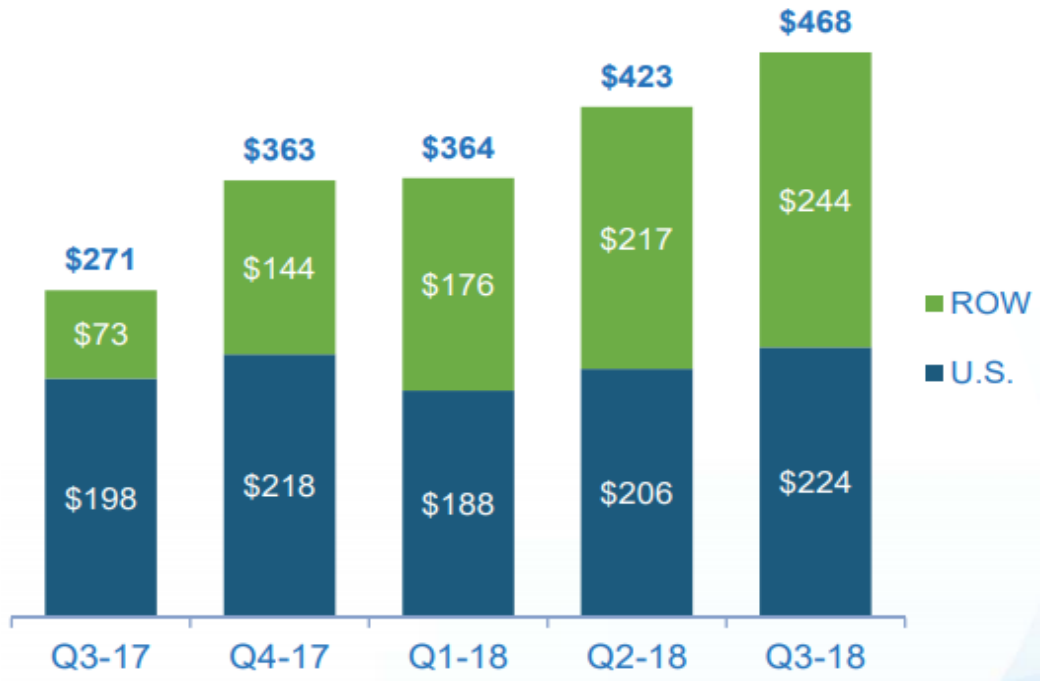
nurture

SPINRAZA® (nusinersen) injection 12 mg/5 mL

Global SPINRAZA Sales Exceed $2 Billion to Date

SPINRAZA Revenues ($M)[1]

Total Royalties to Ionis of **$280 MILLION**



Opportunity for Continued Growth

Continued growth in the U.S. from:

- Continued uptake by adult patients, the largest segment of the prevalent SMA patient population
- Well penetrated in infant patient population with continuing growth with pediatric patients

Continued growth from outside the U.S. from:

- Recent approvals in multiple countries, including 5 approvals in Q3 2018
- Additional approvals and regulatory filings
  - Regulatory reviews underway
  - Multiple additional filings expected by YE 2018

1: Numbers may not foot due to rounding

Source: Biogen Q3 2018 Financial Results and Business Update.

SPINRAZA® (nusinersen) injection 12 mg/5 mL

Treatment with SPINRAZA has Fundamentally Changed the Lives of Patients with SMA and Their Families

SPINRAZA is the standard-of-care for the treatment of all patients with SMA

Pre-symptomatic treatment of infants with SMA is enabling development similar to healthy infants

SPINRAZA is a blockbuster, with more than $2 billion in global sales to date

Nearly $700 million in payments for SPINRAZA to date, including over $280 million in royalties

TEGSEDI: A Transformational Medicine for the Treatment of Polyneuropathy of hATTR Amyloidosis

A Transformational Medicine for the Treatment of Polyneuropathy of hATTR Amyloidosis

Key Takeaways

TEGSEDI is approved around the globe to treat all patients suffering from polyneuropathy of hATTR

The multi-country launch is underway through our commercial affiliate Akcea

TEGSEDI is positioned to add growth in commercial revenue for Ionis and Akcea

Expanding TTR franchise, with AKCEA-TTR-L_{Rx} now in development

Polyneuropathy of hATTR: A Devastating and Fatal Disease

Chuck, Living with hATTR

hATTR is a disease marked by the formation of TTR amyloid deposits leading to multi-organ failure

hATTR patients suffer from progressive neuropathy, cardiac disease, nephropathy and GI symptoms

hATTR is a progressive disease resulting in a rapid decline in quality of life

hATTR patients have a 3 – 15 year life expectancy from disease onset

Improving Diagnostic Rates for Polyneuropathy of hATTR Amyloidosis Represents Opportunity for Revenue Growth

- ~30,000 hATTR patients with symptoms of polyneuropathy worldwide
- ~3,000 patients in the U.S. diagnosed with hATTR with polyneuropathy
- Potential for additional 12,000 patients to be diagnosed in the U.S.
- Currently underdiagnosed, but rates of and time to diagnosis are improving

Now Approved in the U.S., EU and Canada for Adults with Polyneuropathy in hATTR Amyloidosis

- Once-weekly, self-administered subcutaneous dosing enables greater patient independence
- Straight-forward and manageable safety monitoring
- Comprehensive patient support services through Akcea CONNECT ensures patient compliance

Tegsedi™ (inotersen) injection 284 mg/1.5 mL

For safety information about serious side effects, including thrombocytopenia and glomerulonephritis, please see full prescribing information at www.TEGSEDI.com

Treatment with TEGSEDI Significantly Improved Quality of Life and Measures of Neuropathy in the Pivotal Study

Regained ability for simple tasks (e.g. climbing stairs, lifting groceries)

Improved self-care

Re-engaged in social interactions

Increased ability to work and support family

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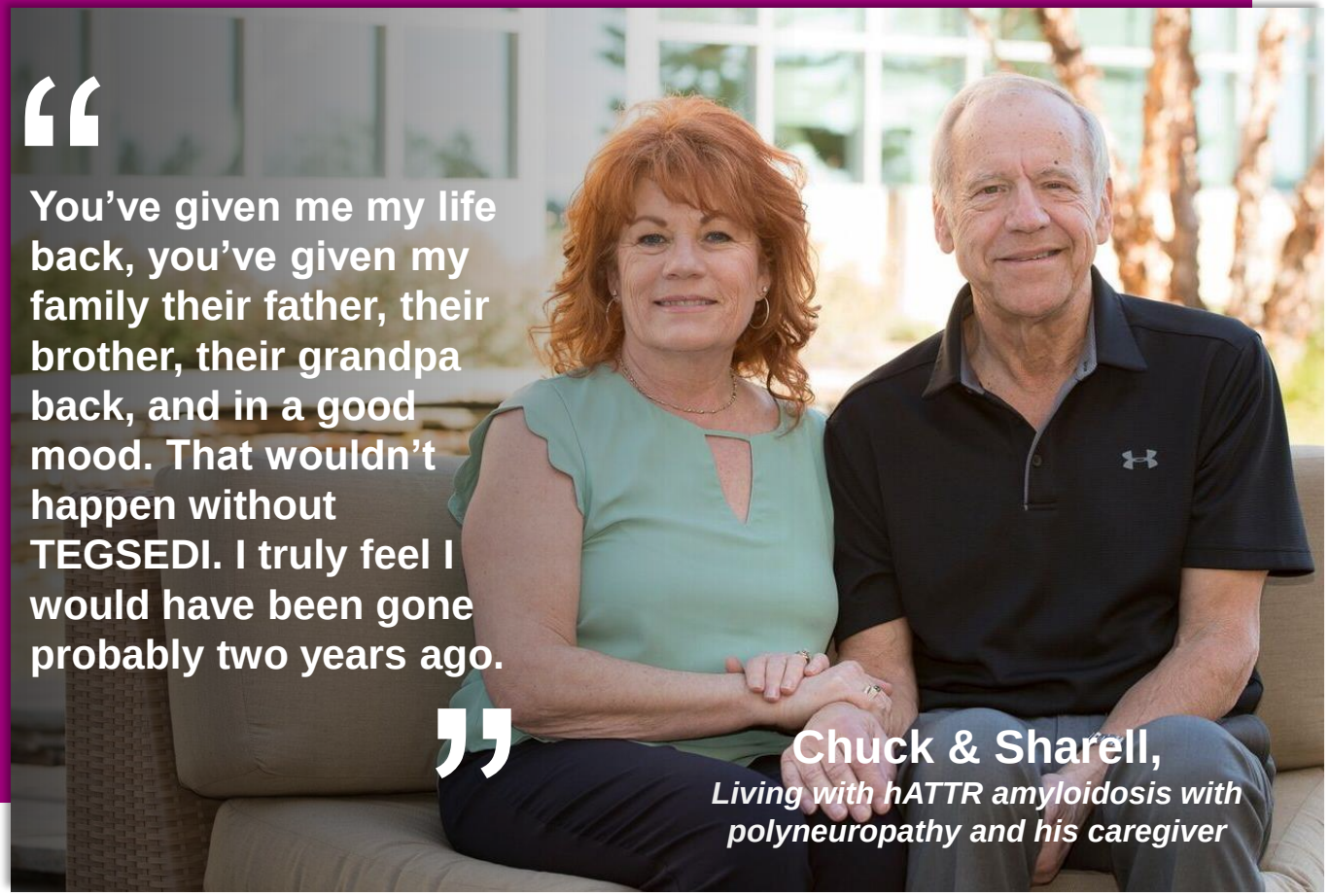
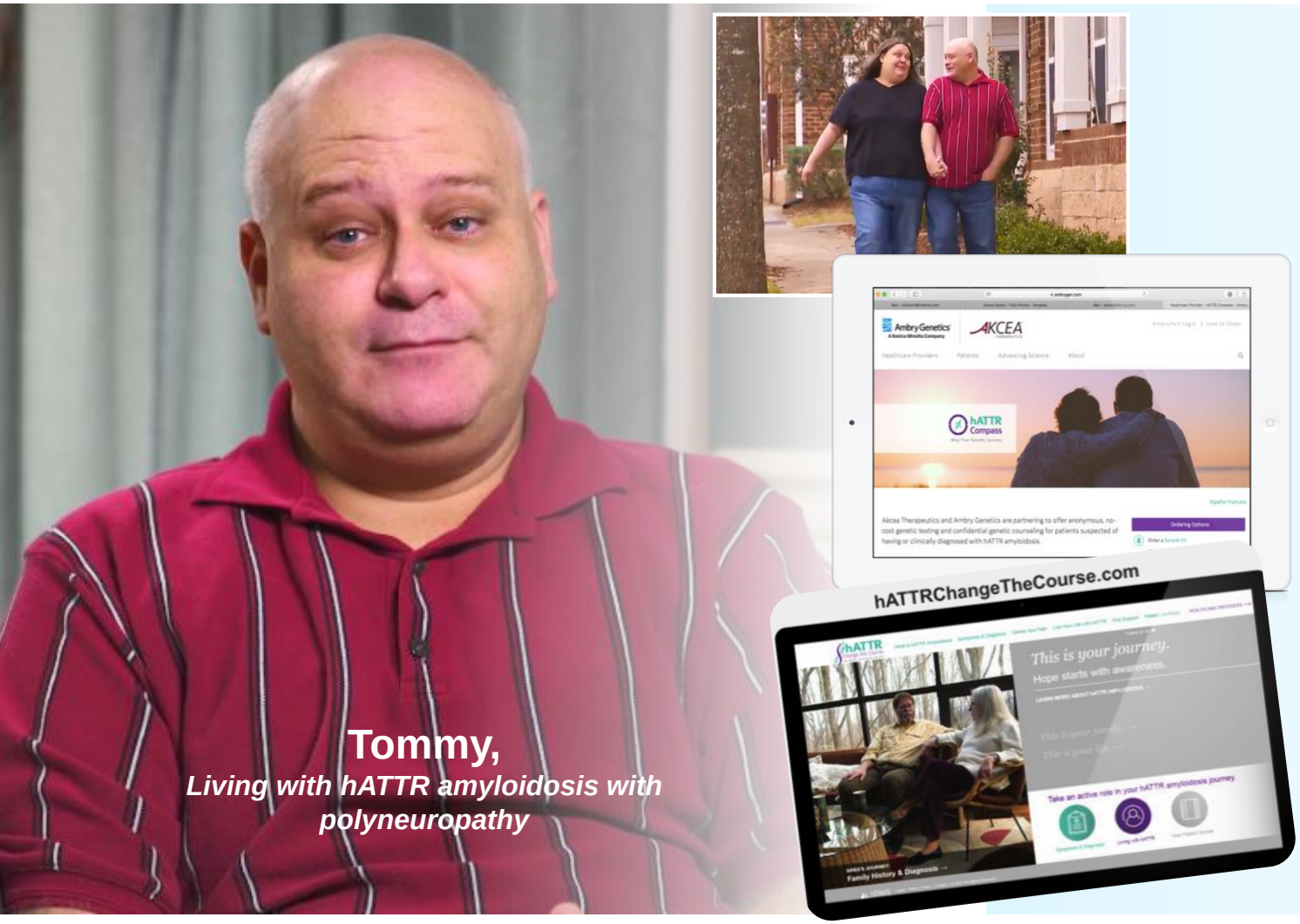
TEGSEDI's Impact on the Lives of Patients and Their Families



Akcea Executing on TEGSEDI Multi-Country Launch



- ✓ Global commercial team and infrastructure in place and deployed
- ✓ Launched high-touch patient support program, AKCEA CONNECT nurse case managers fully staffed
- ✓ Global market access teams executing country by country
- ✓ Presence in nine countries across the U.S., EU and Canada

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Patient Support Program Providing Personalized Support

A multi-disciplinary team to provide tailored patient support

REIMBURSEMENT NAVIGATION

Assess patients' insurance coverage options and determine availability of patient assistance programs that may be helpful

DISEASE EDUCATION

Provide tools and information to help patients learn about their disease and build confidence to manage it daily

INJECTION TRAINING

Reinforce the proper injection technique so patients feel confident injecting on their own

PHARMACY SERVICES

Coordinating shipment to patients through specialty pharmacy

ADHERENCE OPTIMIZATION

High-touch targeted education and monitoring to optimize treatment adherence

For safety information about serious side effects, including thrombocytopenia and glomerulonephritis, please see full prescribing information at www.TEGSEDI.com

TEGSEDI is a Transformational Medicine for the Treatment of Patients with Polyneuropathy of hATTR

TEGSEDI is positioned to add growth in commercial revenue

The multi-country launch is underway through Akcea with patients now on commercial medicine

Partner in Latin America, PTC, is preparing to file for regulatory approval in Latin America, beginning with Brazil

Expanding TTR franchise, with AKCEA-TTR-L_{Rx} now in development

WAYLIVRA: A Potential Breakthrough for the Treatment of Patients with FCS

waylivra™
(volanesorsen sodium)
Injection 300mg in 1.5mL

A Potentially Transformative Medicine for Patients with FCS, a Devastating Disease with No Treatment Options

First medicine to demonstrate significant triglyceride (TG) reductions

Improvements in acute pancreatitis and abdominal pain

Akcea's commercial infrastructure is in place in the EU

Potential opportunity in Latin America with PTC Therapeutics

AKCEA™ THERAPEUTICS

waylivra™
(volanesorsen sodium)
Injection 300mg in 1.5mL

FCS: A Severe, Rare, Potentially Fatal Disease with No Treatment Options

A severe, rare genetic disease affecting ~3000-5000 patients worldwide

Characterized by extremely high levels of triglycerides not improved with lipid-lowering therapies

Patients suffer from symptoms such as potentially fatal, acute pancreatitis and chronic abdominal pain

Quality of life and ability to work severely impacted by chronic symptoms such as pain, fatigue, memory loss, GI issues and numbness and tingling in legs or feet

Alvin, Living with FCS

AKCEA™ THERAPEUTICS

waylivra™ (volanesorsen sodium) Injection 300mg in 1.5mL

A Potentially Transformative Medicine for Patients with FCS, a Devastating Disease with No Treatment Options

Next Steps

- Complete regulatory review in the EU
- Confirm regulatory path forward with FDA
- Continue conducting open-label extension study and early access program
- Complete BROADEN study in FPL in 2019

AKCEA THERAPEUTICS™

Ionis: Fundamentally Improving the Lives of Patients in Need and Delivering Value to Patients and Shareholders

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The Next Wave of Commercial Opportunities

Near- and Mid-term Drivers of Value

Brett Monia, Ph.D.
Chief Operating Officer

Key Takeaways

- More than 10 exciting medicines with the potential to enter pivotal programs in the next 2 years
- Four or more new medicines likely to enter pivotal, Phase 3 programs in 2019
- New Phase 3 studies incorporate different routes of delivery and advanced chemistries, all pioneered by Ionis
- Ionis' antisense medicines address rare and common diseases with great unmet medical needs

More Than 10 Exciting Medicines with the Potential to Enter Pivotal Programs in the Next 2 Years

Four or More Medicines Potentially Entering Pivotal Programs in 2019

MEDICINE	INDICATION	PARTNER
AKCEA-APO(a)-L_{Rx}	Cardiovascular disease	Akcea / Novartis
AKCEA-TTR-L_{Rx}	Transthyretin amyloidosis	Akcea / Ionis
IONIS-HTT_{Rx} (RG6042)	Huntington's disease	Roche
IONIS-$SOD1_{Rx}$ (BIIB067)	Amyotrophic lateral sclerosis	Biogen
IONIS-HBV_{Rx}/IONIS-HBV-L_{Rx}	Hepatitis B virus infection	GSK
Danvatirsen (IONIS-STAT3-2.5_{Rx})	Cancer	AstraZeneca
AKCEA-APOCIII-L_{Rx}	Cardiovascular disease	Akcea / Novartis
IONIS-$MAPT_{Rx}$ (BIIB080)	Alzheimer's disease/ Frontotemporal dementia	Biogen
IONIS-FXI_{Rx}/IONIS-FXI-L_{Rx}	Clotting disorders	Bayer
AKCEA-ANGPTL3-L_{Rx}	Rare Hyperlipidemias	Akcea / Ionis
IONIS-GHR-L_{Rx}	Acromegaly	Ionis
IONIS-TMPRSS6-L_{Rx}	β-Thalassemia	Ionis

Near- and Mid-term Value Drivers: Next Wave of Commercial Opportunities to Treat Large, Medium and Small Patient Populations

AKCEA-APO(a)-L_{Rx} – 8 - 10 million patients with cardiovascular diseases and high Lp(a)
- In collaboration with Akcea, our commercial affiliate
- Novartis will develop and commercialize upon licensing

AKCEA-TTR-L_{Rx} – Hundreds of thousands of patients with transthyretin amyloidosis (ATTR)
- In collaboration with Akcea, our commercial affiliate

IONIS-HTT_{Rx} (RG6042) – Hundreds of thousands of patients with Huntington's disease (HD)
- In partnership with Roche, an expert in developing novel medicines for neurodegenerative diseases

IONIS-$SOD1_{Rx}$ (BIIB067) – More than 1,000 ALS diagnosed patients with SOD1 mutations
- In partnership with Biogen, an expert in neurodegenerative diseases

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Lipoprotein(a):
A Major Risk Factor for Cardiovascular Disease

Lp(a) level genetically determined at birth

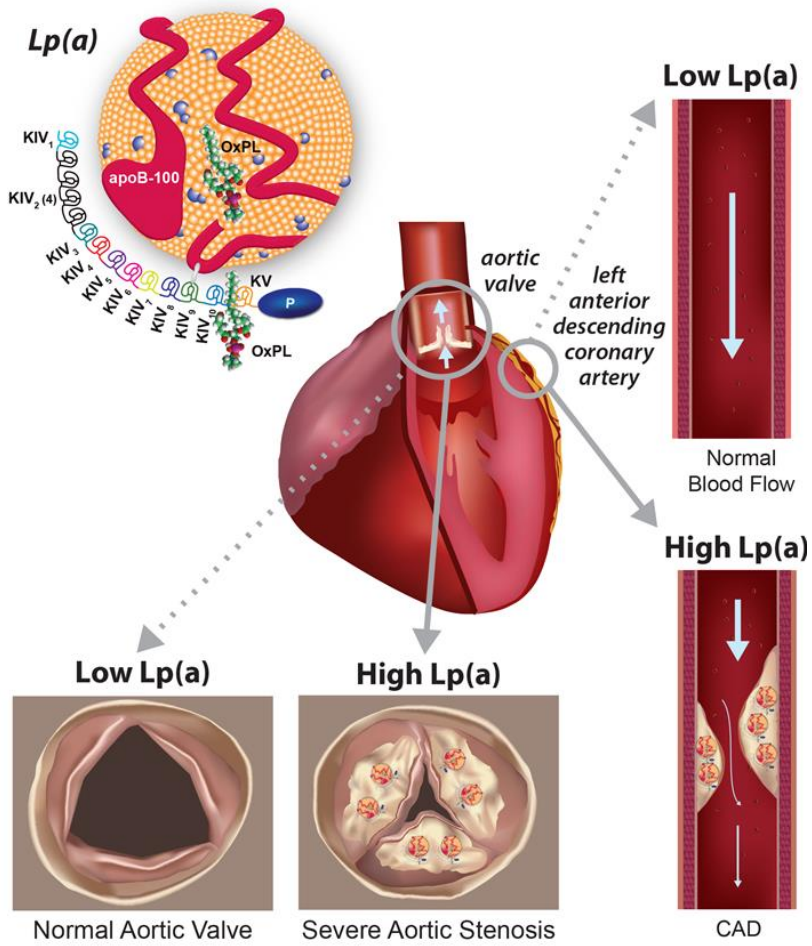
Recognized by the medical community as the major untreated cardiovascular risk factor

No approved pharmacological therapies – statins ineffective

~8-10 million people worldwide have Lp(a) > 50mg/dL, the recognized risk factor level of Lp(a)

Lp(a) causes cardiovascular disease through multiple mechanisms

- Atherogenicity through LDL moiety
- Anti-fibrinolytic activity
- Pro-inflammatory effects of oxidized phospholipids



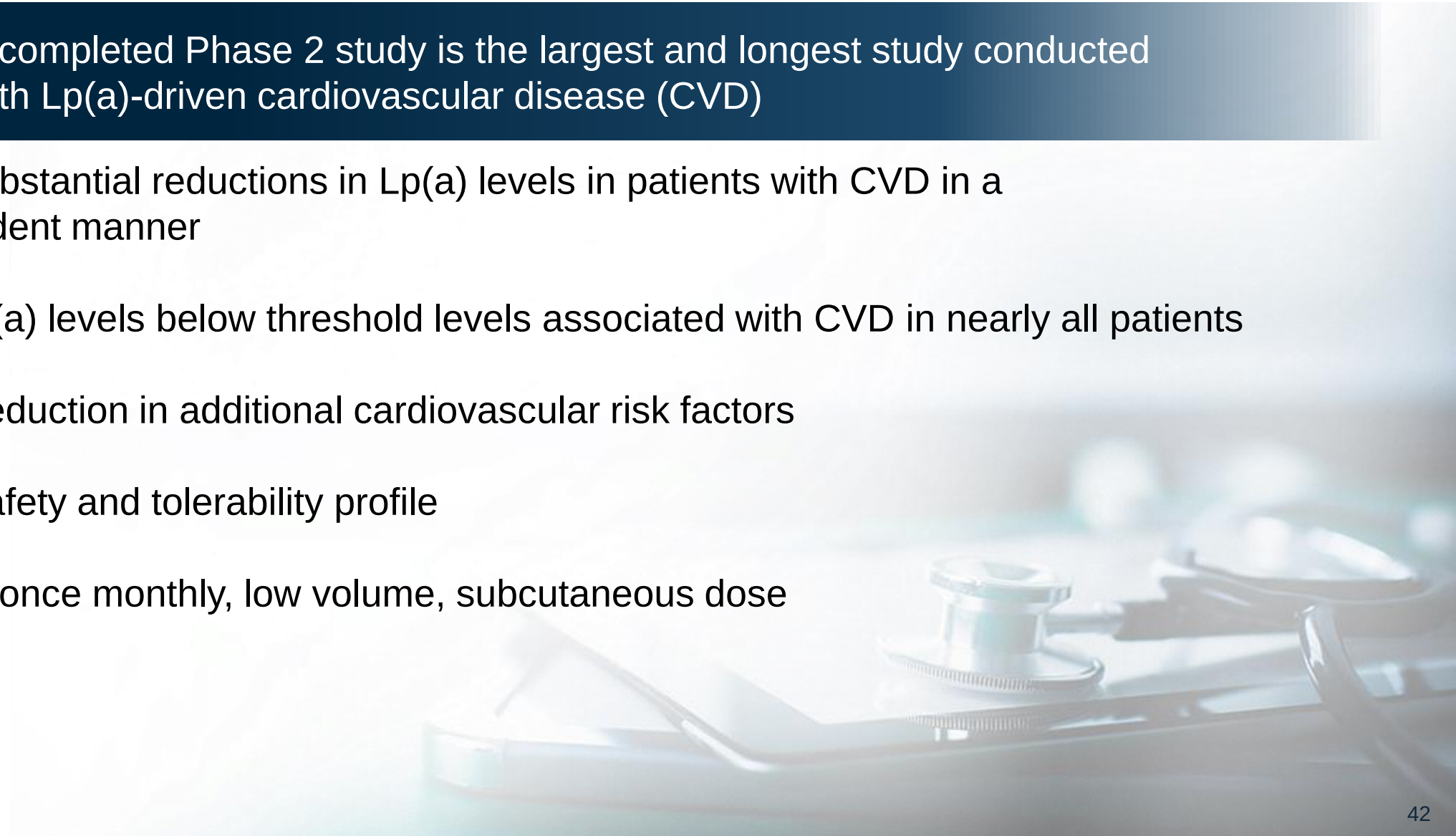
Only Ionis' antisense technology has demonstrated the ability to selectively and robustly reduce Lp(a) levels in a clinical study

