Neurological Disease Pipeline Webcast

Forward Looking Language Statement

This presentation includes forward-looking statements regarding our business, financial guidance and the therapeutic and commercial potential of SPINRAZA® (nusinersen), 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, 2018, which is 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.

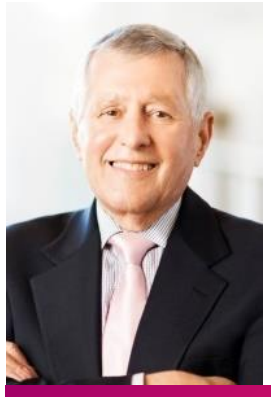
IONIS

Ionis: The Leader in RNA-Targeted Therapeutics

Stanley Crooke, M.D., Ph.D.

Chief Executive Officer and Chairman

Today's Presenters



Stanley Crooke, M.D., Ph.D.
CEO and Chairman
Ionis Pharmaceuticals

C. Frank Bennett, Ph.D.
SVP Research
Ionis Pharmaceuticals

Brett Monia, Ph.D.
Chief Operating Officer
Ionis Pharmaceuticals

Eric Swayze, Ph.D.
VP, Chemistry & Neurological Drug Discovery
Ionis Pharmaceuticals

Holly Kordasiewicz, Ph.D.
ED, Neurological Drug Discovery
Ionis Pharmaceuticals

Merit E. Cudkowicz, M.D.
Mass General
Chief of Neurology

IONIS

Today's Agenda

Welcome and Introductions	Wade Walke
Ionis – The Leader in RNA-Targeted Therapeutics	Stan Crooke
The Impact of Antisense on the Treatment of Neurological Diseases	Merit Cudkowicz
Ionis – Drug Discovery and Development Leaders in Neurological Diseases	Frank Bennett
SPINRAZA – The Standard of Care for SMA	Frank Bennett
TEGSEDI – Now the Medicine of Choice for Many People with hATTR PN	Brett Monia
Tofersen (IONIS-SOD1$_{Rx}$) & BIIB078 (IONIS-C9$_{Rx}$) Potential Breakthrough Medicines for ALS	Frank Bennett
IONIS-HTT$_{Rx}$ (RG6042) Potential Breakthrough Medicine for Huntington's Disease & IONIS-MAPT$_{Rx}$ a Potential Breakthrough Medicine for Alzheimer's and Frontotemporal Dementia	Holly Kordasiewicz
Next Neurodegenerative Transformative Medicines	Eric Swayze
Ionis – Delivering Value Today and in the Future	Stan Crooke
Q&A	All

Ionis: Purposefully Designed to Maximize Value for Patients and Shareholders

- Create a better, more efficient drug discovery platform
- Leader in new, innovation-centered business model
- Maximize value of each medicine; implement optimal commercialization strategy

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Ionis: The Leader in RNA-Targeted Therapeutics

- **Antisense:** A novel and more efficient drug discovery platform
- **Rapidly** incorporate the advances in the technology into our pipeline
- **Focusing** on bringing maximum value to the patients who need it the most
- **Focus** on the truly novel molecular targets that revolutionize therapy
- **Constantly** expand and advance our pipeline in both rare and common diseases
- **Continuing** to retain an ever greater fraction of commercial revenues

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Ionis: Delivering Sustained Revenue Growth Driven by a Pipeline of Transformative Medicines

Pioneer of **RNA** technology

Novel business model

Culture of **YES**

30 years advancing technology

Ever-**better** performance

Greater commercial opportunities

3 commercial medicines

40+ in development

10+ phase 3 potentially in **2020**

4+ phase 3 planned in **2019**

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Ionis' Antisense is Emerging as the Dominant Drug Discovery Platform for Neurological Diseases

- **Our** technology is broadly enabling and has been validated in the clinic and commercially
- **We** are continuing to advance our technology for neurological diseases
- **We** have discovered and developed two breakthrough commercial medicines
- **We** have advanced a large pipeline of medicines for rare and common neurological diseases that continues to grow
- **Ionis-owned** neurological pipeline is growing and exciting

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Chief of Neurology

Merit E. Cudkowicz, M.D.