Illustration concept by Sotiros Tsimikas, adaptation by Tracy Reigle

AKCEA-APO(a)-L_{Rx}: The First and Only Medicine to Selectively and Robustly Reduce Lp(a) Levels

The recently completed Phase 2 study is the largest and longest study conducted in patients with Lp(a)-driven cardiovascular disease (CVD)

- Produced substantial reductions in Lp(a) levels in patients with CVD in a dose-dependent manner
- Reduced Lp(a) levels below threshold levels associated with CVD in nearly all patients
- Significant reduction in additional cardiovascular risk factors
- Favorable safety and tolerability profile
- Convenient, once monthly, low volume, subcutaneous dose



AKCEA-APO(a)-L_{Rx} Phase 2 Study in Patients with Elevated Lp(a) and Established Cardiovascular Disease (CVD)

Multicenter, randomized, double-blind, placebo-controlled, dose-ranging study in 286 patients with pre-existing cardiovascular disease (coronary artery disease, myocardial infarction, peripheral artery disease, stroke) and baseline Lp(a) ≥ 60 mg/dL (60mg/dl - 250 mg/dl)

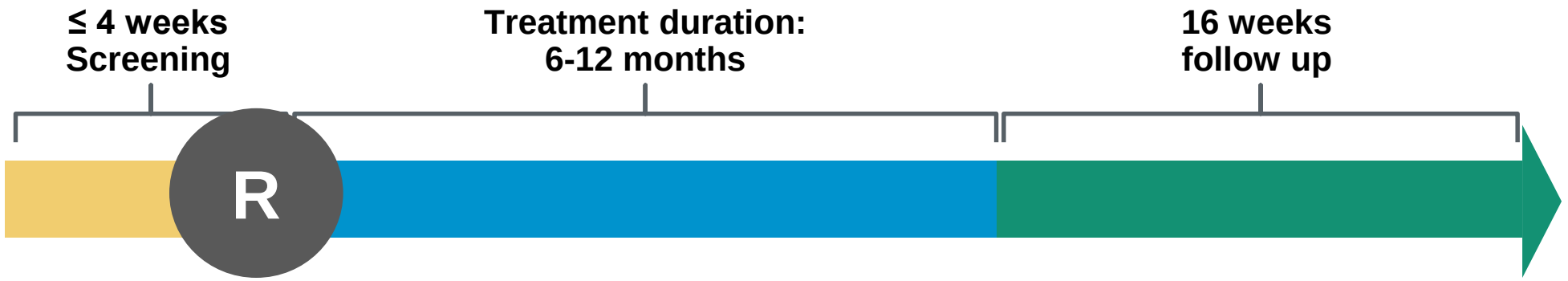
Primary Objectives

- Assess safety and tolerability
- Assess Lp(a) reductions at different doses and dosing regimens to inform potential Phase 3 pivotal study

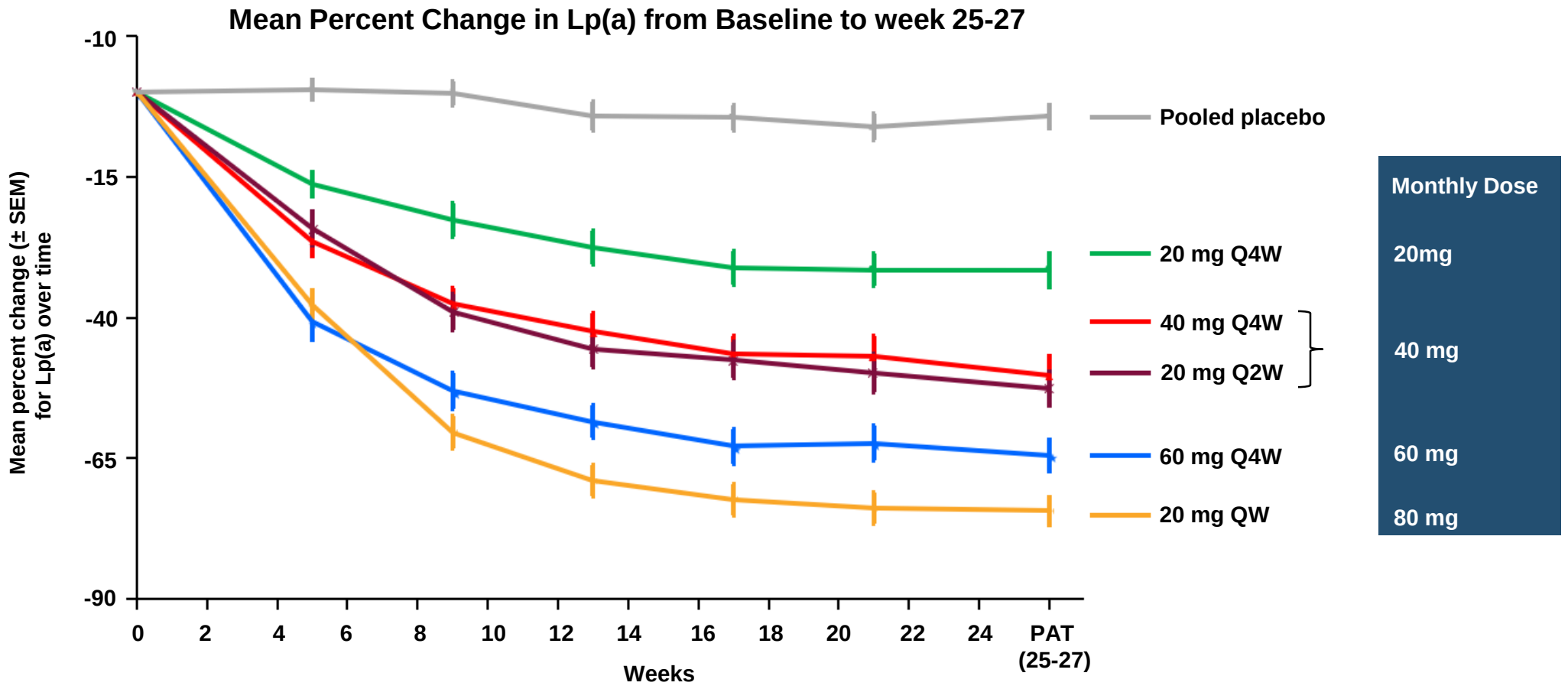
Secondary Objectives

- Evaluate efficacy on additional CVD risk factors: LDL-C, ApoB and Oxidized Phospholipids (OxPL)

Cohort	Frequency
20 mg	Weekly
20 mg	Bi-weekly
20 mg	Monthly
40 mg	Monthly
60 mg	Monthly



AKCEA-APO(a)-L_{Rx} Phase 2 Study: Significant Dose-dependent Reductions in Lp(a) Achieved at All Doses and Dose Frequencies

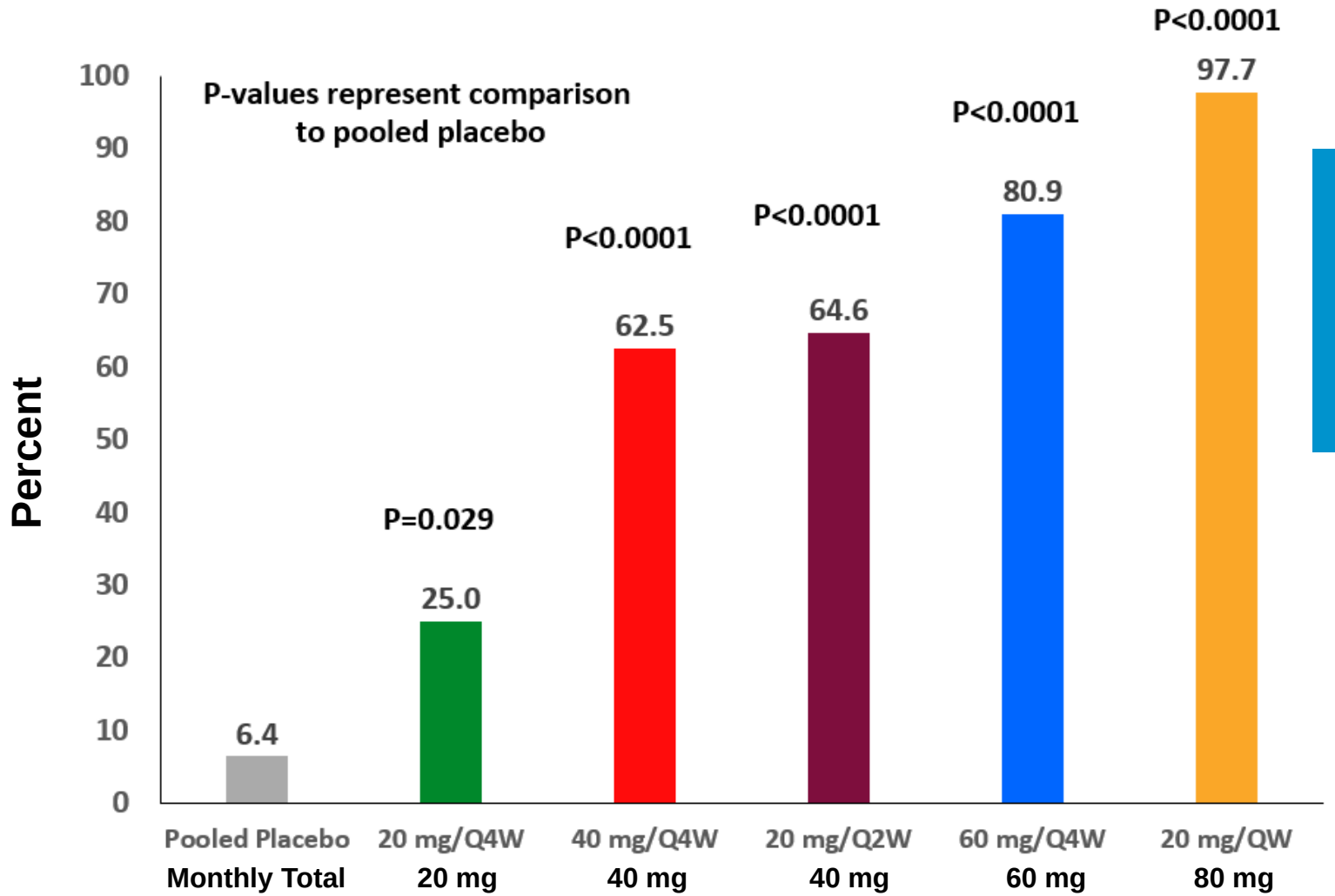


Efficacy not affected by baseline Lp(a) levels nor use of statins or PCSK9 inhibitors

PAT, primary analysis timepoint; QW, once a week; Q2W, every 2 weeks; Q4W, every 4 weeks; Error bars = standard error of the mean

AKCEA-APO(a)-L_{Rx} Phase 2 Study: ~98% of Patients in the High Dose Group Achieved Lp(a) Levels Below 50 mg/dL

Percent of patients achieving Lp(a) ≤50 mg/dL (≤125 nmol/L)



≤50 mg/dL is considered below the threshold for risk of CVD events

QW, once a week; Q2W, every 2 weeks; Q4W, every 4 weeks

AKCEA-APO(a)-L_{Rx} Treatment Led to Significant Reductions in Additional Cardiovascular Risk Factors

Treatment	OxPL-apoB	OxPL-apo(a)	ApoB	LDL-C
AKCEA-APO(a)-L_{Rx}				
20 mg Q4W	-26.8**	-24.8	-1.9	-5.2
40 mg Q4W	-42.4***	-37.5*	-12.8***	-20.4***
20 mg Q2W	-52.8***	-38.6*	-7.6*	-11.1*
60 mg Q4W	-65.5***	-53.5***	-4.0*	-6.9*
20 mg QW	-81.8***	-61.2***	-14.5***	-20.5**
Pooled placebo	22.4	-17.6	2.0	1.2

Reductions in additional cardiovascular risk factors in patients

*P-value vs pooled placebo: * p<0.05; ** p<0.01; *** p<0.001*
%change is at primary analysis timepoint. LDL-C, low-density lipoprotein cholesterol; QW, once a week; Q2W, every 2 weeks; Q4W, every 4 weeks

AKCEA-APO(a)-L_{Rx} Phase 2 Positive Safety Summary

Favorable safety and tolerability profile

Most adverse events were mild

No safety concerns related to platelet counts, liver function or renal function

- No patient in the study experienced a confirmed platelet count below 100,000/mm^3
- The incidence of platelet levels below normal (140,000/mm^3) was comparable between the active (10.5%) and placebo (14.9%) groups

Excellent patient compliance

- Comparable discontinuation between the active (12.1%) and placebo (14.9%) groups
- Approximately 90% of patients completed treatment

AKCEA-APO(a)-L_{Rx}

Next Steps

1. **End-of-Phase 2 meeting with FDA in Q4 2018**
2. **Goal of initiating Phase 3 program by year-end 2019**
3. **Novartis opt-in anticipated in Q1 2019**
   - **$150 million license fee with royalties up to the low 20% range**

Near- and Mid-term Value Drivers: Next Wave of Commercial Opportunities to Treat Large, Medium and Small Patient Populations

AKCEA-APO(a)-L_{Rx} – 8 - 10 million patients with cardiovascular diseases and high Lp(a)
- In collaboration with Akcea, our commercial affiliate
- Novartis will develop and commercialize upon licensing

AKCEA-TTR-L_{Rx} – Hundreds of thousands of patients with transthyretin amyloidosis (ATTR)
- In collaboration with Akcea, our commercial affiliate

IONIS-HTT_{Rx} (RG6042) – Hundreds of thousands of patients with Huntington's disease (HD)
- In partnership with Roche, an expert in developing novel medicines for neurodegenerative diseases

IONIS-$SOD1_{Rx}$ (BIIB067) – More than 1,000 ALS diagnosed patients with SOD1 mutations
- In partnership with Biogen, an expert in neurodegenerative diseases

AKCEA-TTR-L_{Rx}: Expanding the ATTR Franchise

Utilizes our most advanced LICA chemistry, providing high potency with greatly improved convenience and tolerability

In partnership with Akcea, a rapid and comprehensive development strategy is underway to treat all forms of TTR amyloidosis (ATTR)

Streamlined clinical pathway through Phase 3 for hereditary TTR polyneuropathy

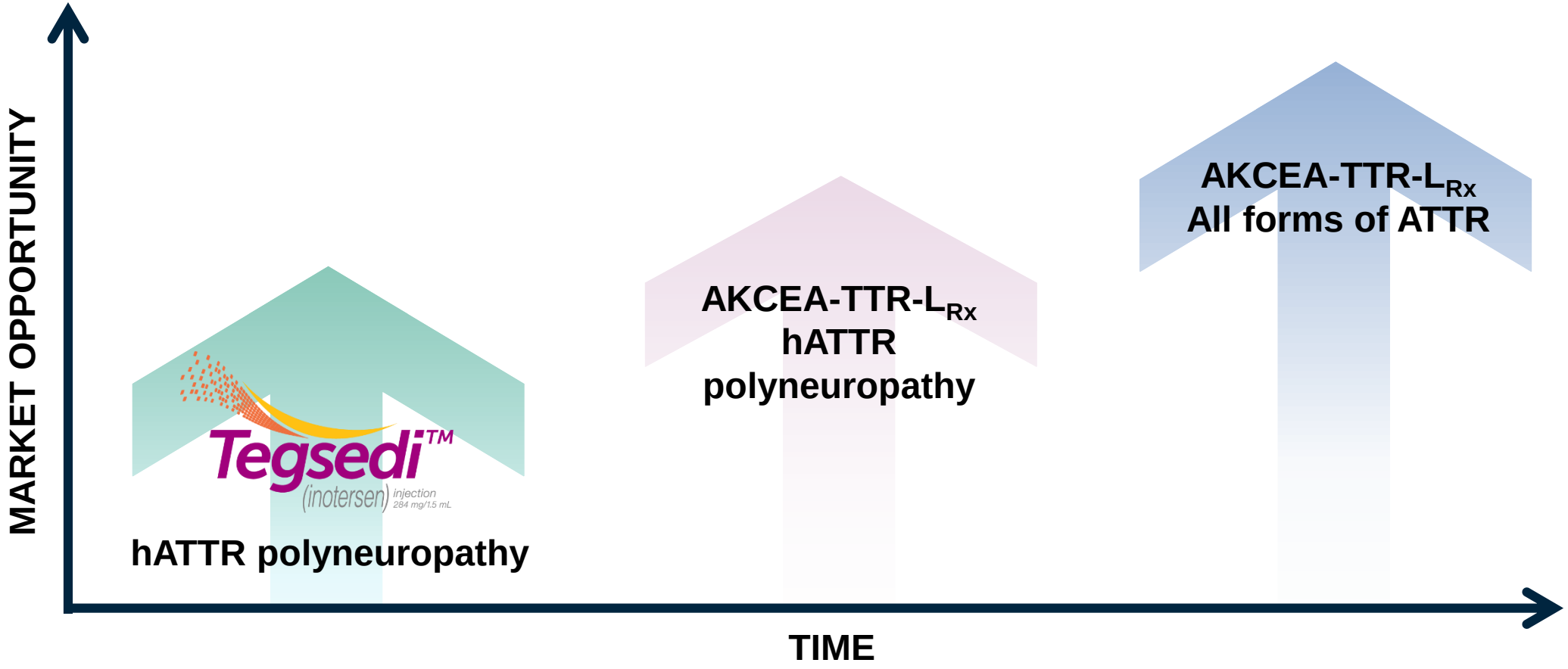
- Pivotal study planned to initiate in 2019

Comprehensive clinical study for all forms of ATTR being finalized

- Polyneuropathy and all forms of cardiomyopathy including wild type
- Pivotal study planned to initiate in 2019

AKCEA-TTR-L_{Rx}: Expanding the Ionis TTR Franchise Through Advances in Antisense Technology

- Tegsedi is our immediate commercial opportunity for hATTR polyneuropathy
- AKCEA-TTR-L_{Rx} is a product of our next-generation LICA technology
- Opportunity to treat all forms of ATTR



AKCEA-TTR-L_{Rx}: Initiating Pivotal Study in 2019

Next Steps

1. Complete Phase 1/2 study in healthy volunteers and patients with hATTR amyloidosis by mid 2019
2. Initiate rapid pivotal study in hATTR polyneuropathy in 2019
3. Initiate pivotal study in ATTR cardiomyopathy in 2019

Near- and Mid-term Value Drivers: Next Wave of Commercial Opportunities to Treat Large, Medium and Small Patient Populations

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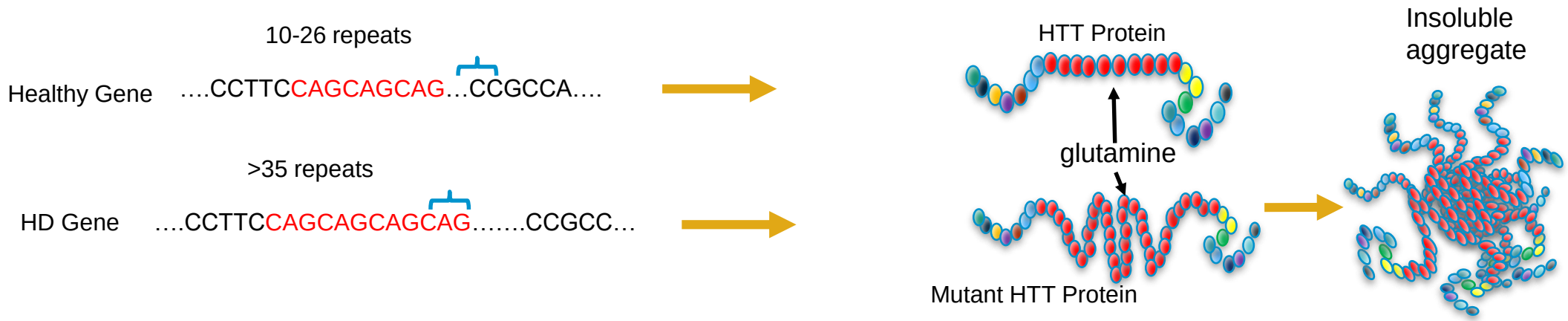
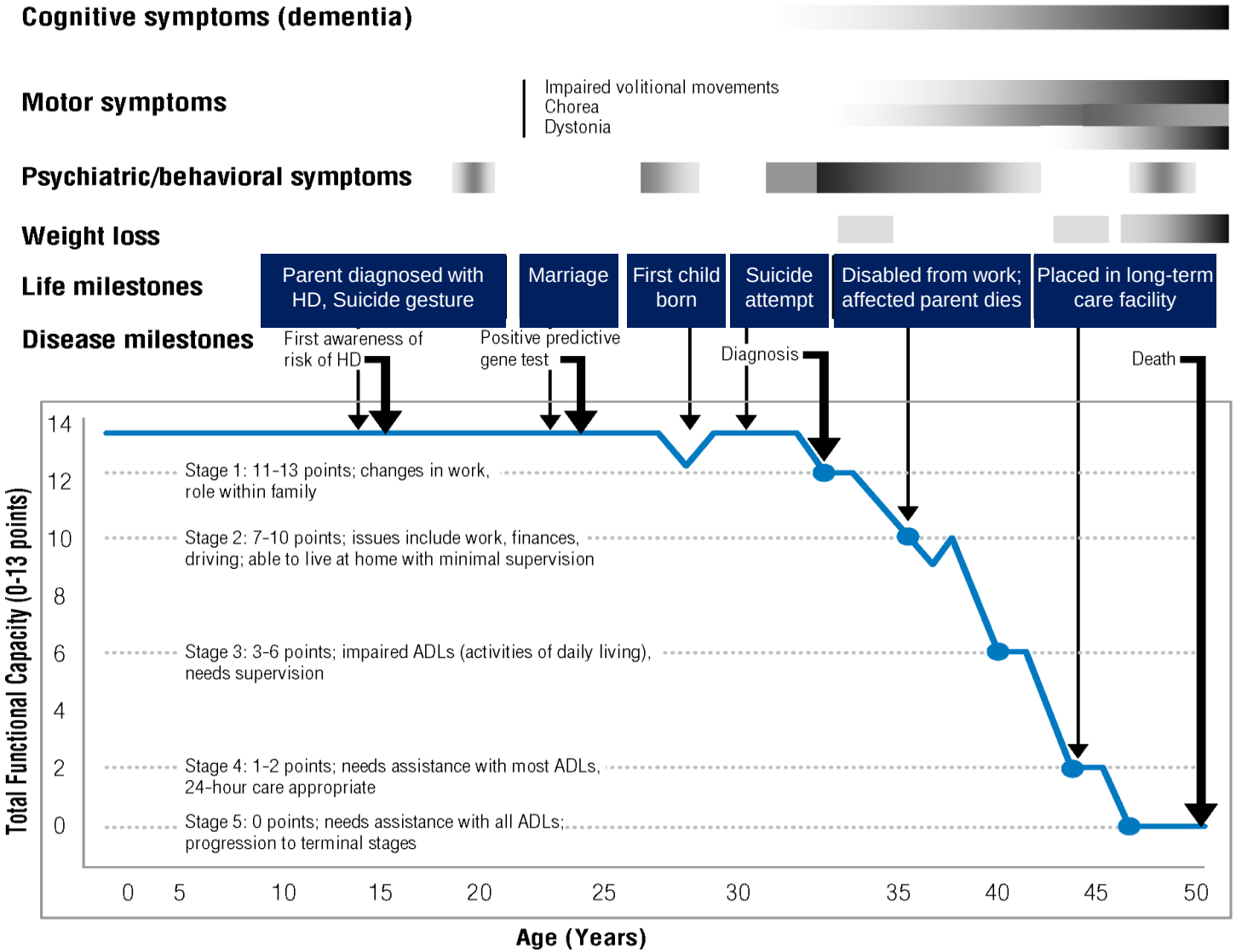
Huntington's Disease (HD): A Rare, Genetic, Fatal Neurodegenerative Disease



Hereditary	Caused by a toxic gain-of-function triplet repeat (CAG) expansion in the huntingtin gene, essentially 100% of individuals who inherit mutation will develop the disease
Devastating	Progressive loss of mental faculties and physical control. Families endure the catastrophic impact of the disease over generations
Fatal	No effective treatments or cure; symptom onset occurs between ages of 30 – 50, characterized by progressive brain and muscle tissue atrophy, leading to death 15-20 years post symptom onset
Widespread	Approximately 3-10 per 100,000 people worldwide; ~30,000 symptomatic patients in the U.S.

Huntington's is a Devasting Disease

The Disease Journey for Afflicted Families



Rosenblatt A, et al. A Physician's Guide to the Management of Huntington's Disease. 2015: 1-136.

IONIS-HTT$_{Rx}$ (RG6042): A Breakthrough Medicine to Treat Huntington's Disease

IONIS-HTT$_{Rx}$ (RG6042)

- An optimized Generation 2.0+ antisense medicine delivered intrathecally that targets mutant and wild type Huntingtin protein (HTT)
- Demonstrated robust and dose-dependent reductions in all relevant cell types in the central nervous system (CNS) in rodents and non-human primate models
- Demonstrated halting, reversal and prevention of disease progression in HTT models
- Shown to be safe in chronic rodent and non-human primate safety studies

HTT can be detected in cerebrospinal fluid (CSF) and reductions in CNS HTT can be correlated with HTT reductions in CSF

Completed a 3-month Phase 1/2 study in early stage symptomatic patients with Huntington's disease

IONIS-HTT$_{Rx}$ (RG6042): Phase 1/2 Study Design

A randomized, double-blind, placebo-controlled, multiple ascending dose study in 46 adult patients with early stage Huntington's disease treated for 3 months

Primary Objectives

- Assess the safety and tolerability of ascending doses of multiple intrathecal administrations of IONIS-HTT$_{Rx}$

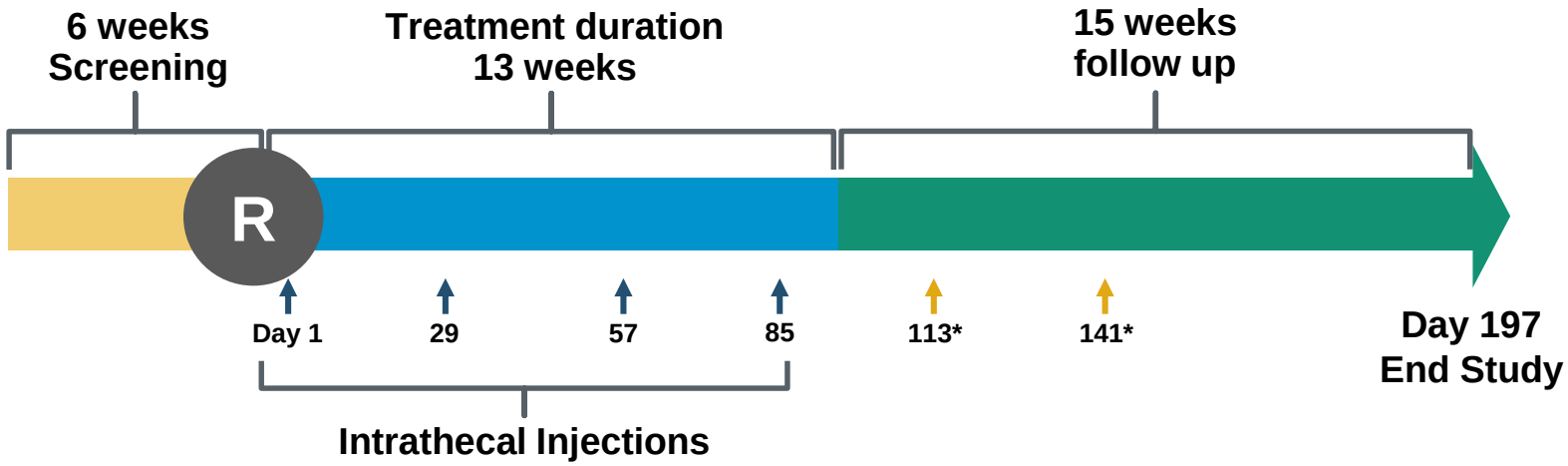
Secondary Objectives

- Assess HTT protein reduction in CSF

Exploratory

- Assess clinical measures for improvement

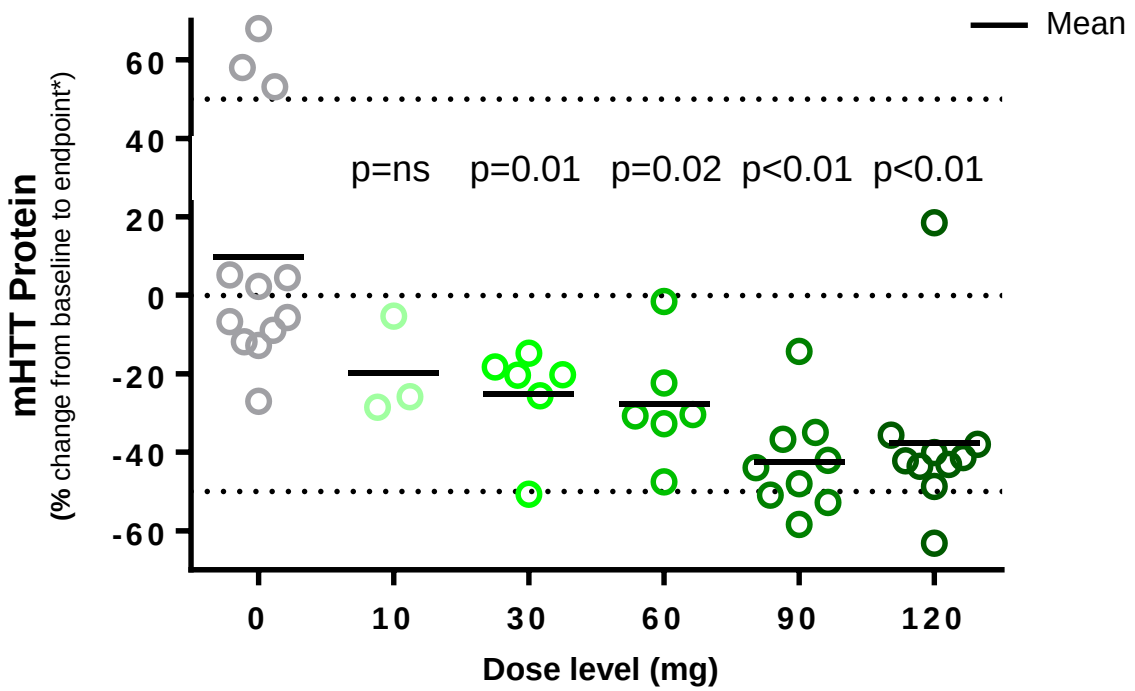
Cohorts	IONIS-HTT$_{Rx}$ (n)	PBO (n)
10 mg	3	1
30 mg	6	2
60 mg	6	2
90 mg	9	3
120 mg	10	4



*Half of patients received lumbar puncture at Day 113 and half at Day 141 to sample; ↑ = IT dose and CSF sample; ↑ = CSF sample

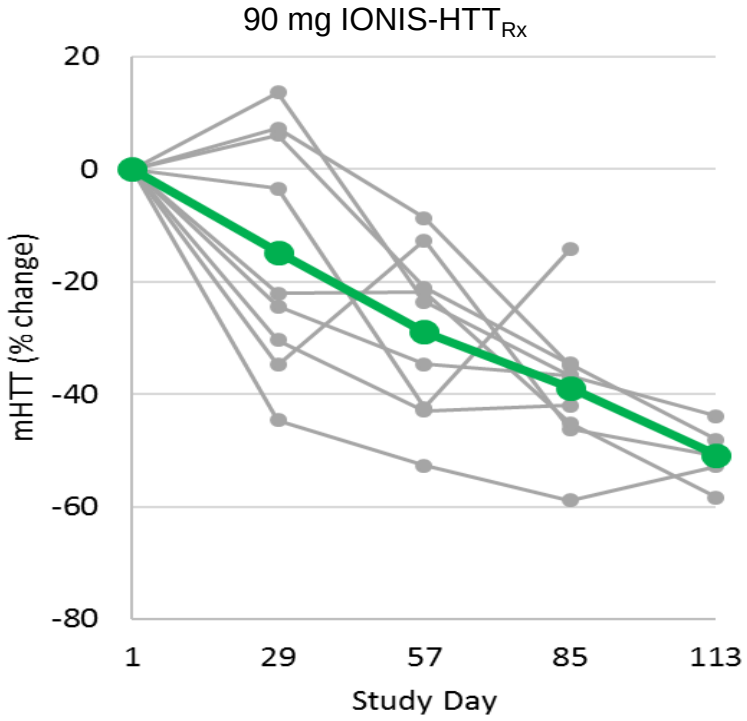
IONIS-HTT$_{Rx}$ Demonstrated Dose-dependent Reduction in HTT Protein in CSF with Maximum Reductions Occurring Beyond Three Months

mHTT protein (in CSF) percent change from baseline at study endpoint*



The magnitude of mHTT reduction in CSF exceeds the reductions that produced disease modification in animal models of HD

mHTT levels still declining at three months of treatment with IONIS-HTT$_{Rx}$



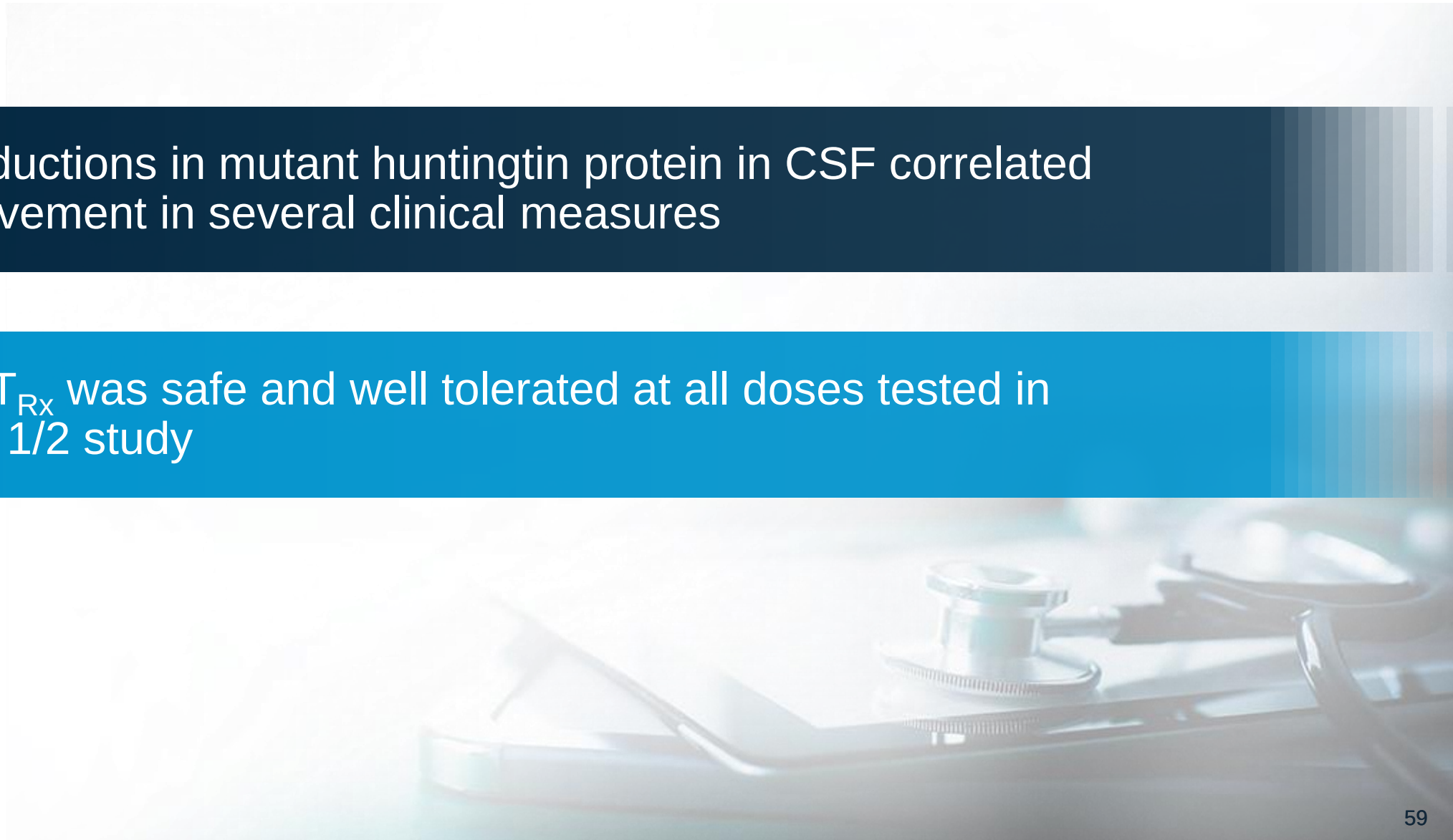
Further mHTT reductions likely with longer treatment

**Endpoint is defined as the later of Day 85 and 113*

IONIS-HTT$_{Rx}$ Positive Phase 1/2 Study

Robust reductions in mutant huntingtin protein in CSF correlated with improvement in several clinical measures

IONIS-HTT$_{Rx}$ was safe and well tolerated at all doses tested in the Phase 1/2 study



Roche is Investing Broadly in a Robust Pivotal Program for IONIS-HTT$_{Rx}$ (RG6042)

Open-label Extension (OLE) Study – Extend understanding of IONIS-HTT$_{Rx}$ (RG6042) over longer follow-up

- Evaluate the magnitude and durability of mHTT reduction with different dosing frequencies
- Provide data on clinical benefit; correlate with reduction in mHTT
- Long-term safety and tolerability

Huntington's Disease Natural History Study – Sites initiated in U.S., UK, Canada and Denmark

- 100 patients over 15 months
- Similar patient population as Phase 1/2 study
- Gather longitudinal data on biomarkers and clinical assessments on Phase 3 endpoints

Pivotal Study – Generation HD1

- Confirm the efficacy and safety in patients with manifest Huntington's
- First targeted therapeutic medicine tested in a large, controlled, randomized study
- Study to initiate in 2018

GENERATION HD1 – RG6042 Pivotal Phase III Study Design

Objective: Evaluate efficacy and safety of intrathecally-administered RG6042 in adult patients with HD

Study launch planned for end of 2018 with patients enrolling by early 2019

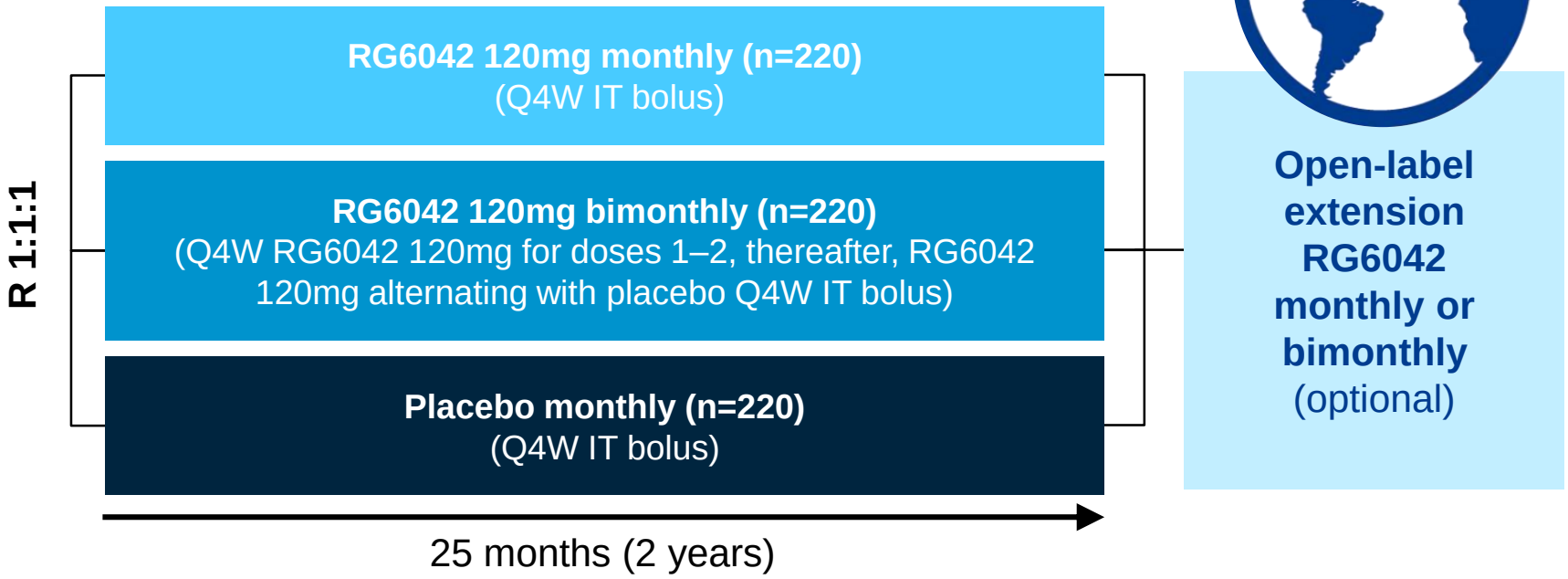
Countries: ~15 countries worldwide (80–90 sites)

Inclusion criteria for pivotal study are broader than OLE and HD NHS studies

KEY INCLUSION CRITERIA

- Clinically diagnosed manifest HD (DCL=4)
- Aged 25–65 years
- CAP >400
- Independence scale >70
- Ambulatory, verbal

n=660



Primary endpoints agreed to by regulatory agencies

CAP, CAG-age product; DCL, diagnostic confidence level; GENERATION HD1, Global EvaluatioN of Efficacy and Safety of Roche/Genentech AnTIsense OligoNucletide for Huntington's Disease; HD, Huntington's disease; IT, intrathecal; NHS, Natural History Study, OLE, open-label extension; Q4W, once-a-month.

IONIS-HTT$_{Rx}$ (RG6042) Phase 3 Primary Endpoints

cUHDRS (composite Unified Huntington Disease Rating Scale) will be the global primary endpoint

- Most sensitive means to track the progression of the disease
  - Motor
  - Cognition
  - Psychiatric
  - Daily function

TFC (Total Functional Capacity) will be the primary endpoint in the U.S.

- Measure of daily function
- A component of the cUHDRS

One global pivotal trial with a single global sample and single endpoint for each regulatory body

FDA requires the primary endpoint to measure daily functional abilities, so TFC will be primary endpoint in US only
CAP, CAG-age product; cUHDRS, composite UHDRS; EMA, European Medicines Association; FDA, Food and Drug Administration; HD, Huntington's disease; HTT, Huntingtin protein; TFC, Total Functional Capacity; UHDRS, Unified Huntington's Disease Rating Scale.
1. Ross CA et al. Nat Rev Neurol. 2014; 10:204–216.

IONIS-HTT$_{Rx}$ (RG6042) for Huntington's Disease

Summary

First potential disease-modifying therapy to be discovered and developed for Huntington's Disease

Roche is conducting a comprehensive Phase 3 program starting now

Ongoing open-label study will continue to provide additional information

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Amyotrophic Lateral Sclerosis (ALS)

Disease Overview

ALS is a fatal, orphan disease with a high unmet medical need

- Devastating and rapidly progressing disease
- Patients become paralyzed, yet still have normal cognitive abilities
- Patients usually die of their disease within 2 to 5 years from symptom onset

Genetic forms (familial) and non-genetic forms (sporadic) of ALS exist

- Approximately 10% of ALS cases are familial

Mutations in superoxide dismutase 1 (SOD1) are dominant gain of function mutations and account for more than 1,000 patients

The natural history of ALS patients with a mutation in SOD1 is variable and mirrors the natural history of sporadic ALS

- Good correlation between specific mutations and disease course, e.g. rapidly progressing mutations and slow progressing mutations

Amyotrophic Lateral Sclerosis (ALS)
“Lou Gehrig’s Disease”

Lou Gehrig
The Iron Horse

Lou Gehrig was an American baseball player who played first base for The New York Yankees. He played 17 seasons and was known for his prowess as a hitter and durability, which earned him the nickname, “the iron horse.” Lou Gehrig played in 2,130 consecutive games, a record that stood for over 55 years.

Lou Gehrig announcing his retirement

- He was an All-Star seven times and a member of six World Series championship teams.
- He was elected into the Baseball Hall of Fame in 1939.
- Lou Gehrig suffered from ALS and retired from baseball at the age of 36. He died just two years later.

IONIS-SOD1$_{Rx}$ (BIIB067): Potential First-in-Class and Best-in-Class Medicine to Treat SOD1 Familial ALS

IONIS-SOD1$_{Rx}$ (BIIB067) directly targets a genetic cause of ALS and is currently in clinical development

Intrathecal delivery to the CSF provides widespread distribution throughout the brain and spinal cord

Proof of concept obtained in several animal models

- Substantial reduction in SOD1 in most relevant regions of the brain and spinal cord
- Improved motor function and survival in animal model of SOD1 ALS
- SOD1 detectable in human CSF, serves as an important biomarker in the ongoing Phase 1/2 study

IONIS-SOD1$_{Rx}$ (BIIB067) Phase 1/2 (ongoing)

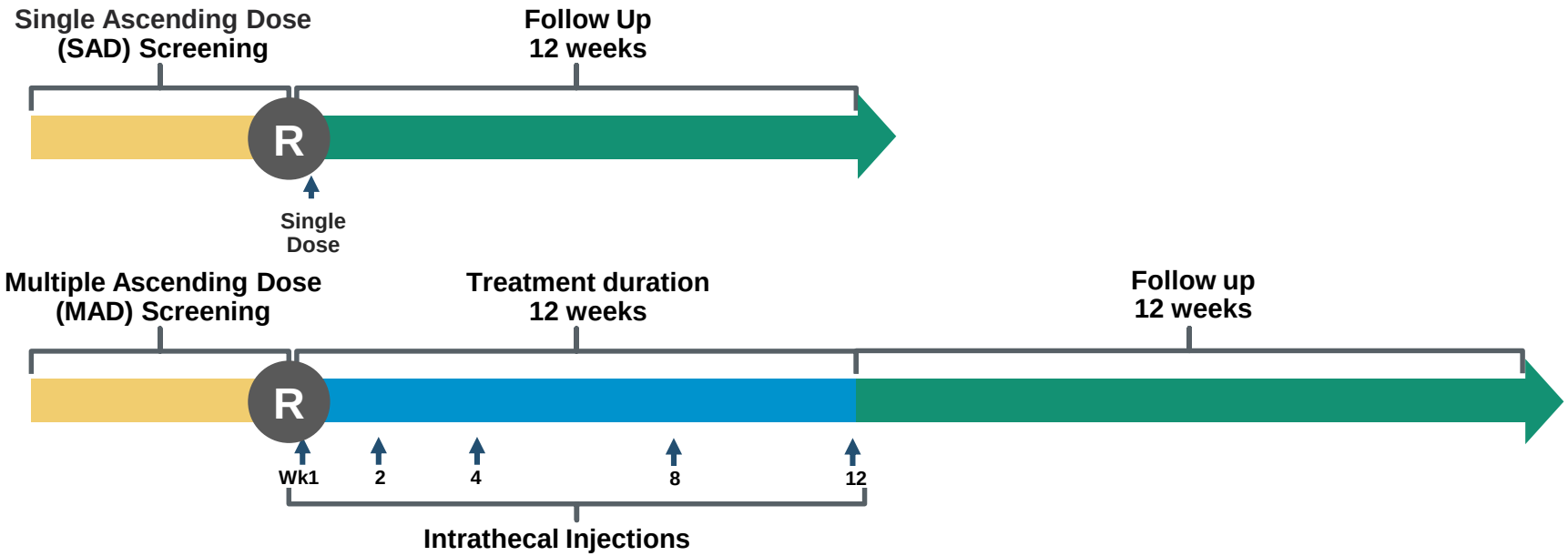
A randomized, blinded, placebo-controlled, study in adult ALS patients with SOD1 mutations (N=70) is being conducted in collaboration with our strategic neurology partner Biogen

Objectives

- Evaluate the safety and tolerability of single and multiple doses of IONIS-SOD1$_{Rx}$

Exploratory

- Changes in SOD1 protein in CSF
- Evaluate effects of IONIS-SOD1$_{Rx}$ on clinical outcomes related to ALS
- ALS functional rating scale



IONIS-SOD1$_{Rx}$ (BIIB067): Biogen Licensed and Plans to Advance into a Pivotal Clinical Study

Positive Phase 1/2 results demonstrated proof-of-biology and proof-of-concept

- At highest dose, treatment over a three-month period resulted in a statistically significant lowering of SOD1 protein levels in the cerebrospinal fluid compared to placebo
- Numerical trend towards slowing of clinical decline as measured by the ALS Functional Rating Scale-Revised compared to placebo
- Safety and tolerability profile supports continued development

Ionis received a $35 million one-time upfront payment plus potential to earn another $55 million in milestone payments

Royalties in the low to mid-teen percentages on annual worldwide net sales

IONIS-SOD1$_{Rx}$ (BIIB067)

Next Steps

1. Final results from the Phase 1/2 study are expected to be communicated at a future scientific forum
2. Based on the positive results of the Phase 1/2 study, Biogen plans to advance IONIS-SOD1$_{Rx}$ to a pivotal clinical study
3. IONIS-SOD1$_{Rx}$ represents the first of multiple ALS-targeted medicines to enter development within the Ionis/Biogen collaboration

Tackling Amyotrophic Lateral Sclerosis with Ionis' Antisense Technology

Ionis and Biogen are committed to developing a broad, first-in-class pipeline of antisense medicines to treat all forms of Amyotrophic Lateral Sclerosis (ALS)

- **Familial (hereditary) ALS**
- **Sporadic ALS**

Our initial entries into ALS targets familial forms

- **IONIS-SOD1$_{Rx}$ (BIIB067) – Phase 1/2 positive data**
- **IONIS-C9$_{Rx}$ (BIIB078) – Phase 1/2 ongoing**

New programs expected to reach development for sporadic ALS and additional forms of familial ALS in the near future

Near- and Mid-term Value Drivers

Summary

More than 10 exciting medicines with the potential to enter pivotal programs in the next 2 Years

Potentially four or more blockbuster medicines entering pivotal programs in 2019

- AKCEA-APO(a)-L_{Rx}: The first and only medicine to selectively and robustly reduce Lp(a) levels
- AKCEA-TTR-L_{Rx}: Expanding the Ionis TTR franchise through advances in antisense technology
- IONIS-HTT_{Rx}: A breakthrough medicine to treat Huntington's Disease
- IONIS-$SOD1_{Rx}$: Potential first-in-class and best-in-class medicine to treat SOD1 familial ALS