Massachusetts General Hospital

Tremendous Unmet Need in Neurology for Effective Therapies

- Neurological Disorders account for major mortality and morbidity globally
- First time addressing this need with transformative medicines
- **Huge Leap Forward in Treating Neurological Disorders**
- Spinal Muscular Atrophy (SMA) - enormous impact
- Amyotrophic Lateral Sclerosis (ALS)
  - We now have biological targets in familial and sporadic ALS that can be modified in people
  - This is extraordinary
  - No longer will be considered untreatable

IONIS™

Targeted Approaches to Neurogenerative Disorders Such as ALS, HD, PD and AD Have a High Chance of Success

- Ionis has a targeted approach to many neurological diseases
  - ALS: SOD1, C9
  - Huntington's Disease, Parkinson's Disease, Alzheimer's Disease, Spinal Cerebellar Ataxias & Frontotemporal Dementias
  - Several medicines in discovery to address the sporadic form of these diseases
- We now can identify genetically those targets that drive the disease process
- Targeting the cause of disease upstream has a much higher probability of success
- We can also start to think about prevention of disorders

IONIS™

Ionis: Leading the Discovery and Development of Medicines to Treat Neurological Diseases

C. Frank Bennett, Ph.D.

Senior Vice President of Research

IONIS

Neurological Disease Drug Discovery and Development Strategy

- **Identify** the cell types and brain regions of the nervous system in which antisense medicines work
  - **Result:** Antisense shown to work well in all cell types and most brain regions

- **Focus** on bringing the highest value to patients with the greatest need
  - **Identify** the optimal organization to develop and commercialize each of our medicines to get them to patients as quickly as possible

- **Leverage** our partners expertise and resources to enhance our capabilities

- **Expand** our Ionis-owned pipeline of medicines for neurological disease by selecting **novel** targets with the potential to **revolutionize** treatment