New Phase 3 studies incorporate different routes of delivery and advanced chemistries, all pioneered by Ionis

Commitment to provide novel, best-in-class medicines that generate meaningful value to patients in great need

Q&A

Break

Key Value Drivers From Mid-stage Pipeline

Advancing and Maturing Pipeline for Underserved Patients – Addressing Diseases Both Rare and Common

Richard Geary, Ph.D.
SVP Development
Ionis Pharmaceuticals

Key Takeaways

Multiple additional medicines with positive clinical data with the potential to enter pivotal programs in the next 2 years

Focus on innovative medicines to transform therapy

Focus on opportunities best suited to our antisense platform

Strategically balanced portfolio

- Very large, moderate, small and rare disease opportunities
- Multiple organs/tissues
- Multiple routes of delivery
- Multiple mechanisms of action
- Balanced relative to types of risks

Continue to rapidly incorporate advances in technology into the pipeline

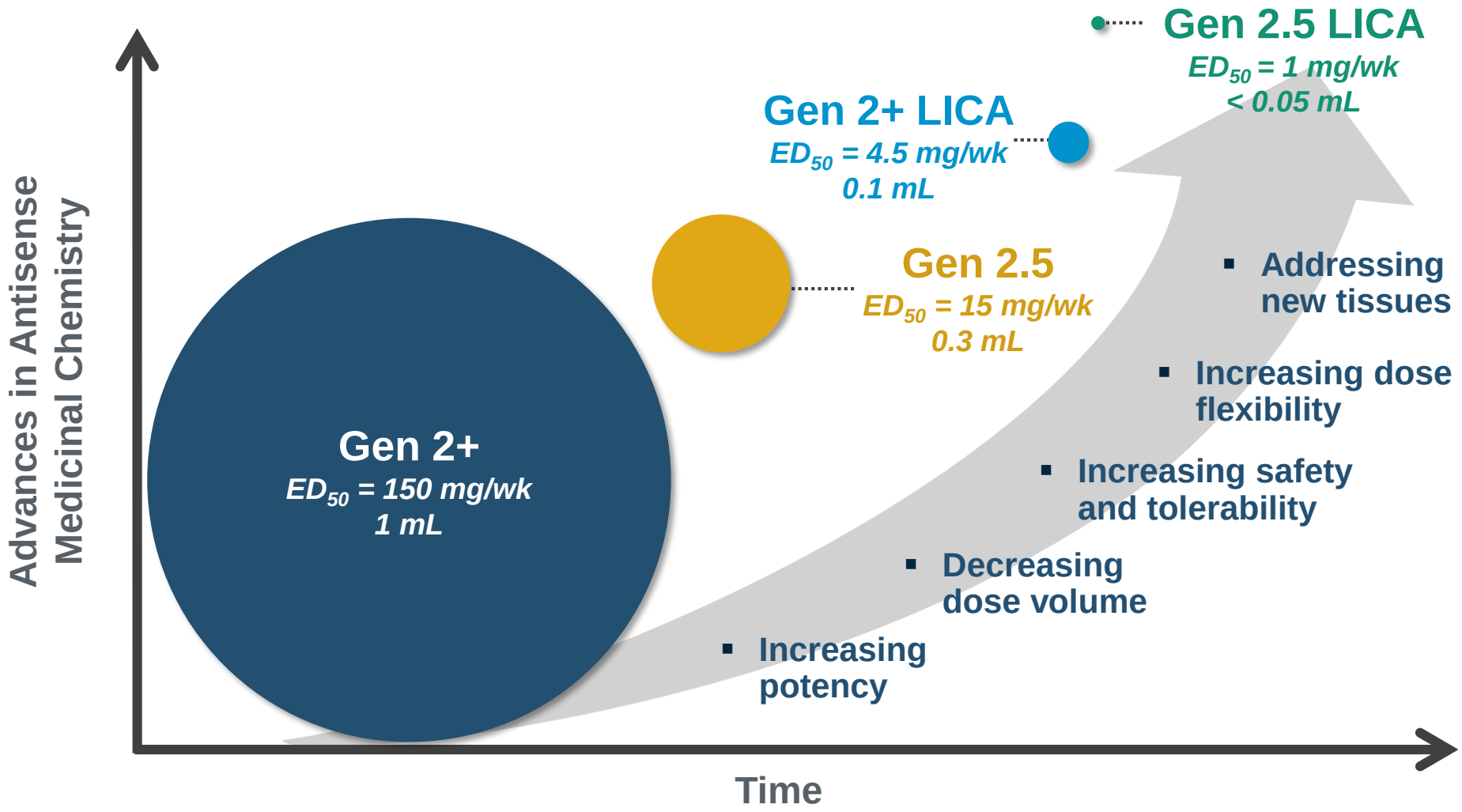
Approach to Today's Presentation

Focus on the key factors for maximizing the commercial value of our pipeline using examples to illustrate

Pipeline today represents four fundamental strategies that we will support with examples

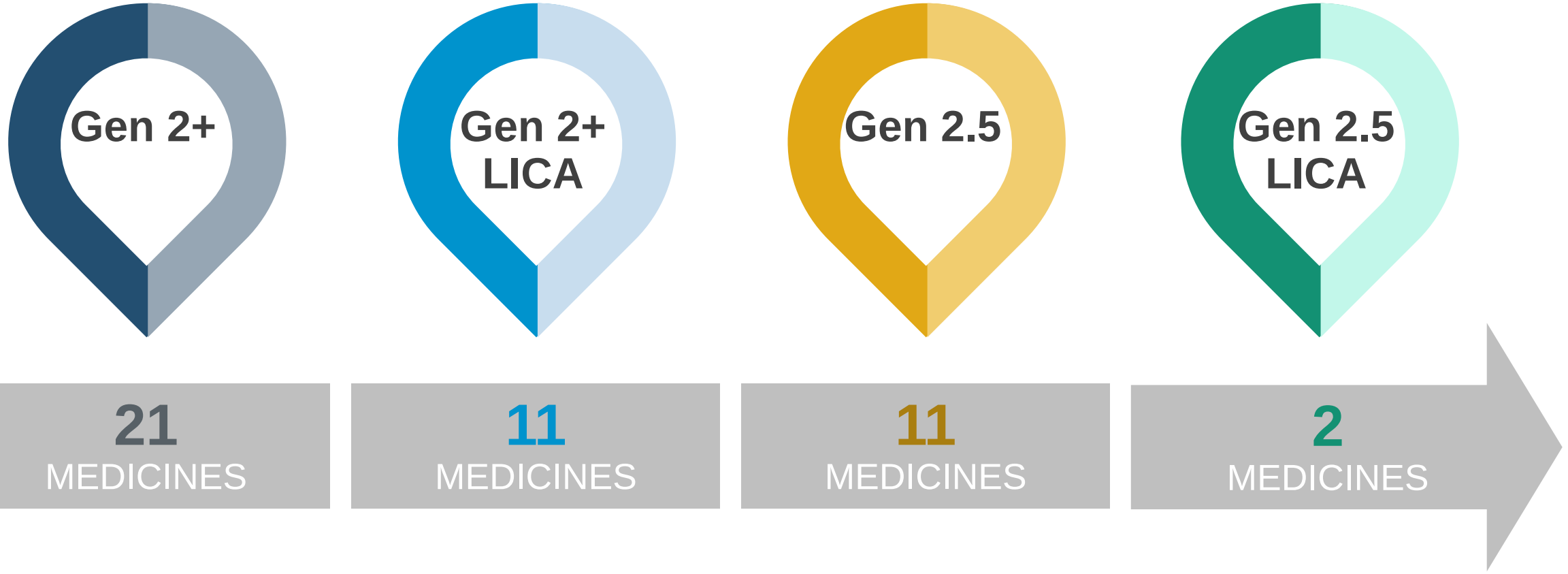
- Rapidly introduce advances in technology to substantially improve utility of antisense
- Focus on high value opportunities that can transform therapy
- Develop multiple medicines for multiple targets and pathways for important therapeutic categories
- Participate in all sizes of patient populations – rare, mid-size and large

Antisense Medicinal Chemistry: Advances in Our Technology Substantially Improve the Utility of Antisense



ED50's and dose volumes are representative of liver targets

Strategic Principle: We Rapidly Introduce Advances in Technology Into Our Pipeline Thereby Enhancing Performance and Value



Continuing Investment in Core Antisense Research

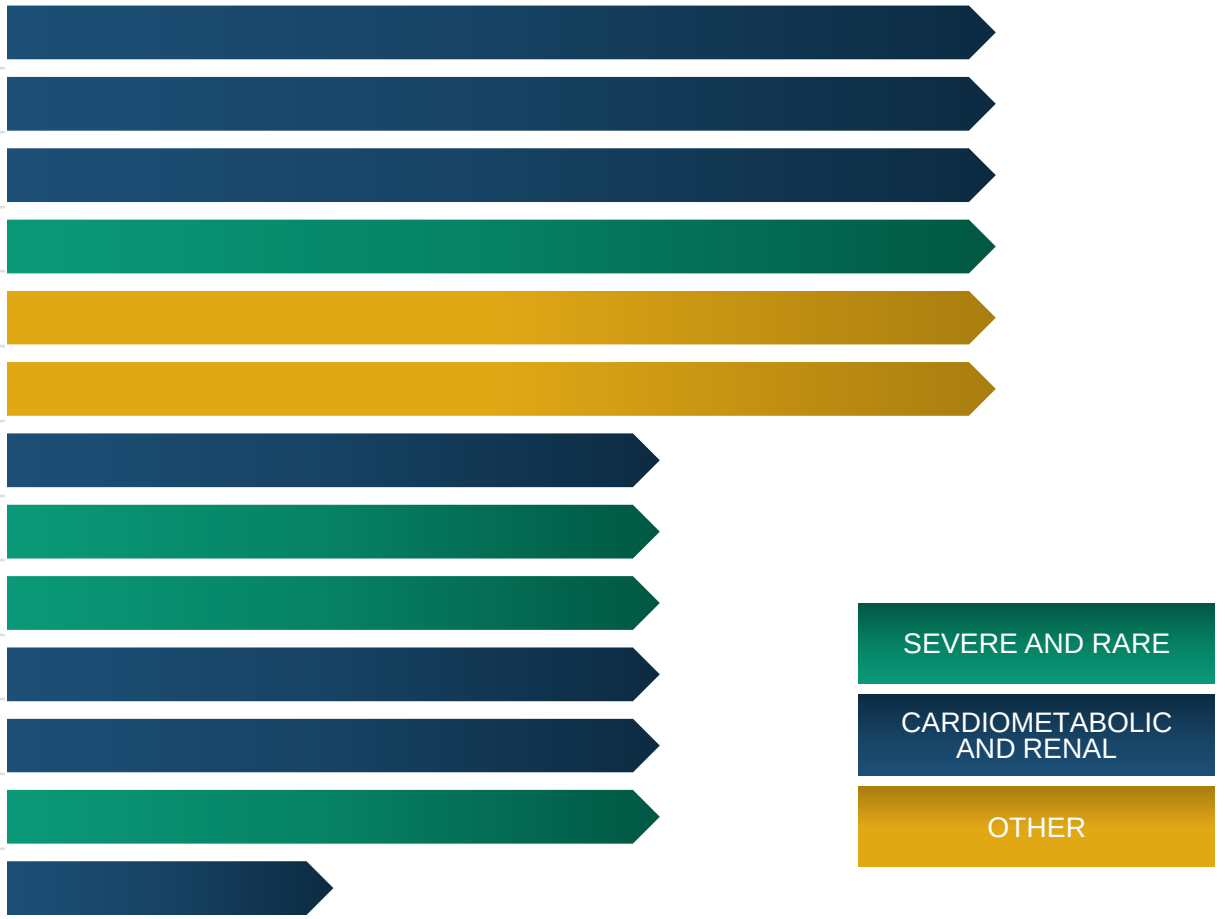
More Than 10 Exciting Medicines with the Potential to Enter Pivotal Programs in the Next 2 Years

MEDICINE	INDICATION	PARTNER
IONIS-HTT$_{Rx}$	Huntington's disease	Roche
AKCEA-APO(a)-L$_{Rx}$	Cardiovascular disease	Akcea / Novartis
AKCEA-TTR-L$_{Rx}$	Transthyretin amyloidosis	Akcea / Ionis
IONIS-SOD1$_{Rx}$	Amyotrophic lateral sclerosis	Biogen
IONIS-HBV$_{Rx}$/IONIS-HBV-L$_{Rx}$	Hepatitis B virus infection	GSK
Danvatirsen (IONIS-STAT3-2.5$_{Rx}$)	Cancer	AstraZeneca
AKCEA-APOCIII-L$_{Rx}$	Cardiovascular disease	Akcea / Novartis
IONIS-MAPT$_{Rx}$	Alzheimer's disease/ Frontotemporal dementia	Biogen
IONIS-FXI$_{Rx}$/IONIS-FXI-L$_{Rx}$	Clotting disorders	Bayer
AKCEA-ANGPTL3-L$_{Rx}$	Non-alcoholic fatty liver disease	Akcea / Ionis
IONIS-GHR-L$_{Rx}$	Acromegaly	Ionis
IONIS-TMPRSS6-L$_{Rx}$	β-thalassemia	Ionis

LICA: An Example of Advances in Technology Enhancing the Value of Our Pipeline

13 LICA MEDICINES IN PIPELINE

MEDICINE	INDICATION
AKCEA-APO(a)-L_{Rx}	Cardiovascular disease
AKCEA-ANGPTL3-L_{Rx}	Rare Hyperlipidemias
AKCEA-APOCIII-L_{Rx}	Cardiovascular disease
IONIS-GHR-L_{Rx}	Acromegaly
IONIS-HBV-L_{Rx}	Hepatitis B virus infection
IONIS-FB-L_{Rx}	Complement-Mediated Diseases
IONIS-AGT-L_{Rx}	Treatment-Resistant Hypertension
IONIS-TMPRSS6-L_{Rx}	β-Thalassemia
IONIS-PKK-L_{Rx}	Hereditary Angioedema
IONIS-FXI-L_{Rx}	Clotting Disorders
IONIS-AZ4-2.5-L_{Rx}	Cardiovascular disease
AKCEA-TTR-L_{Rx}	Transthyretin amyloidosis
IONIS-AZ6-2.5-L_{Rx}	Nonalcoholic steatohepatitis



LICA: An Example of Advances in Technology Enhancing the Value of Our Pipeline

13 LICA MEDICINES IN PIPELINE

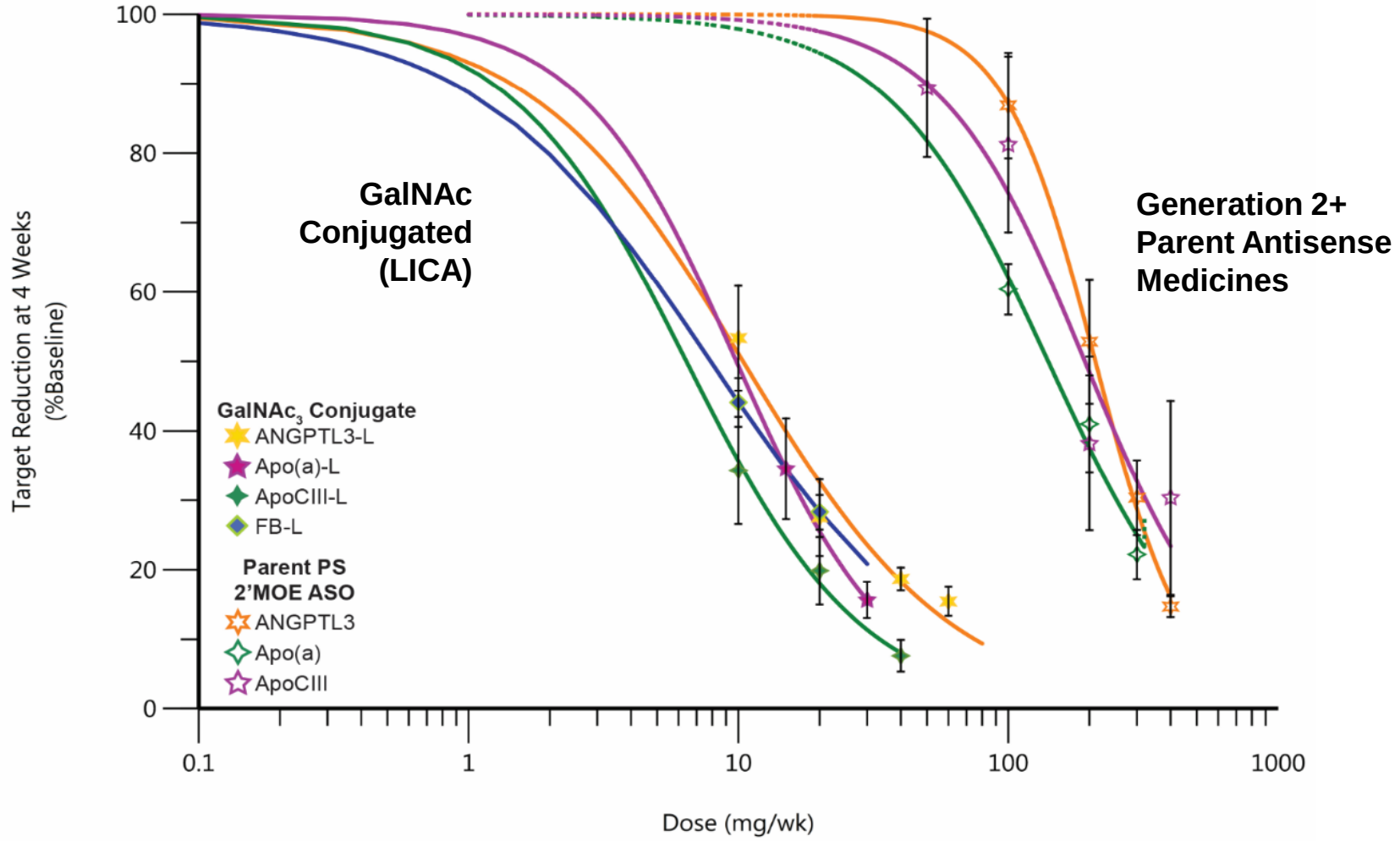
MEDICINE	INDICATION	PC	PHASE I	PHASE II	PHASE III
AKCEA-APO(a)-L_{Rx}	Cardiovascular disease				
AKCEA-ANGPTL3-L_{Rx}	Rare Hyperlipidemias				
AKCEA-APOCIII-L_{Rx}	Cardiovascular disease				
IONIS-GHR-L_{Rx}	Acromegaly				
IONIS-HBV-L_{Rx}	Hepatitis B virus infection				
IONIS-FB-L_{Rx}	Complement-Mediated Diseases				
IONIS-AGT-L_{Rx}	Treatment-Resistant Hypertension				
IONIS-TMPRSS6-L_{Rx}	β-Thalassemia				
IONIS-PKK-L_{Rx}	Hereditary Angioedema				
IONIS-FXI-L_{Rx}	Clotting Disorders				
IONIS-AZ4-2.5-L_{Rx}	Cardiovascular disease				
AKCEA-TTR-L_{Rx}	Transthyretin amyloidosis				
IONIS-AZ6-2.5-L_{Rx}	Nonalcoholic steatohepatitis				

SEVERE AND RARE

CARDIOMETABOLIC AND RENAL

OTHER

Greater than 30-Fold Increase in Potency of LICAs Targeting the Liver

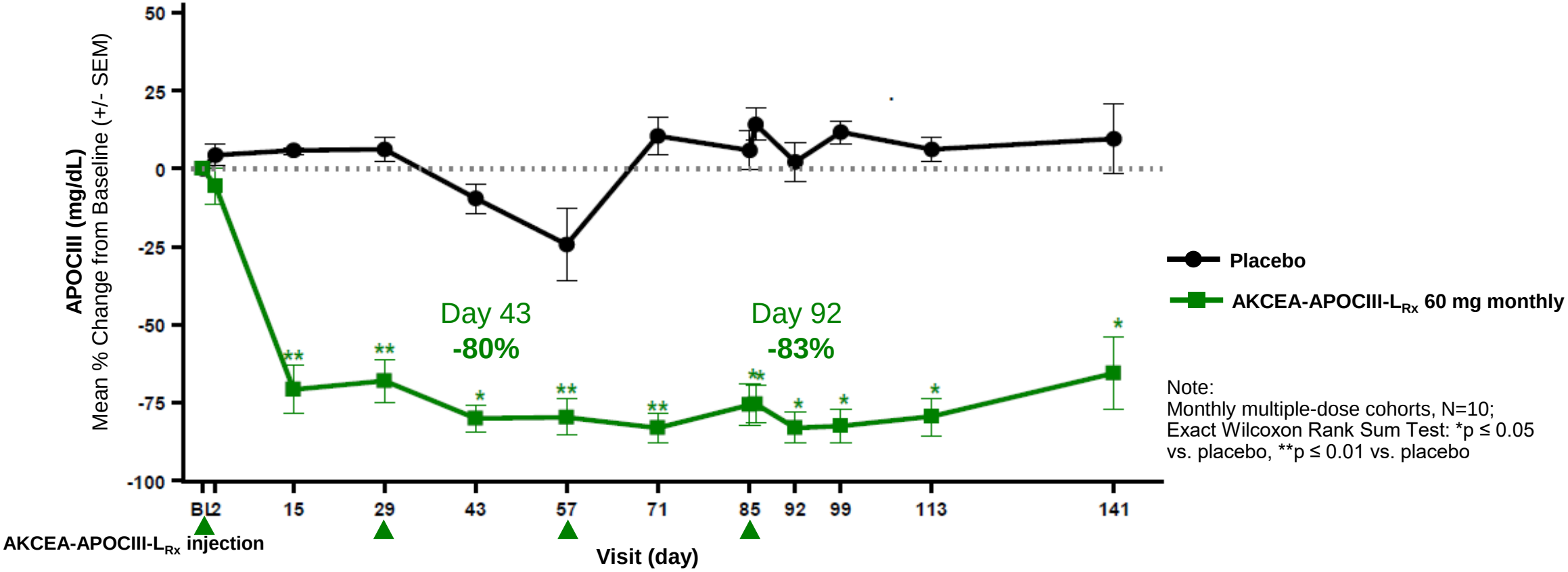


Consistent Performance Enables Rapid Development

Crooke, ST., et al, NAT, in press

Monthly and Less Frequent Dosing Enabled

Mean % Reduction in APOCIII Following Four Monthly Doses of AKCEA-APOCIII-L_{Rx}



Note:
Monthly multiple-dose cohorts, N=10;
Exact Wilcoxon Rank Sum Test: *p ≤ 0.05 vs. placebo, **p ≤ 0.01 vs. placebo

Strong Safety Database for Liver-LICA (GalNAc) Technology

Favorable safety and tolerability profile observed in clinical studies and consistent across the entire LICA platform

- More than 600 subjects with more than 200 subjects on treatment for six months or longer

No safety concerns related to platelets

No liver or kidney safety concerns

No flu-like symptoms

Very low incidence of mild injection site observations

Safety margins greatly improved

The AKCEA-APO(a)-L_{Rx} Phase 2 study is important technologically

- Adds 286 patients to the database with up to one year duration of treatment
- Patients with significant cardiovascular disease and were being treated with multiple medications
- Excellent compliance in patients with many health complications related to their disease

Crooke, ST., et al, NAT, in press

Next Steps for the LICA Technology

Advance multiple Generation 2+ liver-LICA medicines into pivotal trials

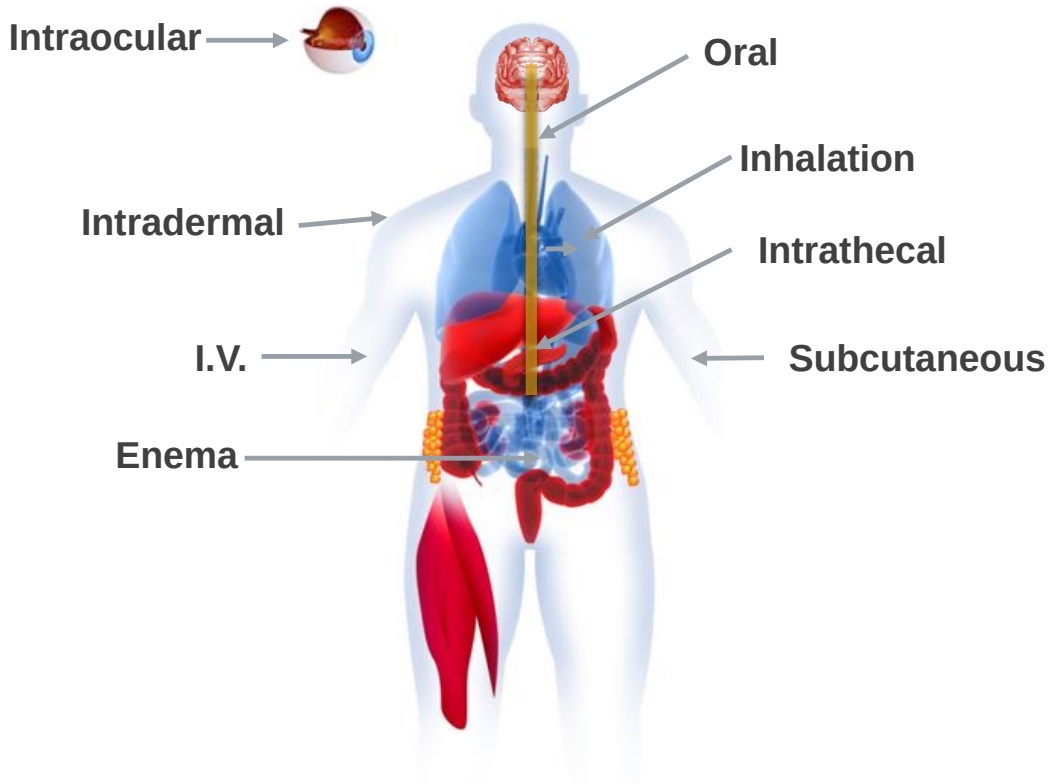
Advance multiple more potent Generation 2.5 liver-LICAs