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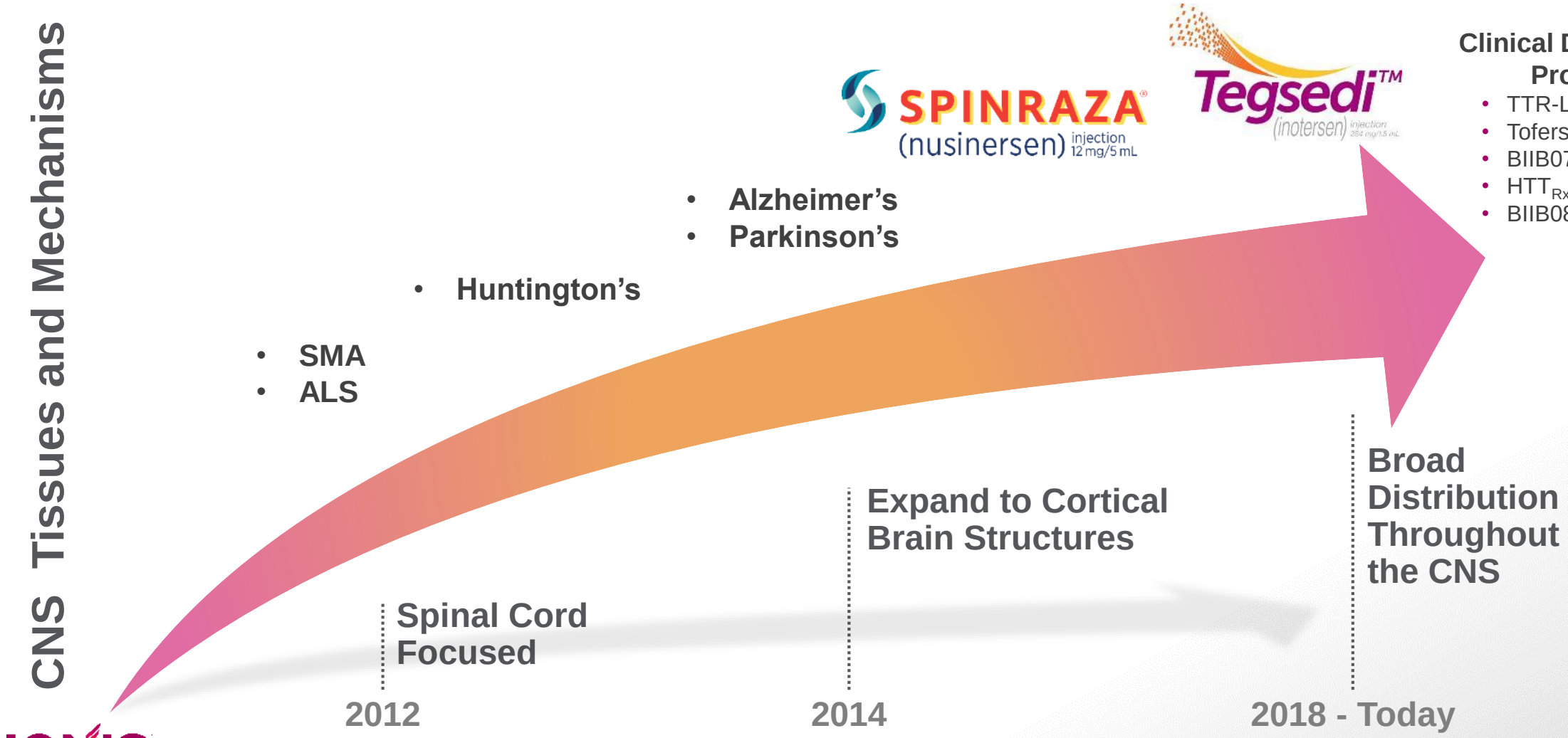
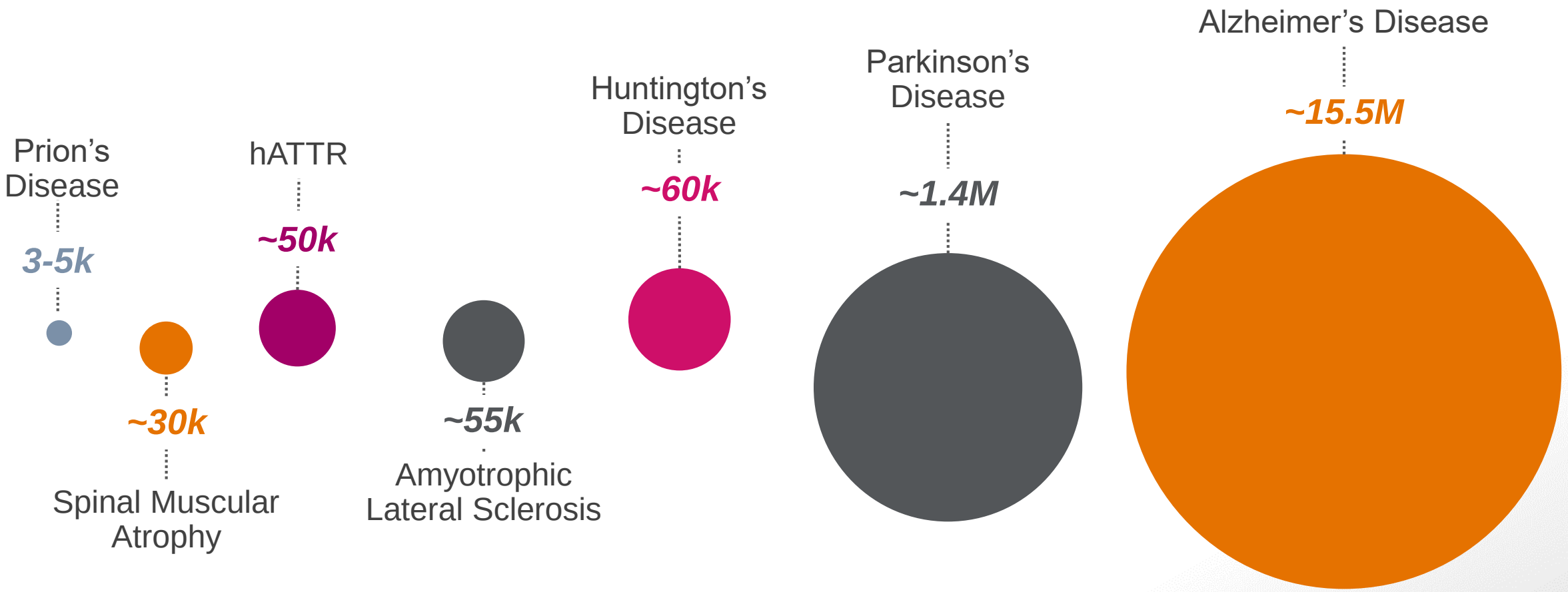
Significant Growth in Understanding CNS Distribution and Mechanisms of Action of Antisense Medicines