Use the pancreas-LICA (GLP1) to advance multiple medicines to treat pancreatic disorders

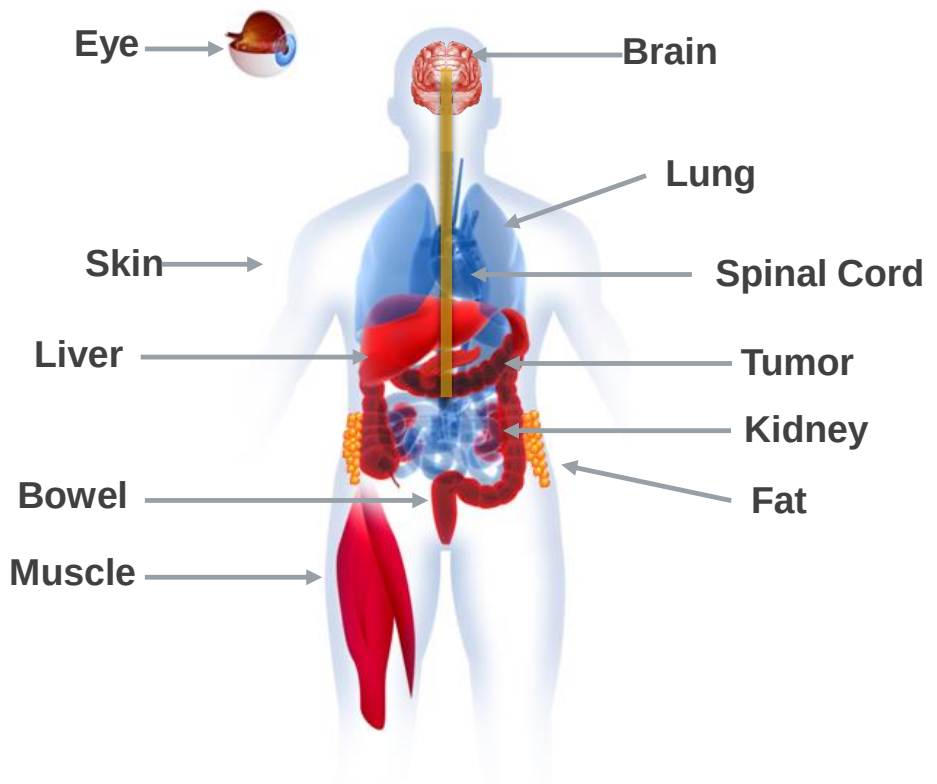
Create additional LICAs that target other tissues such as skeletal muscle

Methods of Administration and Technology Advances Create Breadth in Our Pipeline Today

ADMINISTERED THROUGH MULTIPLE ROUTES OF DELIVERY



BROAD CLINICAL ACTIVITY IN MULTIPLE TISSUES DEMONSTRATED



Multiple Routes of Administration, Multiple Target Tissues

Maximizing the Commercial Value of Our Pipeline

Cannot possibly cover all the exciting advances today – will focus on strategic principles that drive construction of the pipeline

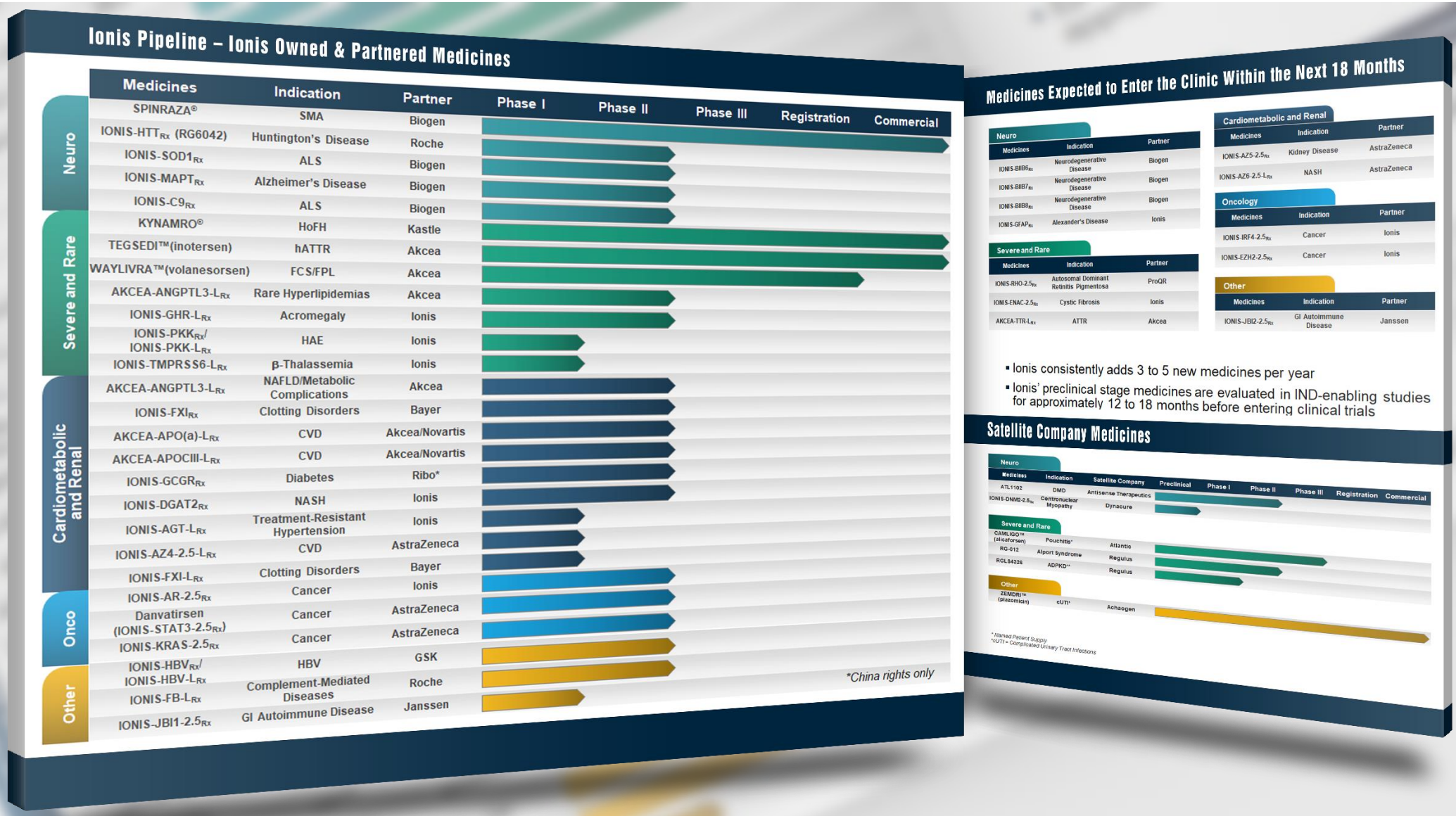
Efficient technology of a broad, deep and mature pipeline

- Potential to drive steady, sustainable growth in the short, mid and long-term
- Participate in all major therapeutic categories
- Take advantage of our partners global clinical trial infrastructure and expertise in diseases to de-risk very large outcome studies

Additional pipeline principles exemplified today

- Focus on high value opportunities that can transform therapy
- For important therapeutic categories develop multiple medicines for multiple targets and pathways
- Participate in all sizes of patient populations – rare, mid and large

Ionis Today: Advancing and Growing Pipeline of Over 40 Medicines



Strategic Principle: Focus on High-value Opportunities that Could Transform Therapy

Examples

SPINRAZA and IONIS-HTT_{Rx} (RG6042) represent the unique ability of antisense to tackle terrible diseases at their fundamental core

AKCEA-APO(a)-L_{Rx} is an example of a program where Ionis was exploring the frontier of cardiovascular risk even before much of the data supporting this important risk factor was published

IONIS-FXI_{Rx}/IONIS-FXI-L_{Rx} represents a fundamental shift in the treatment of thrombosis by removing the risk of bleeding from the treatment paradigm

IONIS-$SOD1_{Rx}$ (BIIB067) and IONIS-$C9_{Rx}$ (BIIB078) represent the first entries in ALS with more to come

The entire pipeline is enriched with this level of high-value opportunities

IONIS-TMPRSS6-L_{Rx} is a Promising Medicine for β-thalassemia

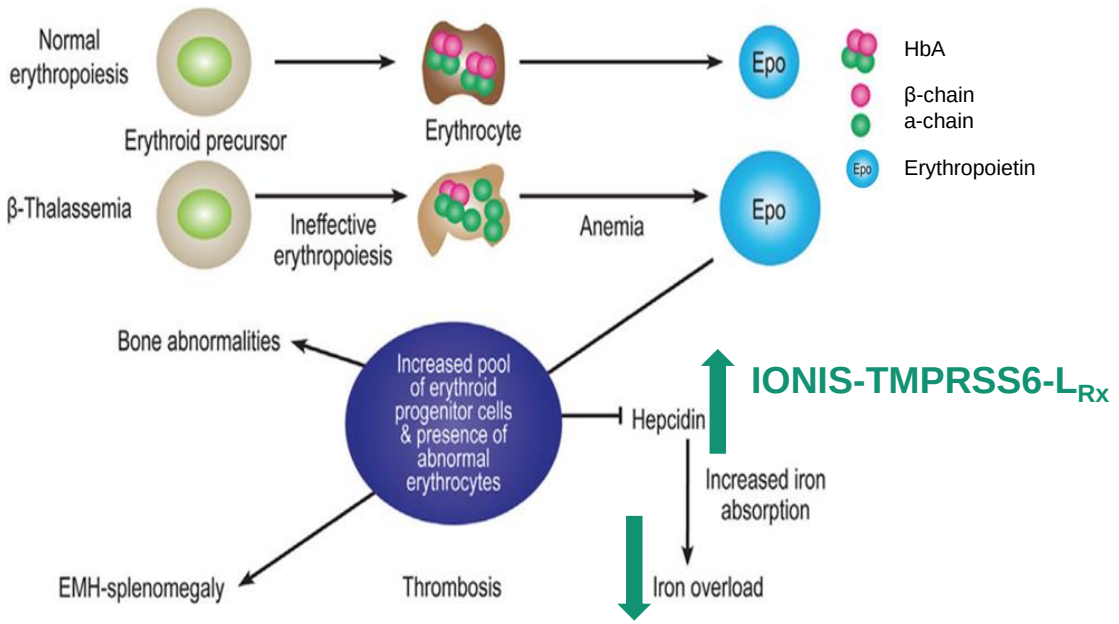
An Example of Potential Breakthrough Opportunities

TMPRSS6 (transmembrane protease serine 6) is expressed and secreted in the liver and plays an important role in regulating the body's iron homeostasis

IONIS-TMPRSS6-L_{Rx} inhibits the production of TMPRSS6 thereby increasing hepcidin expression and reducing the chronic cycle of ineffective red blood cell production, anemia and iron toxicity

- Numerous therapeutic opportunities for inhibitors of TMPRSS6 including thalassemias, myeloproliferative neoplasms, iron overload
- IONIS-TMPRSS6-L_{Rx} is a Generation 2+ liver LICA advancing into Phase 2 Studies

IONIS-TMPRSS6-L_{Rx} MOA



Rivella S. Blood (2012)

IONIS-TMPRSS6-L_{Rx} for β-Thalassemia Intermedia

Non-Transfusion-Dependent Thalassemia (NTDT)

β-thalassemia is an inherited blood disorder caused by a genetic mutation in the β-globin gene resulting in defective red blood cell production

- Non-transfusion-dependent thalassemia (NTDT) or transfusion-dependent thalassemia (TDT)[1]
- NTDT patients suffer a serious, fatal disease stemming from ineffective erythropoiesis (IE), chronic anemia, and iron toxicity in the heart, liver and endocrine glands due to low hepcidin levels

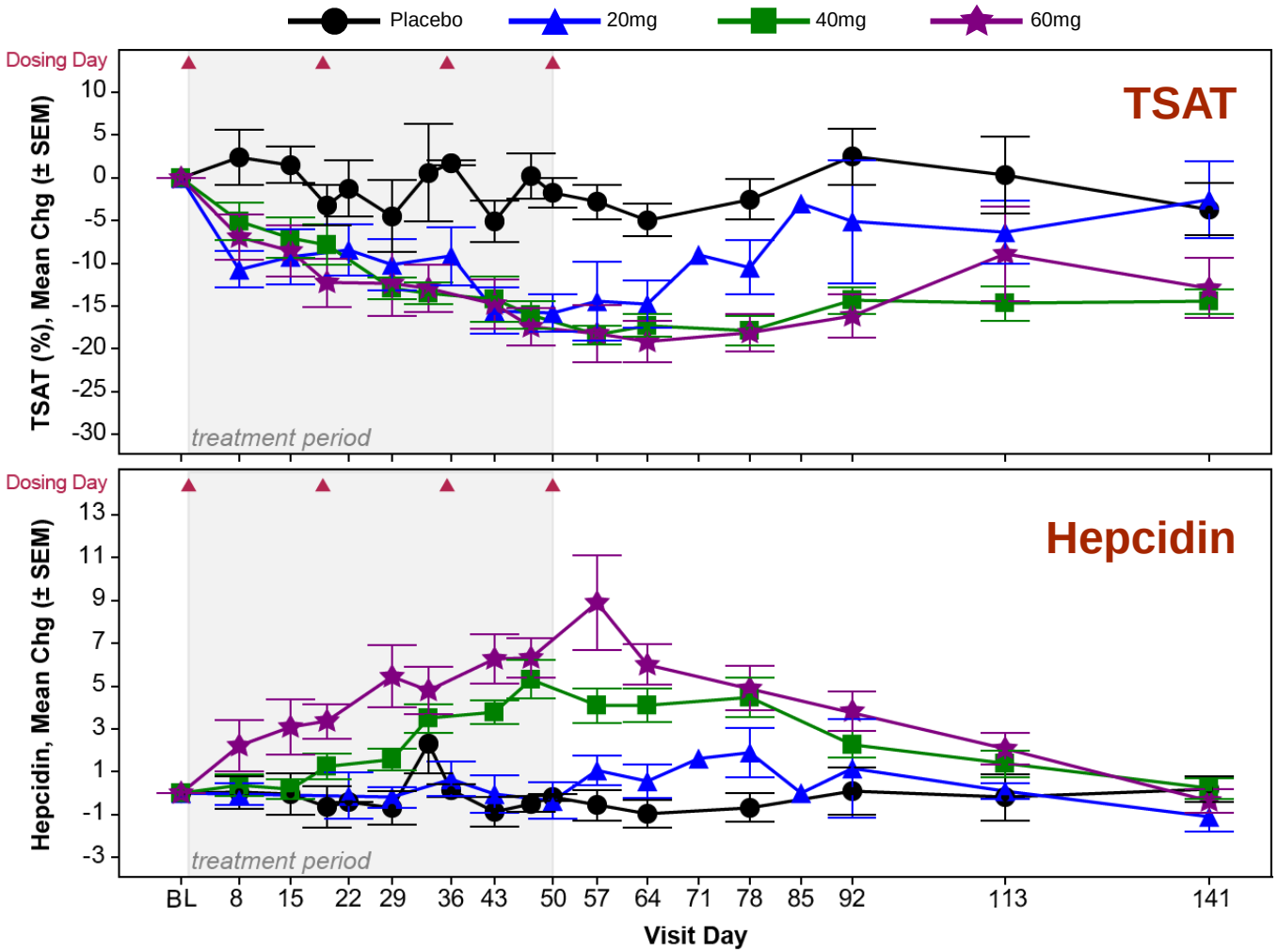
Prevalence of NTDT ranges from 1 in 100,000 to 1 in 100 depending on geographic location[2]

- An estimated 20,000 NTDT patients in North America and Europe[3]

No effective pharmacological treatment for patients with β-thalassemia intermedia (NTDT)

1. Musallam KM, et al. Haematologica. 2013;98:833-44. 2. Taher A, Isma'eel H, Cappellini MD. Thalassemia intermedia: revisited. Blood Cells Mol Dis 2006; 12-20. 3. Viprakasit V, Tyan P, Rodmai S, Taher AT. Identification and key management of non-transfusion-dependent thalassaemia patients: not a rare but potentially under-recognised condition. Orph J Rare Dis 2014; 131: 1-11.

IONIS-TMPRSS6-L_{Rx}: A Potential Major Advance in the Treatment of β-thalassemia



A double-blind, randomized, placebo-controlled, dose-escalation Phase 1 study in healthy volunteers

Pharmacodynamic Activity

- Dose-dependent reduction of:
  - Serum Iron
  - Serum Transferrin Saturation (TSAT)
- Increase of serum Hepcidin
- Predicted changes in hemoglobin

Favorable safety and tolerability profile

- There were no serious adverse events and the TEAEs were generally mild

IONIS-TMPRSS6-L_{Rx} has the potential to treat patients with β-thalassemia and related disorders

IONIS-TMPRSS6-L_{Rx}

Next Steps

1 **Plan for an accelerated development path for IONIS-TMPRSS6-L_{Rx}**

2 **Single Phase 2 proof of concept study prior to advancing to a pivotal study**

- Phase 2 POC study in β-thalassemia intermedia patients planned to start in 2019
- Plan to initiate pivotal trial in 2020

Strategic Principle: For Important Therapeutic Categories Develop Multiple Medicines Targeting Different Targets in the Disease Pathway

Examples

Lipid Risk Factors for Diseases

- AKCEA-APO(a)-L_{Rx}: Apo(a) causal factor in cardiovascular disease
- WAYLIVRA™ (volanesorsen): Familial chylomicronemia syndrome and familial partial lipodystrophy
- AKCEA-APOCIII-L_{Rx}: Elevated triglycerides remain a risk factor for multiple diseases
- AKCEA-ANGPTL3-L_{Rx}: Mixed dyslipidemias and remnant cholesterol in cardiovascular disease
- IONIS-AZ4-2.5-L_{Rx} (AZD8233): Cardiovascular disease

Nonalcoholic Steatohepatitis (NASH)

- Liver fat reduction
  - IONIS-DGAT2$_{Rx}$ and IONIS-DGAT2-L_{Rx}
  - AKCEA-ANGPTL3-L_{Rx}
- Fibrosis
  - IONIS-AZ6-2.5-L_{Rx} (AZD2693)
  - Several targets coming

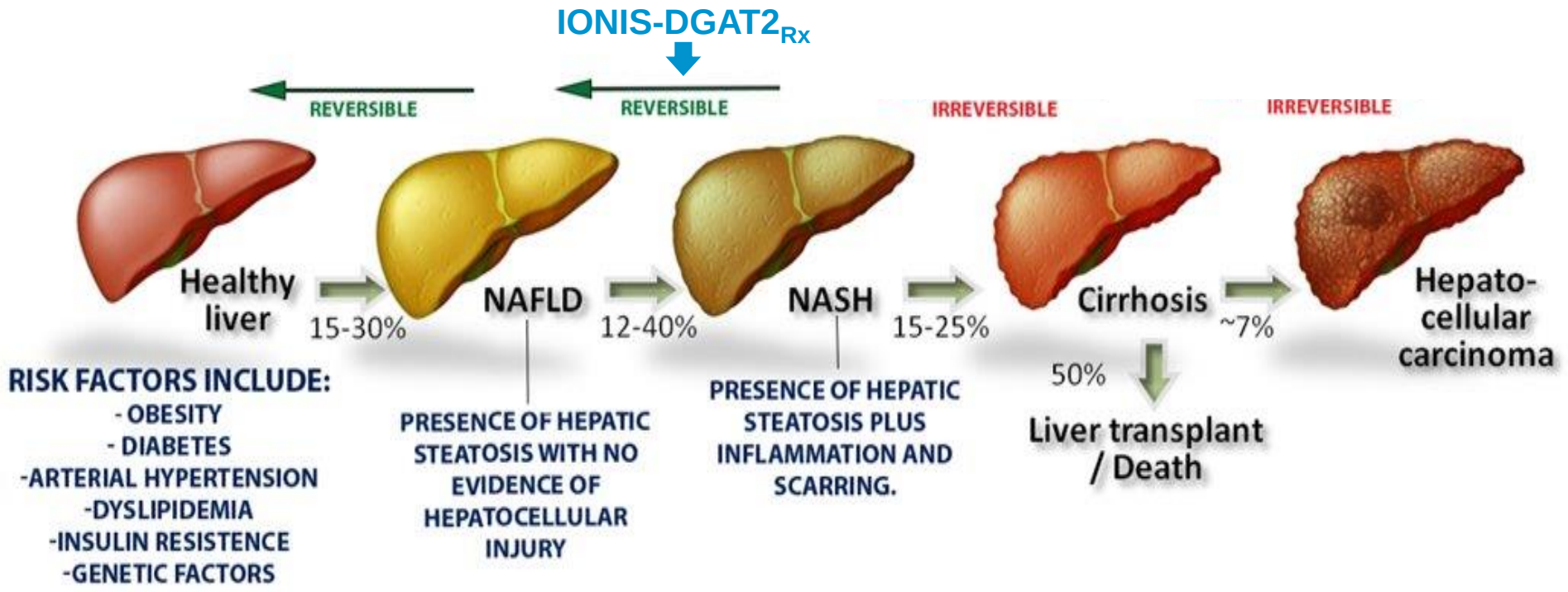
IONIS-DGAT2$_{Rx}$: Attractive and Differentiated Approach for Treating NASH

DGAT2 is an enzyme that catalyzes the final step in triglyceride synthesis in the liver

IONIS-DGAT2$_{Rx}$ works by inhibiting the production of DGAT2 thereby reducing levels of fat in the liver

DGAT2 inhibition also results in secondary reductions of several other enzymes resulting in cumulative pharmacological benefit

- Biochemical (mechanistic) evidence for reduced triglyceride synthesis and increased fatty acid oxidation



Positive IONIS-DGAT2$_{Rx}$ Phase 2 Proof-of-Concept

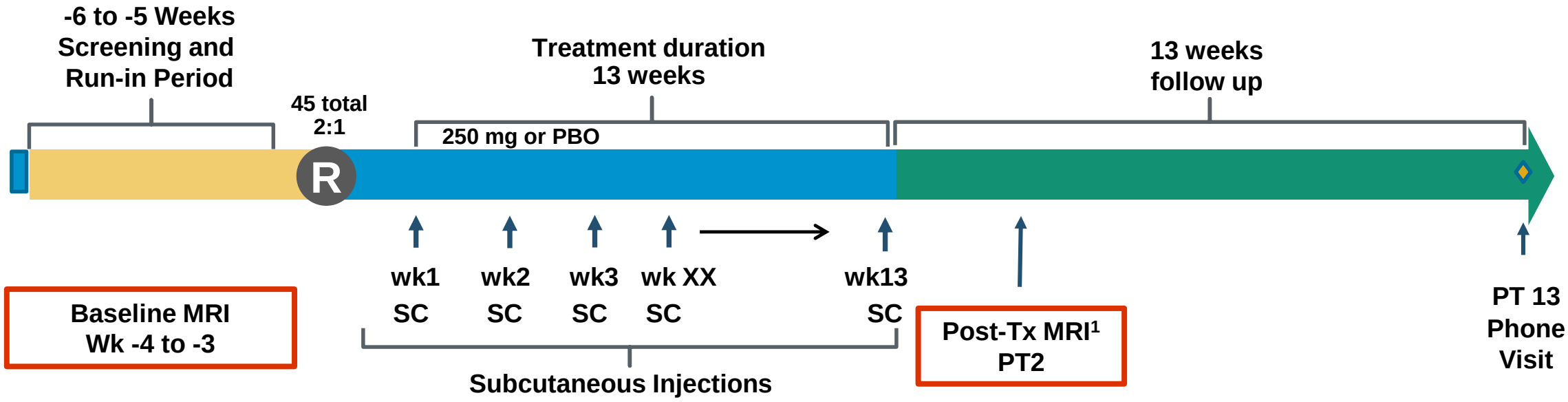
Study Design Dosing Schedule

A double-blind, randomized, placebo-controlled study

44 adult patients with hepatic steatosis (>10% HFF) with Type 2 Diabetes

Primary Objectives

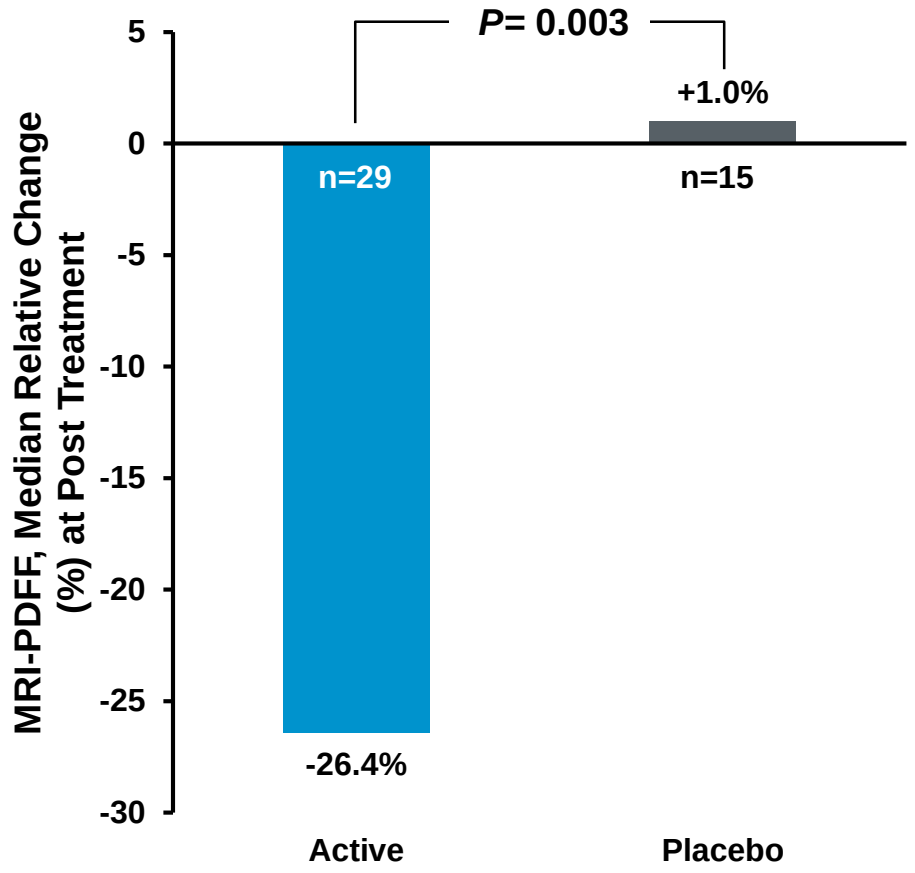
- Reduction in liver fat (measured as %) as quantified by MRI proton density fat fraction (PDFF)



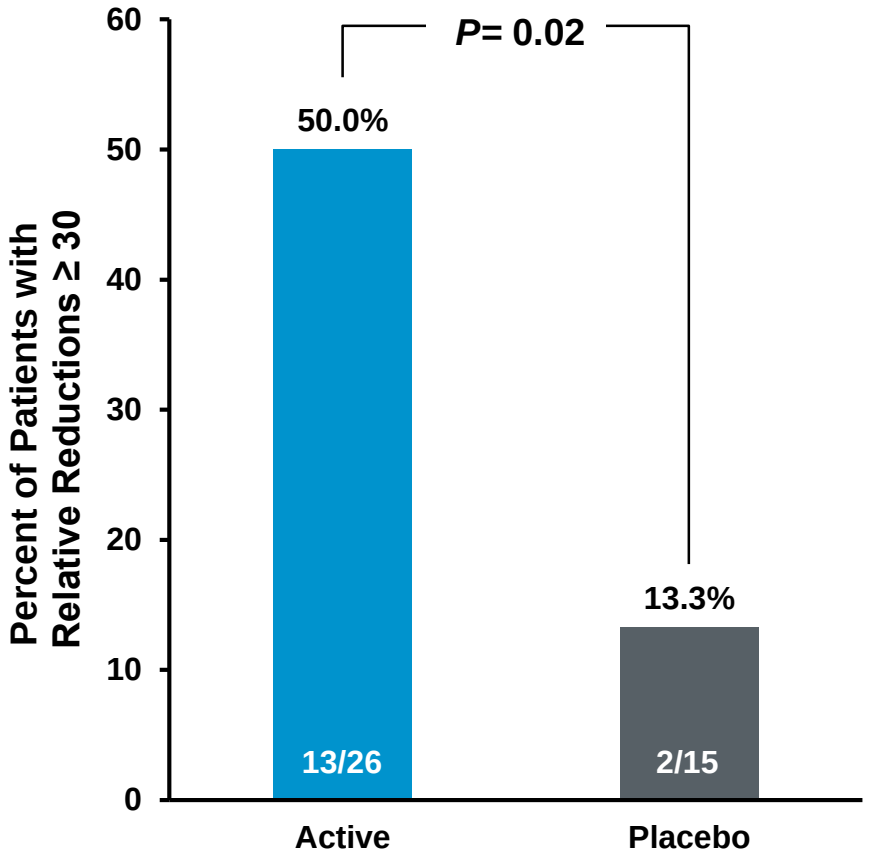
1. post-treatment MRI typically 2 weeks after last dose

IONIS-DGAT2$_{Rx}$ Substantially Reduced Liver Fat After Only 3 Months of Treatment

Percent Liver Fat Reduction



Percent of Patients with ≥ 30% Reduction in Liver Fat



50% of IONIS-DGAT2$_{Rx}$ treated patients had relative liver fat reduction of ≥ 30%

IONIS-DGAT2$_{Rx}$ Phase 2 Study: Favorable Safety and Tolerability Profile

- No safety concerns related to liver, kidney, and platelets
- No deaths, no medicine-related SAEs
- No flu-like symptoms
- No increase in triglycerides or cholesterol (LDLs)
- No liver enzyme increases with robust liver fat reduction

IONIS-DGAT2$_{Rx}$ Program:

Next Steps

1. Move program immediately to a liver-LICA of the parent medicine now – initiate IND in 2019

2. Rely on data from parent medicine to move rapidly to Phase 2/3 program in NASH patients

Strategic Principle: Participate in All Sizes of Patient Populations

Examples

SMALL (RARE)	MID-SIZED	LARGE
IONIS-TMPRSS6-L_{Rx} β-thalessemias	**AKCEA-ANGPTL3-L_{Rx}** Rare Hyperlipidemias	**AKCEA-APO(a)-L_{Rx}** Cardiovascular disease
IONIS-GHR-L_{Rx} Acromegaly	**AKCEA-APOCIII-L_{Rx}** Cardiovascular disease	**IONIS-MAPT$_{Rx}$ (BIIB080)** Alzheimer's disease
IONIS-SOD1$_{Rx}$ (BIIB067) Familial ALS	**IONIS-DGAT2-L_{Rx}** Nonalcoholic steatohepatitis (NASH)	**IONIS-AGT-L_{Rx}** Treatment-Resistant hypertension
IONIS-C9$_{Rx}$ (BIIB078) Familial ALS	**Danvatirsen (IONIS-STAT3$_{Rx}$):** Head and neck cancer	**IONIS-FXI$_{Rx}$ & IONIS-FXI-L_{Rx}** Thrombosis

Strategic Principle: Participate in All Sizes of Patient Populations

Mid- to Late-term Examples

SMALL (RARE)	MID-SIZED	LARGE
IONIS-TMPRSS6-L_{Rx} β-thalessemias	**AKCEA-ANGPTL3-L_{Rx}** Rare Hyperlipidemias	**AKCEA-APO(a)-L_{Rx}** Cardiovascular disease
IONIS-GHR-L_{Rx} Acromegaly	**AKCEA-APOCIII-L_{Rx}** Cardiovascular disease	**IONIS-$MAPT_{Rx}$ (BIIB080)** Alzheimer's disease
IONIS-$SOD1_{Rx}$ (BIIB067) Familial ALS	**IONIS-DGAT2-L_{Rx}** Nonalcoholic steatohepatitis (NASH)	**IONIS-AGT-L_{Rx}** Treatment-Resistant hypertension
IONIS-$C9_{Rx}$ (BIIB078) Familial ALS	**Danvatirsen (IONIS-$STAT3_{Rx}$)** Head and neck cancer	**IONIS-FXI_{Rx} & IONIS-FXI-L_{Rx}** Thrombosis

IONIS-GHR-L_{Rx}: An Example of a Treatment for a Rare Disease

Acromegaly is a chronic disease most often caused by oversecretion of growth hormone (GH) by benign pituitary tumors, which leads to:

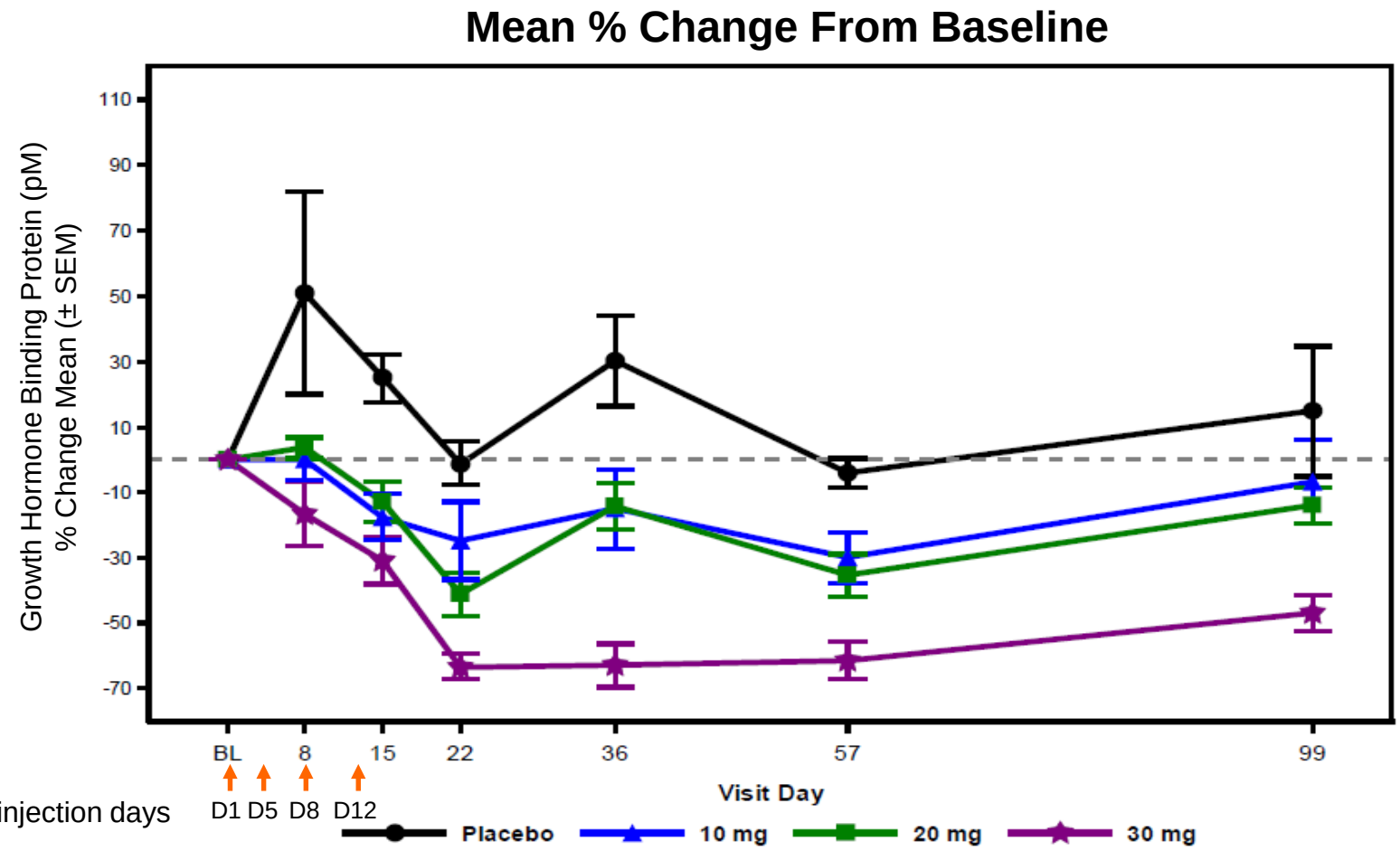
- Hypertension
- Sleep apnea
- Insulin resistance
- Physical disfigurement
- Decreased quality of life
- Mortality

The prevalence of acromegaly is approximately 25,000 patients in the U.S.[1]

- Approximately 3,000 new cases are diagnosed in the U.S. each year[1]

1. Broder MS, Chang E, Cherepanov D, Neary MP, Ludlam WH. Incidence And Prevalence Of Acromegaly In The United States: A Claims-based Analysis. Endocr Pract. 2016; 11: 1327-1335.

IONIS-GHR-L_{Rx}: Up to 63% Reduction in Growth Hormone Receptor Demonstrated in Phase 1 Study



Dose-dependent pharmacological activity of IONIS-GHR-L_{Rx} was observed as a reduction in GHBP (a biomarker of GHR inhibition)

Importantly, no increase in GH was observed

- No correlation between a GH increase and GHBP decrease

IONIS-GHR-L_{Rx}: Favorable Safety and Tolerability in Phase 1 Study

IONIS-GHR-L_{Rx} was well tolerated and demonstrated a favorable safety profile in Phase 1 study

- There were no reports of deaths, no serious adverse events and nearly all adverse events were mild
- No effects on platelets, no renal changes, no hepatic changes
- No adverse event led to study discontinuation

Clear unmet need for a novel, effective, safe and well tolerated medicine with improved convenience

IONIS-GHR-L_{Rx} has the potential to bring substantial benefit to patients with acromegaly with at home monthly SC dosing

Rowland J., et al. 2005 In vivo analysis of growth hormone receptor signalling domains and their associated transcripts. Molecular and Cellular Biology 25 66–77.

IONIS-GHR-L_{Rx} Phase 2 Study Design

Initiated Phase 2 POC in acromegaly patients this year (November, 2018)

A randomized, double-blind, placebo-controlled, multi-center study in patients with acromegaly uncontrolled on select long-acting somatostatin receptor ligands (SRL)

Up to 42 adult patients to receive once monthly IONIS-GHR-L_{Rx} or placebo subcutaneous injections: 4 months treatment

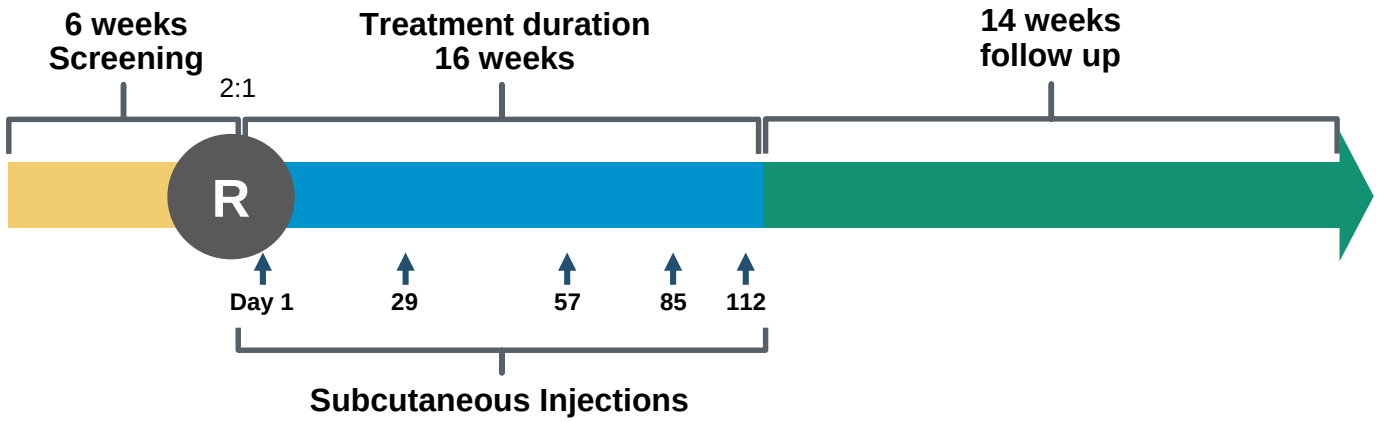
Primary Objectives

- Evaluate safety and efficacy of IONIS-GHR-L_{Rx} on IGF-1 as an add-on therapy to long acting SRL

Secondary Objectives

- Evaluate effect of IONIS-GHR-L_{Rx} to normalize IGF-1 levels

Cohorts	IONIS-GHR-L_{Rx} (n)	PBO (n)
1	~14	~7
2	~14	~7



IONIS-GHR-L_{Rx} Next Steps

1 **Currently planning Phase 3 study in acromegaly patients uncontrolled on existing therapies**

2 **We anticipate an accelerated development path because of the limited patient population and rare nature of the disease**

- Planning to complete ongoing Phase 2 study by YE 2019
- Planning to rapidly advance into a single pivotal study in 2020

Danvatirsen (IONIS-STAT3-2.5$_{Rx}$ – AZD9150):

An Example of a Mid-sized Patient Population

Danvatirsen (IONIS-STAT3-2.5$_{Rx}$) is a Generation 2.5 antisense medicine candidate targeted against STAT3, discovered and initially developed by Ionis and licensed to AstraZeneca for a broad range of cancers

Demonstrated robust anti-tumor activity in a broad range of preclinical cancer models[1]

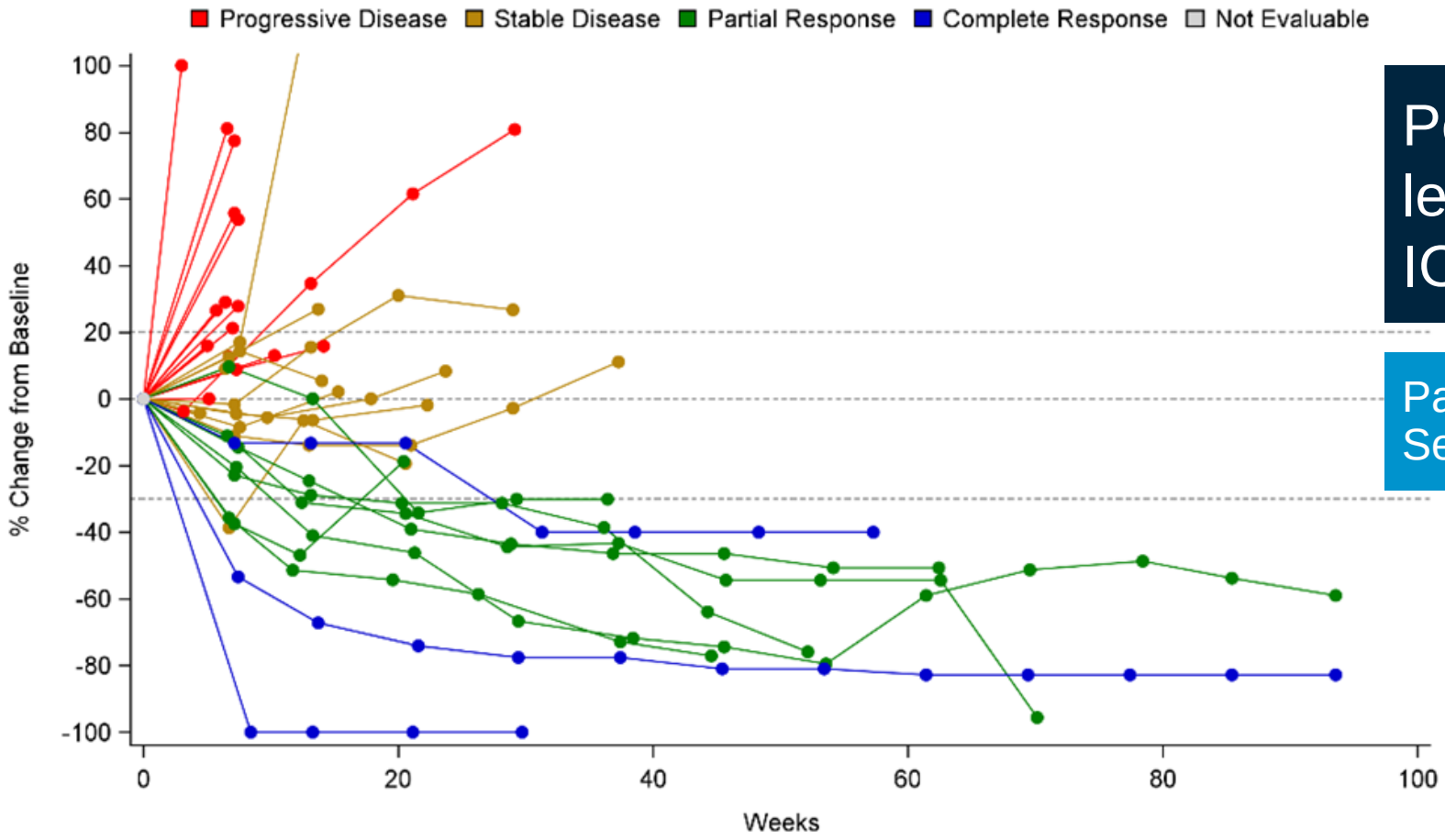
- Direct tumor target
- Tumor-associated immune cell target
- Anti-tumor activity as mono-therapy with augmented activity in combination with checkpoint inhibitors (e.g., PD1/PD-L1)

Demonstrated anti-tumor activity in humans as a monotherapy

Demonstrated promising activity in combination with the PD-L1 inhibitor durvalumab in patients with refractory head and neck cancer[2]

1. Hong et al. Science Translational Medicine, 2015; 2. Cohen et al. ESMO, 2018

Danvatirsen (IONIS-STAT3-2.5$_{Rx}$) Demonstrated Doubled Response Rate with Danvatirsen + Durvalumab vs. Durvalumab Monotherapy



Percent change in target lesions over time in 2L+ IO-naive R/M-HNSCC

Partial and complete responses in Second-line HNSCC patients

Target lesions evaluated per RECIST v1.1.

CR, complete response; IO, immuno-oncology; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; 1. Sui L, et al. Presented at: Multidisciplinary Head and Neck Cancers Symposium; February 15-17, 2018; Scottsdale, AZ [abstract 1]; 2. Zandberg DP, et al. Presented at ESMO 2017. Ann Onc. (2017) 28 (suppl_5): v372-v394. 10.1093/annonc/mdx374; 3. Ferris RL, et al. N Engl J Med. 2016;375:1858-1867; 4. Cohen E, et al. Presented at: European Society for Medical Oncology Annual Meeting; September 8-12, 2017; Madrid, Spain [abstract LBA45_PR]; 5. Cohen E, et al. Presented at: European Society for Medical Oncology Annual Meeting; October 19-23, 2018, Munich, Germany

Danvatirsen (IONIS-STAT3-2.5$_{Rx}$) as a Novel Therapeutic Strategy for Cancer

Demonstrated anti-tumor activity in humans as a monotherapy

Demonstrated a response rate of approximately double in combination with durvalumab compared to durvalumab alone in refractory head and neck cancer

- Durable partial responses
- Complete responses

Combination therapy is associated with a reduction of immunosuppressive gene expression not previously documented in patients with checkpoint inhibitors alone

Currently under further evaluation in combination with immuno-oncology agents in a range of cancer types

Potential to advance into pivotal Phase 3 studies

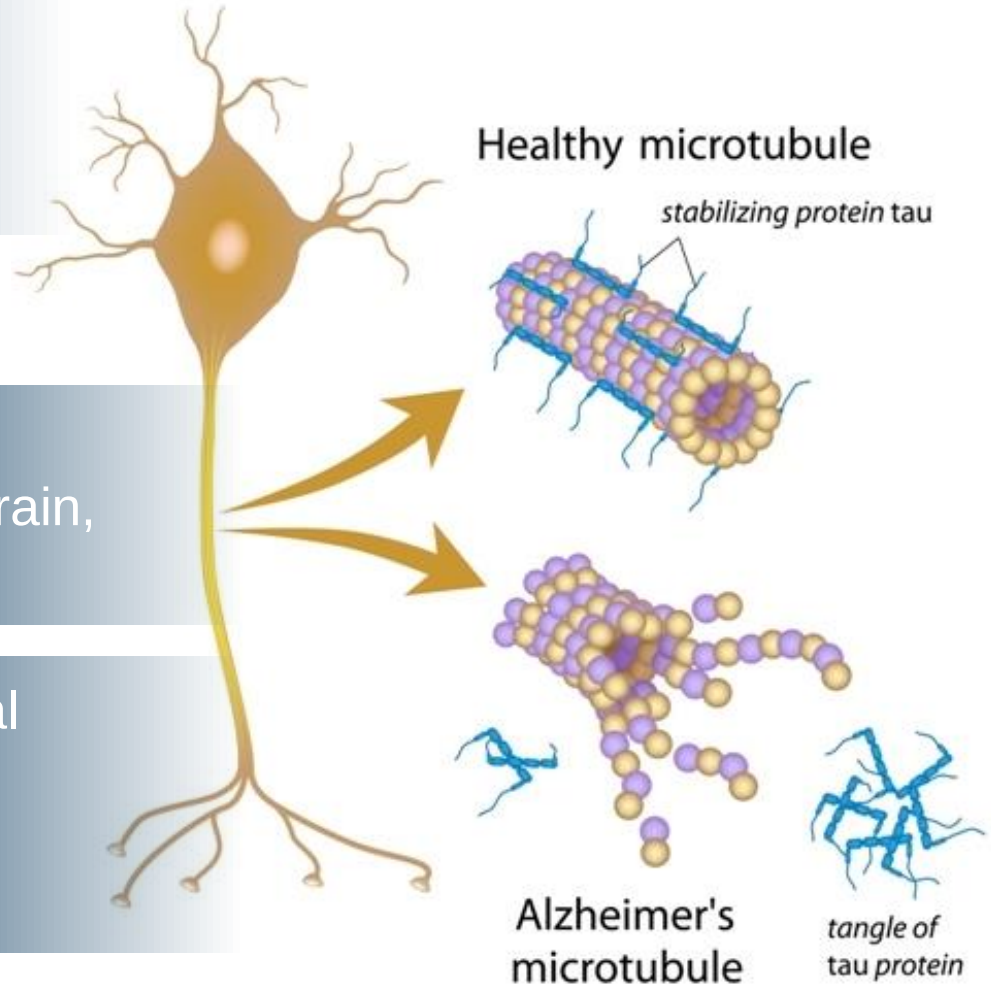
An Example of a Large-sized Patient Population: Microtubule-associated Protein Tau (MAPT)

MAPT, or tau protein, a typically unfolded and highly soluble protein is primarily found in neuronal cells

- Pathologic tau protein is believed to contribute to certain tauopathies

Tau abnormalities lead to the accumulation of toxic neurofibrillary tangles inside nerve cell bodies in the brain, the hallmark feature of tauopathies

A 50% reduction in tau prevents hippocampal neuronal loss and prevents tau pathology, yet does not lead to an adverse phenotype as seen in a transgenic mouse model of tauopathy[1,2]



Tau Protein Leads To Neuronal Death in Alzheimer's. Alzheimer's News Today (2014).

1. Morris M, Maeda S, Vossel K, Mucke L. The many faces of tau. Neuron 2011; 70: 410-426. 2. DeVos, S. L. et al. Tau reduction prevents neuronal loss and reverses pathological tau deposition and seeding in mice with tauopathy. Science Translational Medicine 9, eaag0481 (2017).

Alzheimer's Disease and Frontotemporal Dementia: Progressive, Neurodegenerative Diseases

Alzheimer's disease (AD) and frontotemporal dementia (FTD) are common forms of dementia

- AD amyloid beta (β) deposits accumulate for 20 years prior to the onset of the disease symptoms. Accumulation of pathologic tau, the other hallmark of AD pathology, appears to closely correlate with cognitive decline in AD.[1]
- FTD typically occurs following the accumulation of neuronal proteins, including tau.

AD and FTD are primarily characterized by predominant memory impairment and behavioral changes, resulting in a progressive person's inability to perform daily activities independently, and eventually death

Both diseases may manifest mid-life, at dementia onset, and progress to death in approximately 5-20 years, with FTD often showing a faster disease progression

In developed countries, approximately 1 in 10 people 65 years or older are affected by some degree of dementia[2]

- Approximately 5.5 million people are living with AD in the U.S.[3]
- Approximately 50,000 – 60,000 people are affected by FTD in the U.S.[4]

1. Huang Y and Mucke L. Alzheimer mechanisms and therapeutic strategies. Cell 2012; 148(6): 1204-1222; 2. Corrada MM, Brookmeyer R, Berlau D, et al. Prevalence of dementia after age 90: results from the 90+ study. Neurology 2008; 71(5): 337-343; 3. Latest Alzheimer's Facts and Figures. Latest Facts & Figures Report | Alzheimer's Association (2013). Available at: //www.alz.org/facts/overview.asp.; 4. Knopman DS and Roberts RO. Estimating the number of persons with frontotemporal lobar degeneration in the US population. J Mol Neurosci 2011; 45: 330-335

IONIS-MAPT$_{Rx}$ (BIIB080) Phase 1/2 (ongoing)

A double-blind, randomized, placebo-controlled study in patients with mild AD aged 50-74 years

Up to 44 patients
Evaluating 4 different dose levels

Objectives

- Assess safety and tolerability of ascending dose-levels of IONIS-MAPT$_{Rx}$ (BIIB080)
- Evaluate the exploratory effects of IONIS-MAPT$_{Rx}$ (BIIB080) on CSF levels of total tau protein
- Phase 2/3 study planned in frontotemporal dementia

Phase 1/2 data expected 2020

More Than 10 Exciting Medicines with the Potential to Enter Pivotal Programs in the Next 2 Years

MEDICINE	INDICATION	PARTNER
IONIS-HTT$_{Rx}$	Huntington's disease	Roche
AKCEA-APO(a)-L$_{Rx}$	Cardiovascular disease	Novartis
AKCEA-TTR-L$_{Rx}$	Transthyretin amyloidosis	Akcea / Ionis
IONIS-SOD1$_{Rx}$	Amyotrophic lateral sclerosis	Biogen
IONIS-HBV$_{Rx}$/IONIS-HBV-L$_{Rx}$	Hepatitis B virus infection	GSK
Danvatirsen (IONIS-STAT3-2.5$_{Rx}$)	Cancer	AstraZeneca
AKCEA-APOCIII-L$_{Rx}$	Cardiovascular disease	Novartis
IONIS-MAPT$_{Rx}$	Alzheimer's disease/ Frontotemporal dementia	Biogen
IONIS-FXI$_{Rx}$/IONIS-FXI-L$_{Rx}$	Clotting disorders	Bayer
AKCEA-ANGPTL3-L$_{Rx}$	Non-alcoholic fatty liver disease	Akcea / Ionis
IONIS-GHR-L$_{Rx}$	Acromegaly	Ionis
IONIS-TMPRSS6-L$_{Rx}$	β-thalassemia	Ionis

Conclusions

We have systematically constructed a large, innovative, balanced pipeline of first-in-class medicines

The pipeline is mature with >10 medicines with the potential to enter pivotal programs in the next 2 years

We have integrated advances in our technology rapidly to enhance the performance of our medicines in development

We are using multiple routes of administration and our medicines work in multiple organs for a large range of diseases

We are expanding our overall and Ionis-owned pipelines

We have enormous potential to increase value in the near- to mid-term

Ionis' Financial Strength

Positioned for Continued Growth and Sustained Profitability

Beth Hougen
Chief Financial Officer

Ionis is a Commercial Stage Company Positioned for Strong Revenue and Earnings Growth in the Near-, Mid- and Longer-term

Key Takeaways

Commercial revenues are **growing** and becoming a **larger** portion of our revenue

R&D revenues are **substantial** and are expected to **grow**

Sustained earnings growth driven by **growing** commercial and R&D revenues

Strong financial foundation to drive value creation

Q3 2018 YTD Financials

$25 million in operating income*

More than **15% increase** in revenue over 2017

*Pro forma – please see reconciliation to GAAP in 3Q18 press release

Q3 2018 YTD Financials

$408 million
in revenue

Nearly three-fold increase in SPINRAZA® revenues over 2017

SPINRAZA® (nusinersen) injection 12 mg/5 mL

Q3 2018 YTD Financials

$168 million in

royalties

Ionis' Financial Strength Continues in 2018

On track to exceed 2017 revenues of $508 million; 7th consecutive year of growth

On track to achieve third consecutive year of **operating income**

On track to finish with nearly **$2 billion** in cash; **cash accretive** for six out of the last seven years.

Commercial Revenue has Potential to Drive Sustained Earnings Growth

Revenue from high value products = **high margins**

Revenue from royalties

Tegsedi™ (inotersen) injection 284 mg/1.5 mL

waylivra™ (volanesorsen sodium) Injection 300mg in 1.5mL

R&D revenue funds non-commercial expenses

Sustained earnings growth

Commercial Revenue has Potential to Drive Sustained Earnings Growth

Revenue from high value products = **high margins**

Revenue from royalties ≈ **100% profit**

SPINRAZA® (nusinersen) injection 12 mg/5 mL

Non-commercial expenses

Multiple New Medicines

Sustained earnings growth

Substantial R&D Revenues Continuing to Drive Earnings Growth

- AstraZeneca
- Bayer
- Biogen
- GSK

Revenue from high-value products
≈ **high margins**

- J&J/Janssen
- Novartis
- Roche

Revenue from royalties
≈ **100% profit**

R&D revenue funds non-commercial expenses

Sustained earnings growth

Commercial and R&D Revenue has Potential to Drive Sustained Earnings Growth

Revenue from high value products = **high margins**

+

Revenue from royalties ≈ **100% profit**

+

R&D revenue funds non-commercial expenses

=

Sustained earnings growth

Growing commercial revenue building on a substantial base of R&D revenue

Ionis: Driving Growth by Continuing to Deliver Transformational Medicines to People in Need

POSITIONED FOR SUBSTANTIAL GROWTH

DRIVEN BY

SPINRAZA® (nusinersen) injection 12 mg/5 mL

Tegsedi™ (inotersen) injection 284 mg/1.5 mL

waylivra™ (volanesorsen sodium) Injection 300mg in 1.5mL

R&D Revenue

Ionis: Driving Growth by Continuing to Deliver Transformational Medicines to People in Need

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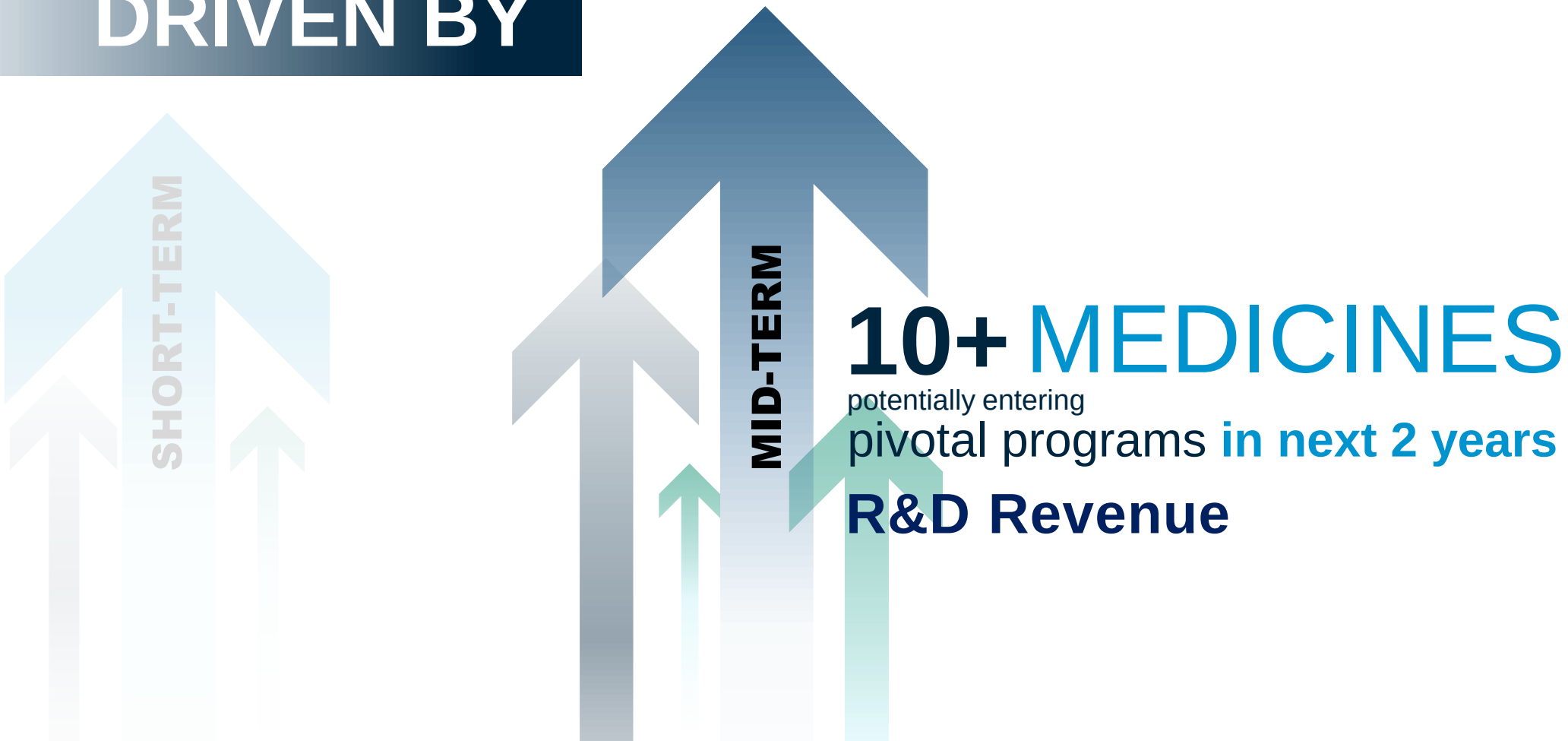


10+ MEDICINES
potentially entering
pivotal programs **in next 2 years**

R&D Revenue

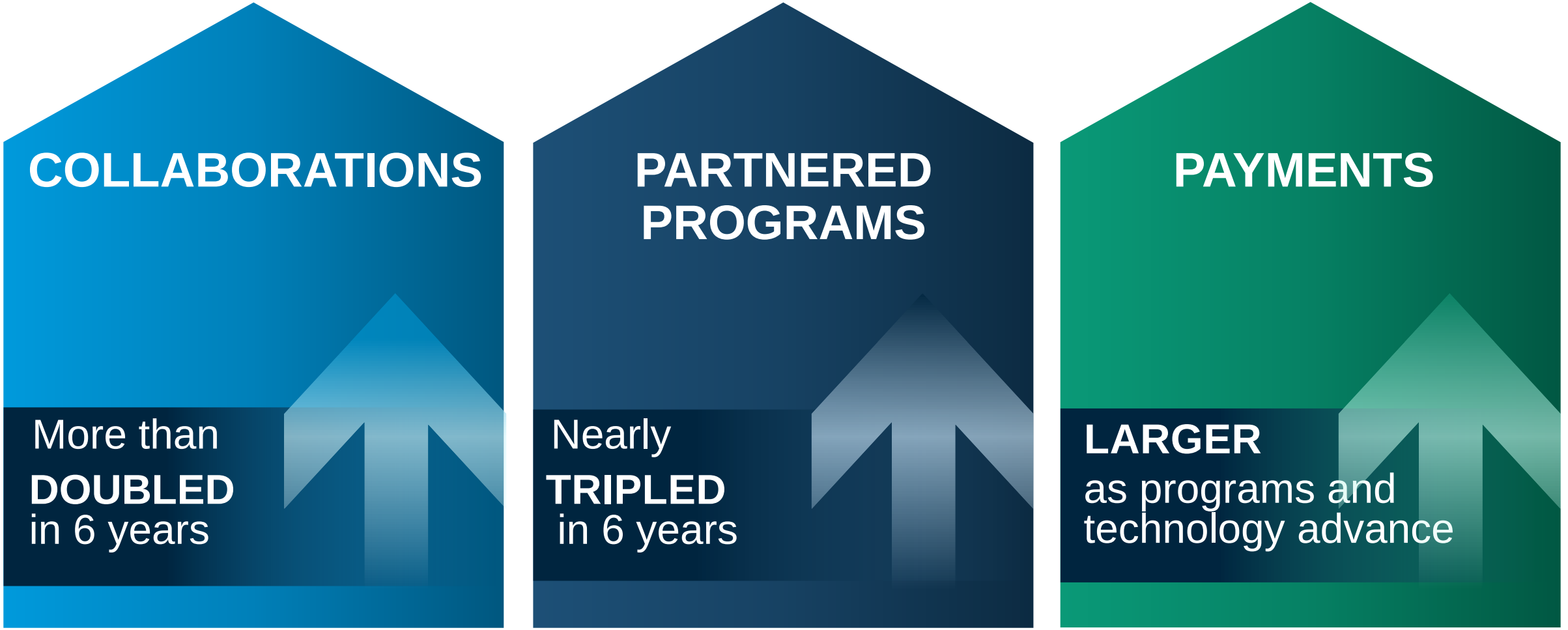
Ionis: Driving Growth by Continuing to Deliver Transformational Medicines to People in Need

POSITIONED FOR SUBSTANTIAL GROWTH

DRIVEN BY

Maximizing success, optimizing commercial value for each of our medicines

Three Key Drivers of R&D Revenue Growth



Potential for Substantial Revenue and Earnings Growth

Multiple New Medicines

TOTAL REVENUE

SPINRAZA® (nusinersen) injection 12 mg/5 mL
R&D Revenue

Tegsedi™ (inotersen) injection 284 mg/1.5 mL

SPINRAZA® (nusinersen) injection 12 mg/5 mL
R&D Revenue

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R&D Revenue

waylivra™ (volanesorsen sodium)

Tegsedi™ (inotersen) injection 284 mg/1.5 mL

SPINRAZA® (nusinersen) injection 12 mg/5 mL
R&D Revenue

TIME

Growing revenues with prudent expense management – sustained earnings growth

Strong Financial Foundation to Drive Value Creation

~$2 billion in cash

ENABLING INVESTMENT
in commercial products, pipeline and technology advancements

- **Continue to advance and expand our pipeline**
- **Focus on growing our Ionis-owned pipeline**
- **Continue to advance our technology**
- **Invest in new commercial affiliates**

Ionis Delivering Value Today and in the Future

Stanley Crooke, M.D., Ph.D.
Chief Executive Officer & Chairman

The Ionis Business Model: A Response to Declining Productivity in the Drug Discovery and Development Industry

Origin

Evidence of a Similar Successful Approach

Evidence that the Ionis Business Model is Working Today

The Ionis Business Model: Delivering Value Today and in the Future

Key Takeaways

1 **Innovation and productivity in the drug discovery and development industry has been declining for decades**

2 **Ionis was built to respond to the decline in innovation and productivity**

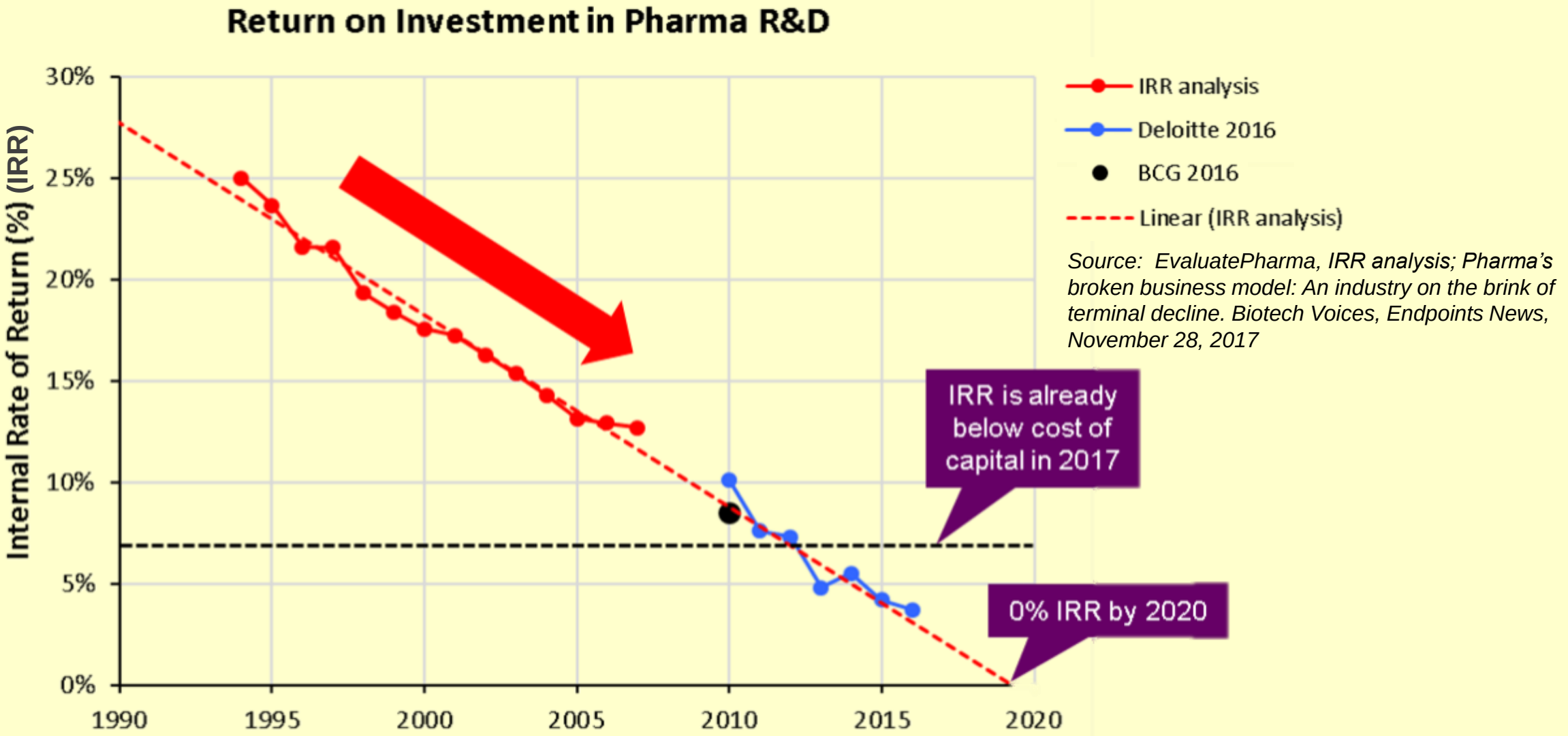
- More efficient drug discovery and development platform
- Innovation centered business model
- Optimal organization selected to develop and commercialize each medicine in the Ionis pipeline

3 **Ionis' business model recreates biotech model on a smaller scale**

4 **Ionis' business model coupled with more efficient antisense technology results in significant competitive advantage that will increase with time**

5 **Ionis is delivering value today and plans to deliver even greater value going forward**

Decline in Productivity in the Pharmaceutical Industry



Source: EvaluatePharma, IRR analysis; Pharma's broken business model: An industry on the brink of terminal decline. Biotech Voices, Endpoints News, November 28, 2017

Major Contributors to Declining Productivity in the Pharmaceutical Industry (1 of 2)

Failure to invest productively in new, more efficient drug discovery technologies

No more “low-hanging fruit”

- Acute and sub-acute diseases generally well cared for
- Focus on chronic diseases

Substantial increases in regulatory demands

- Requirement for outcomes studies

Major Contributors to Declining Productivity in Pharma: The Fully Integrated Pharmaceutical Company (FIPCO) Model (2 of 2)

Large size and complexity of big pharma organizations coupled with

- High failure rates
- Long product development cycles
- Size and complexity of most product development activities

A single conduit for products to move from discovery to commercialization

Net impact: Substantial contribution to the decline in innovation and productivity

The Biotechnology Model: A Response to the Decline in FIPCO Productivity

Biotechnology Model Thesis

- A distributed set of investments with a wide range of investment risks and risk tolerance, approaches and timelines would lead to more innovation and productivity

Result of Biotechnology Model

- Highly efficient, requiring fewer resources to achieve greater innovation and productivity compared to FIPCOs
- All new drug discovery platforms came from nascent biotechnology companies
- Most first-in-class breakthrough medicines have been derived from biotechnology companies
- Progressive externalization of FIPCO R&D (innovation “buyers” instead of innovators)

Net impact: Substantial and sustained increase in innovation and productivity

Successful Biotech Companies Become FIPCOs

Result of successful biotech companies becoming FIPCOs

- Explosive growth in size and complexity of organization
- Productivity and innovation rapidly decline
- Become ***innovation buyers*** instead of ***primary innovators***

Ionis Business Model Recreates the Biotechnology Model on a Smaller Scale

Couple a novel, more efficient drug discovery technology (antisense) to an innovation-centered business model

- Maintain a small, focused, simple organization driven by innovation
- Select the optimal organization to develop and commercialize each medicine in the Ionis pipeline

Net impact: Substantial and sustained increase in innovation and productivity

Competitive Advantages of Antisense Technology

Competitive Advantages of Antisense

MOST DIRECT ROUTE FROM GENE TO PATIENT	RAPID PATH THROUGH PRECLINICAL DEVELOPMENT	RAPID, MORE SUCCESSFUL PATH THROUGH CLINICAL POC
▪ Rapid, efficient target validation ▪ Rapid, efficient drug identification for animal studies	▪ Advanced chemical synthesis processes serve all antisense medicines ▪ Predictable therapeutic index within chemical classes ▪ Consistent potency within chemical classes	▪ Shared clinical properties ▪ Rapid, straight-forward Phase 1 studies ▪ ~90% success rate to clinical POC studies*
Rapid, efficient, cost-effective drug discovery	**Rapid, efficient, cost-effective preclinical development**	**Far more efficient development**

Large and growing commercial opportunities

** Based on internal company data for programs that enter a phase 1 clinical study*

Time and Cost of Antisense Drug Development: An Example Comparing Ionis to Industry Average

CARDIO-METABOLIC PROGRAM	
IONIS	**TRADITIONAL**
~10 scientists	**>100** scientists
1-2 novel medicines enter development per year	**1 novel medicine** to enter development per decade

Ionis is highly productive with very efficient use of resources

The Antisense Advantage: The Ionis Business Model and Technology Result in Proven, Efficient Platform for Creating New Medicines

Ionis

1 medicine / 10 employees

Traditional Pharma

1 medicine / >1,000 employees

2018 Ionis-Biogen Strategic Collaboration: Increased Value of Ionis' Antisense Technology Resulting in Superior Economics

	PREVIOUS BIOGEN COLLABORATION (Sept 2013)	NEW BIOGEN COLLABORATION (April 2018)
Upfront payment	$100M	$1B*
Research term	6 years	10 years
Option timing	After clinical proof-of-concept	At IND filing
Additional payments per typical program	$230M	$270M
Royalty rate	Low- to mid-teens	Mid-teens to twenty

One of the Largest Research-stage Collaborations in History

**Includes $625 million for Ionis stock at 25% cash premium*

Advantages of the Ionis Business Model

Advantages of the Ionis Business Model

Multiple sources of revenue

- Financial foundation to build a large, Ionis-owned pipeline, and invest in commercial activities
- A significant buffer to the risks inherent in our business

Partners' expertise and resources leveraged to maximize success and value

Supports a large, growing and mature pipeline

Optimal organization selected to develop and commercialize each medicine in the Ionis pipeline

Financial Foundation to Invest in Value Creation

~$2 billion in cash

ENABLING INVESTMENT
in commercial products, pipeline and technology advancements

- **Continue to advance and expand our pipeline**
  - **Focus on growing our Ionis-owned programs**
- **Continue to advance our technology**
  - **New commercial affiliates**

The Ionis Business Model: Maximizing Value by Matching Each Medicine to the Optimal Development and Commercialization Strategy

Early–Mid Stage COLLABORATIONS

- Expertise and experience from partner could provide increased likelihood of success
- Significant technical/target risk
- Complex, difficult, expensive Phase 2 and Phase 3 programs

Biogen
Neurodegenerative Diseases

AstraZeneca
Cancer
Cardiometabolic / Renal

Early–Mid Stage LICENSE

- Complex, large, expensive Phase 3 development
- Multiple indications adds to complexity
- Large patient population
- Large marketing and sales effort
- Partner adds clinical and therapeutic expertise

Roche
IONIS-FB-L_{Rx}

Bayer
IONIS-FXI$_{Rx}$
IONIS-FXI-L_{Rx}

COMMERCIALIZE VIA AFFILIATES

- Clear path to approval
- Low to moderate total development costs
- Potential for initial rare disease opportunity
- Consistent with Ionis intellectual franchises

TEGSEDI
WAYLIVRA

Akcea
AKCEA-APOCIII-L_{Rx}
AKCEA-APO(a)-L_{Rx}
AKCEA-ANGPTL3-L_{Rx}
AKCEA-TTR-L_{Rx}

Ionis' Business Model Enables Partnering at the Optimal Time and Developing Medicines for Our Own Account

IONIS-OWNED PIPELINE

MEDICINES	INDICATION	PC	PHASE I	PHASE II	PHASE III	REGISTRATION	COMMERCIAL
TEGSEDI™(inotersen)	hATTR						
WAYLIVRA™(volanesorsen)	FCS						
WAYLIVRA™(volanesorsen)	FPL						
IONIS-GHR-L_{Rx}	Acromegaly						
AKCEA-ANGPTL3-L_{Rx}	NAFLD/Metabolic Complications						
IONIS-$DGAT2_{Rx}$	NASH						
IONIS-$GCGR_{Rx}$*	Diabetes						
IONIS-AR-2.5_{Rx}	Cancer						
IONIS-TMPRSS6-L_{Rx}	β-Thalassemia						
IONIS-PKK-L_{Rx}	HAE						
IONIS-AGT-L_{Rx}	Treatment-Resistant Hypertension						
IONIS-TTR-L_{Rx}	ATTR						
IONIS-ENAC-2.5_{Rx}	Cystic Fibrosis						
IONIS-IRF4-2.5_{Rx}	Cancer						
IONIS-EZH2-2.5_{Rx}	Cancer						
IONIS-$GFAP_{Rx}$	Alexander's Disease						

SEVERE AND RARE

CARDIOMETABOLIC AND RENAL

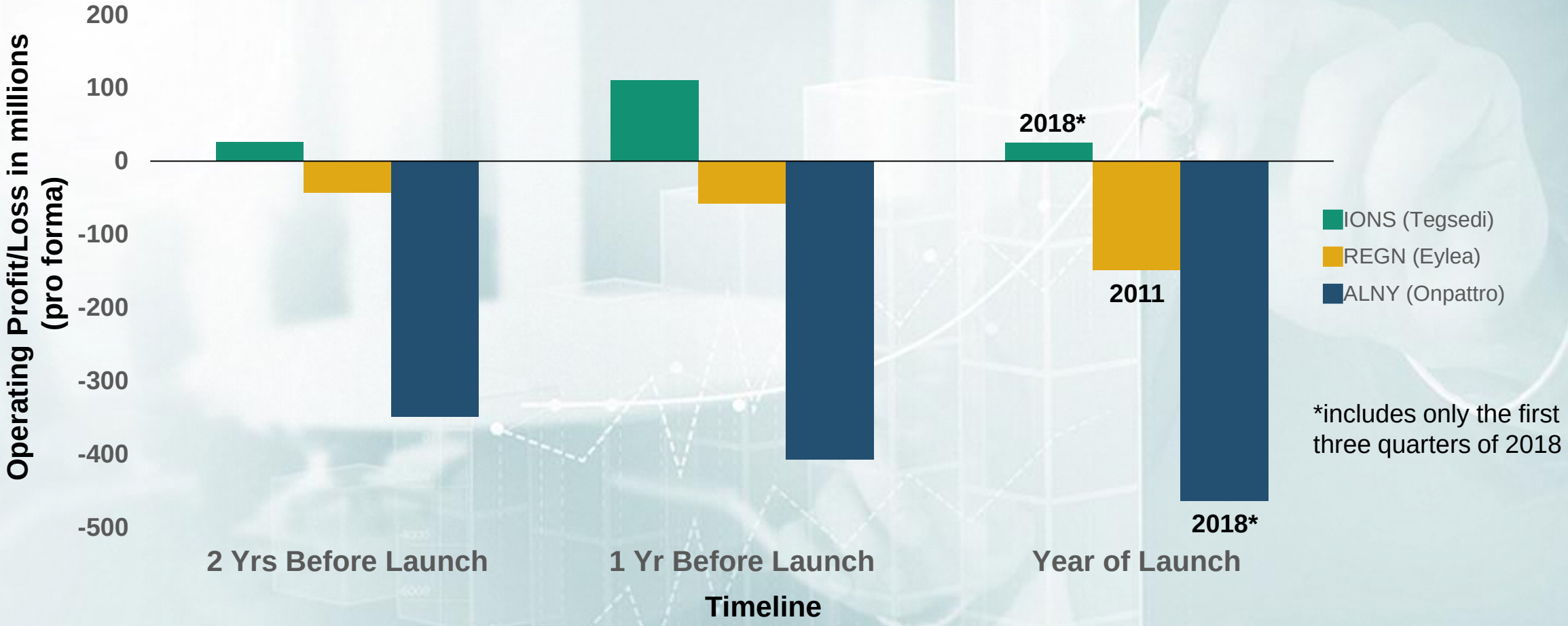
ONCOLOGY

NEURO

*Licensed in China

The Ionis Business Model: Proof it is Working

Ionis is profitable and cash accretive while launching two new medicines and advancing a pipeline of over 45 medicines in development and continuing to advance the technology



*includes only the first three quarters of 2018

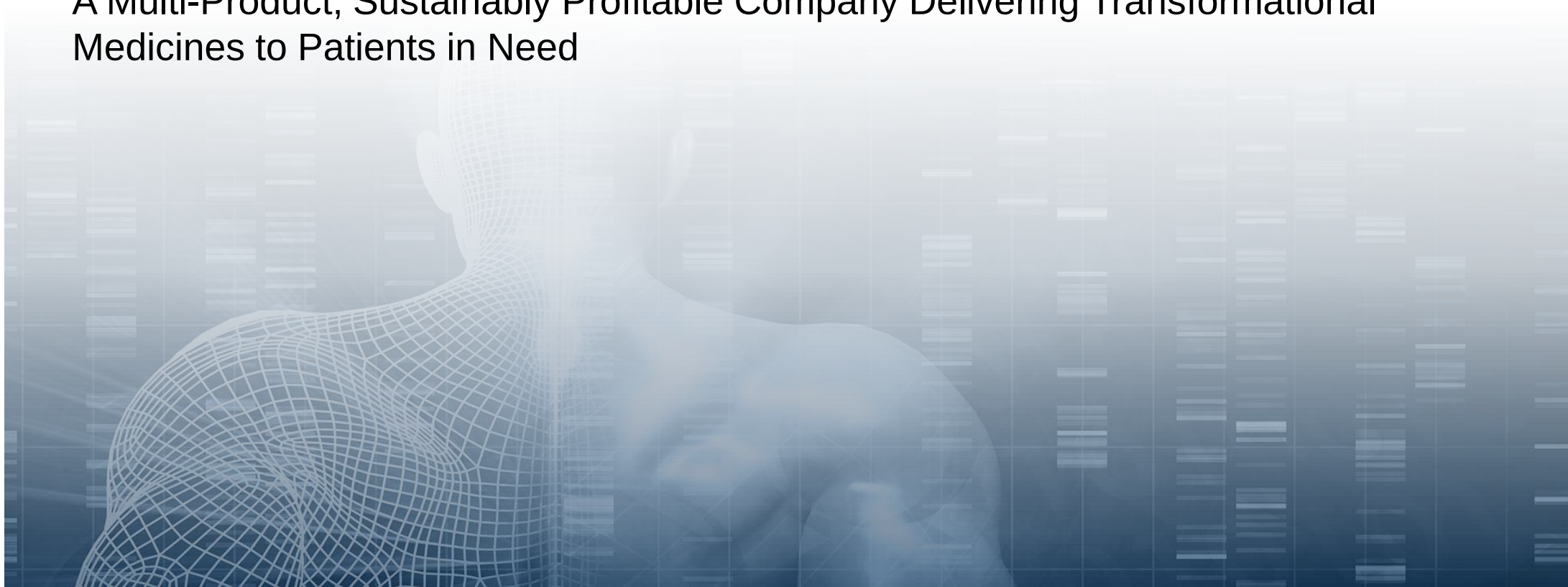
Source: company annual earnings reports and press releases

The Result: Greater Productivity Driven by the Business Model and Antisense Technology to Develop Better Medicines

Greater Efficiency	Fewer employees per medicine, predictable efficacy and safety profiles and consistent manufacturing across medicines results in less time and lower cost to develop each medicine
Higher Success Rate	Consistent efficacy and safety profiles lead to higher probability of success from preclinical through proof-of-concept
Increasing Innovation	Our technology platform and pipeline of medicines continues to advance and improve
Greater Competitive Advantage	We select the optimal organization to develop and commercialize each medicine and leverage their resources and expertise

The Future of Ionis

A Multi-Product, Sustainably Profitable Company Delivering Transformational Medicines to Patients in Need



Drivers of Stock Price Growth in the Next 4 Years: Potential for Significant Accretion in Shareholder Value

MEET or EXCEED expectations on TEGSEDI

SUCCESSFULLY LAUNCH WAYLIVRA assuming approval

ADVANCE a significant number of medicines into Phase 3 and beyond

DEMONSTRATE we can consistently deliver safe, effective and well-tolerated medicines

CONTINUE to tangibly advance the technology

CONSISTENTLY GROW profits while investing aggressively in our future

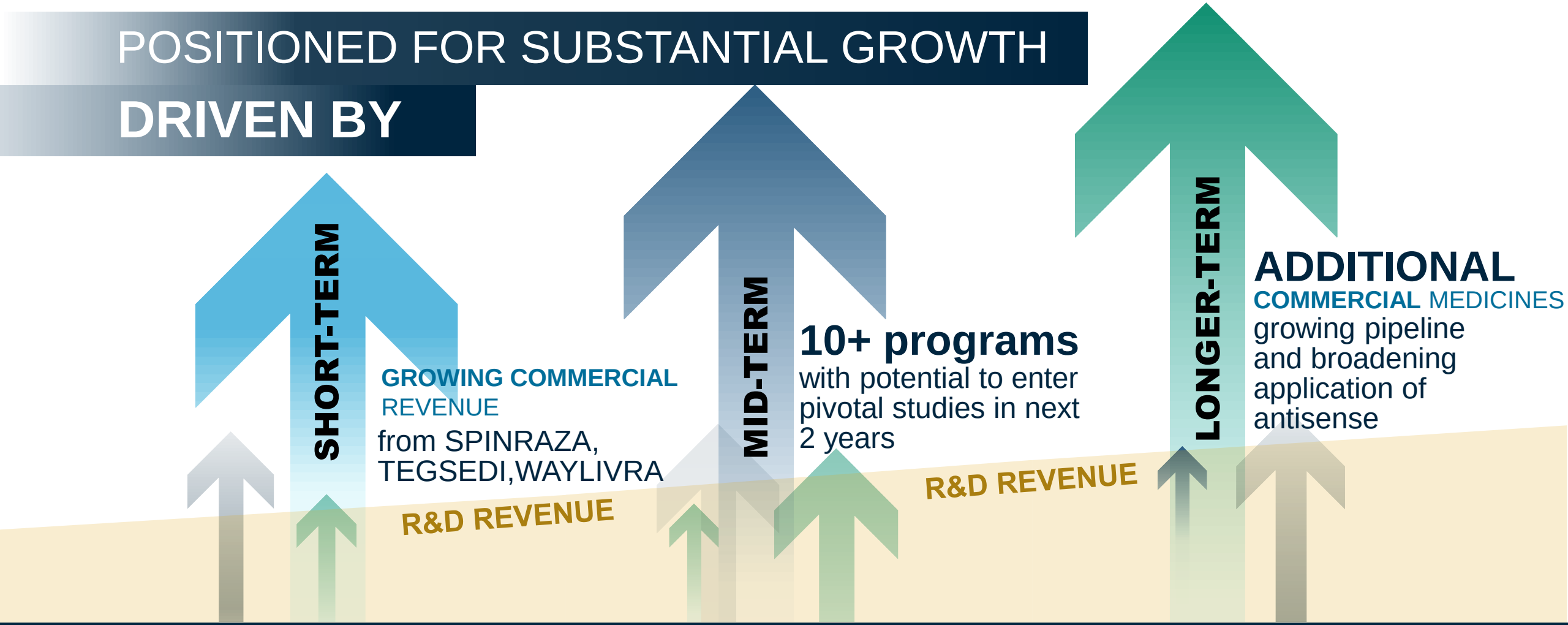
Numerous Phase 3 Opportunities in 2018 – 2020

MEDICINE	INDICATION	PARTNER
IONIS-HTT$_{Rx}$	Huntington's disease	Roche
AKCEA-APO(a)-L$_{Rx}$	Cardiovascular disease	Akcea / Novartis
AKCEA-TTR-L$_{Rx}$	Transthyretin amyloidosis	Akcea / Ionis
IONIS-SOD1$_{Rx}$	Amyotrophic lateral sclerosis	Biogen
IONIS-HBV$_{Rx}$/IONIS-HBV-L$_{Rx}$	Hepatitis B virus infection	GSK
Danvatirsen (IONIS-STAT3-2.5$_{Rx}$)	Cancer	AstraZeneca
AKCEA-APOCIII-L$_{Rx}$	Cardiovascular disease	Akcea / Novartis
IONIS-MAPT$_{Rx}$	Alzheimer's disease/ Frontotemporal dementia	Biogen
IONIS-FXI$_{Rx}$/IONIS-FXI-L$_{Rx}$	Clotting disorders	Bayer
AKCEA-ANGPTL3-L$_{Rx}$	Non-alcoholic fatty liver disease	Akcea / Ionis
IONIS-GHR-L$_{Rx}$	Acromegaly	Ionis
IONIS-TMPRSS6-L$_{Rx}$	β-thalassemia	Ionis

Ionis: A Multi-Product, Sustainably Profitable Company Delivering Transformational Medicines to Patients in Need

POSITIONED FOR SUBSTANTIAL GROWTH

DRIVEN BY



Maximizing success, optimizing commercial value for each of our medicines

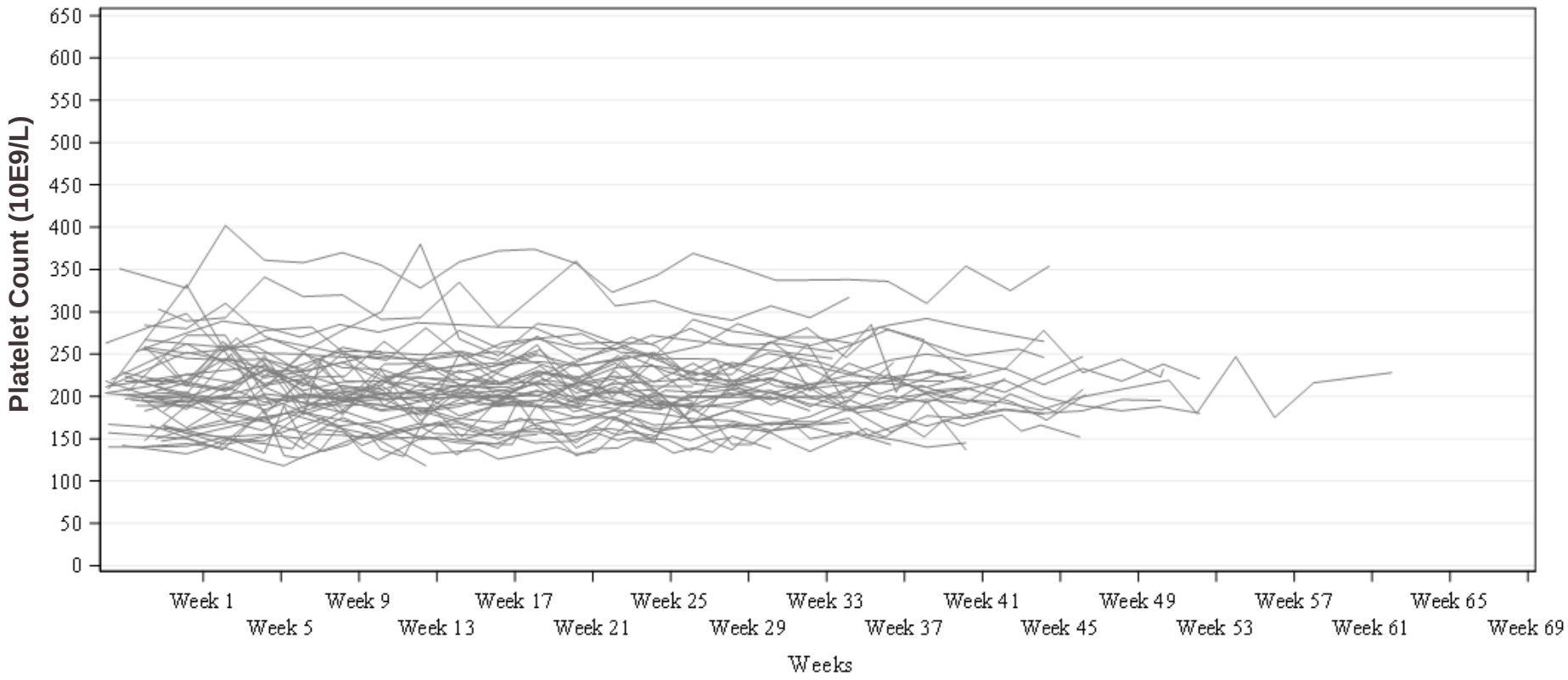
Final Q&A

Revolutionizing Medicine. Saving Lives.

IONIS™
PHARMACEUTICALS

Appendix

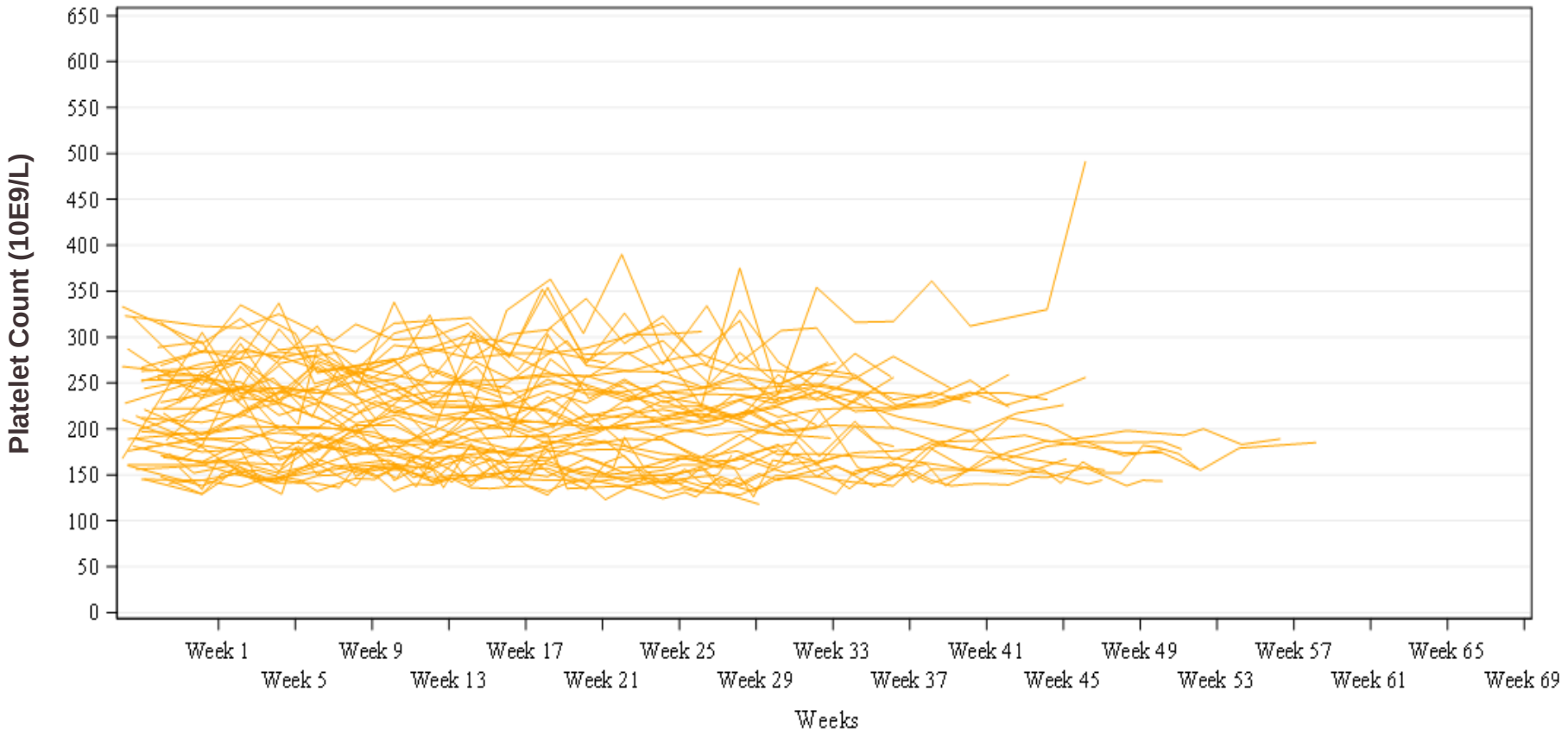
No Effect in Platelet Levels with Placebo in AKCEA-APO(a)



No platelet levels below 100,000mm^3

No Significant Changes in Platelet Levels in AKCEA-APO(a)

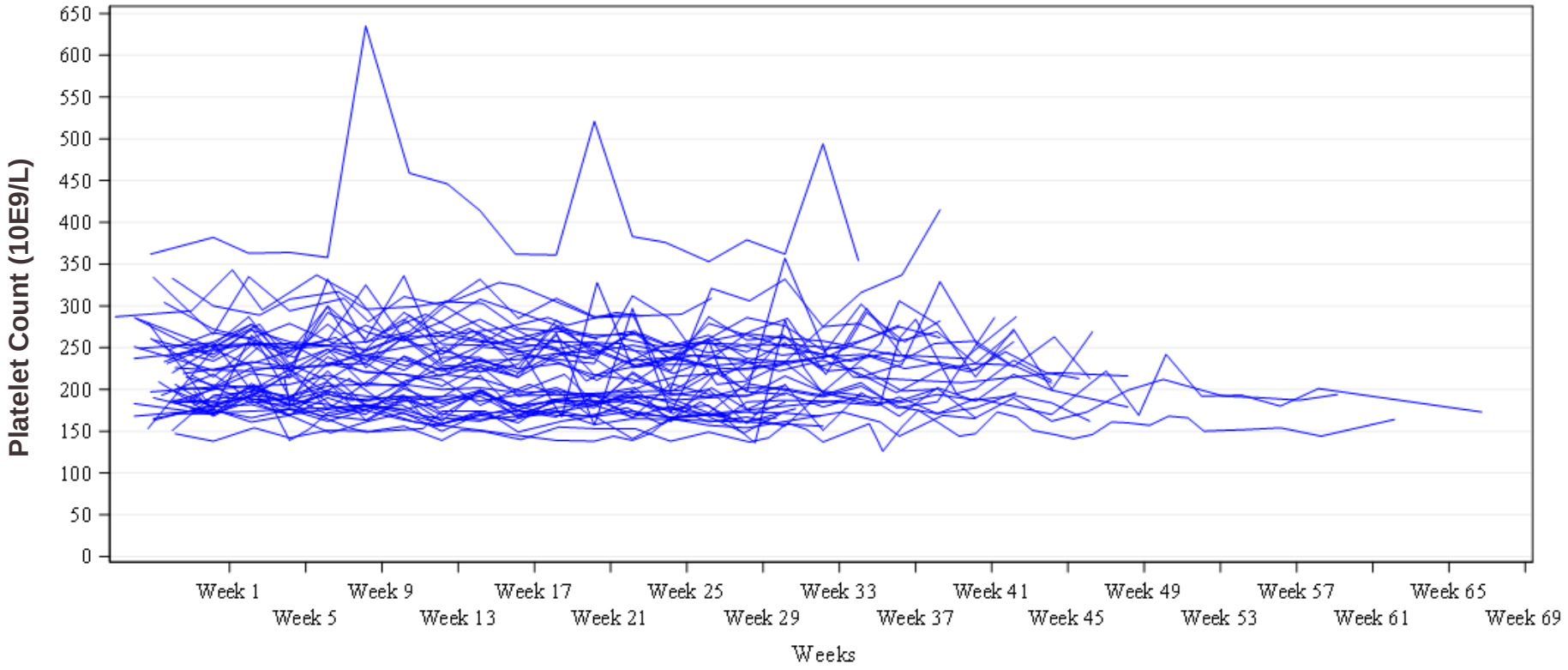
Platelet Levels with 20mg/week dose in AKCEA-APO(a) Counts Over Time



No platelet levels below 100,000mm^3

No Significant Changes in Platelet Levels in AKCEA-APO(a)

Platelet Levels with 60mg/month dose in AKCEA-APO(a) Counts Over Time



No platelet levels below 100,000mm^3