Advances in Knowledge Support Expanding Antisense Medicines to Common Diseases



Ionis' Antisense Optimized the Platform for Neurological Diseases

- **Address** previously undruggable targets
- **Broad** distribution throughout the CNS
- **Activity** in all major brain regions
- **Activity** in all CNS cell types (e.g. neurons, astrocytes, microglia, oligodendrocytes)
- **Durable** effects in the CNS
- **Favorable** safety and tolerability profile in the CNS
- **Continuous** advancement in our technology

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Ionis Programs Highlighted at AAN Covering All Major Brain Regions and Central Nervous System

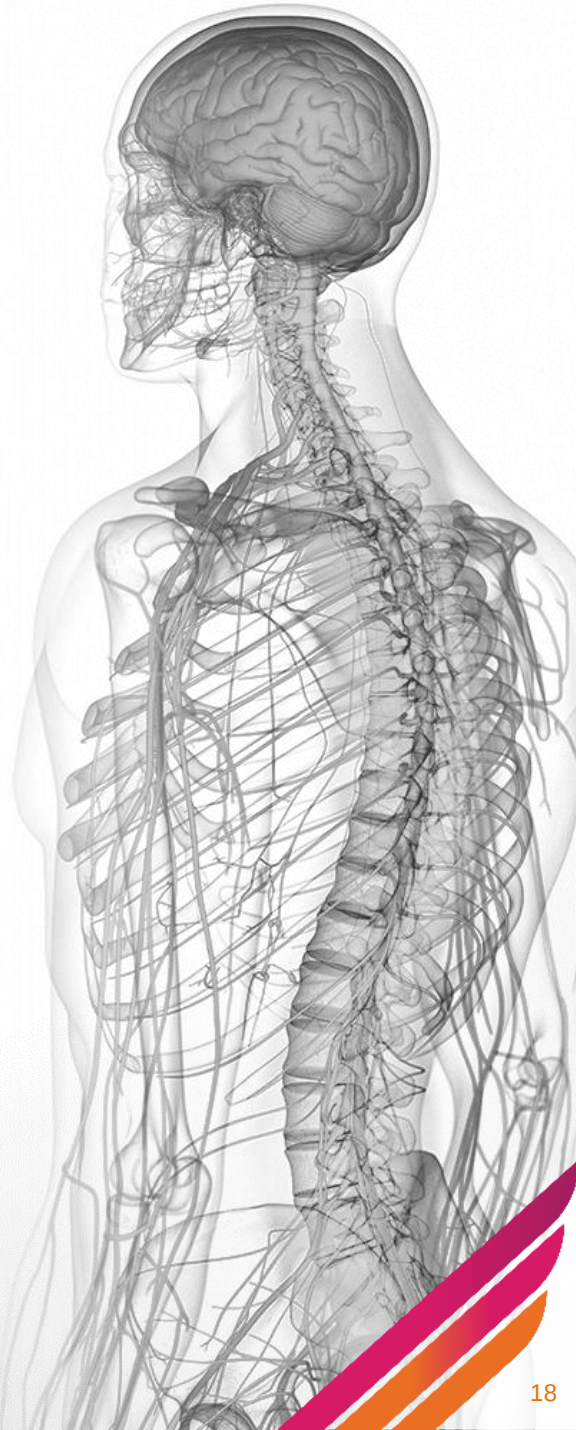
SPINRAZA
Spinal Muscular Atrophy

TEGSEDI
hATTR

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

Tofersen (IONIS-SOD1$_{Rx}$)
Amyotrophic Lateral Sclerosis

Prion
Prion Disease



IONIS

Breakthrough Neurological Commercial Medicines Bringing Significant Value to Patients Today

SPINRAZA® (nusinersen) injection 12 mg/5 mL

- The **standard-of-care for all forms of SMA**
- **Blockbuster** medicine with more than **$3 billion** in global sales since launch in December 2016
- Commercialized by Biogen, a leader in treatments for neurological and neurodegenerative diseases

Tegsedi™ (inotersen) injection 284 mg/1.5 mL

- **Multi-country launch is going well** through our commercial affiliate, Akcea
- Preparing to **expand into new jurisdictions**
- Positioned to **add growth** in commercial revenue

IONIS

The First and Only Treatment for All Forms of Spinal Muscular Atrophy

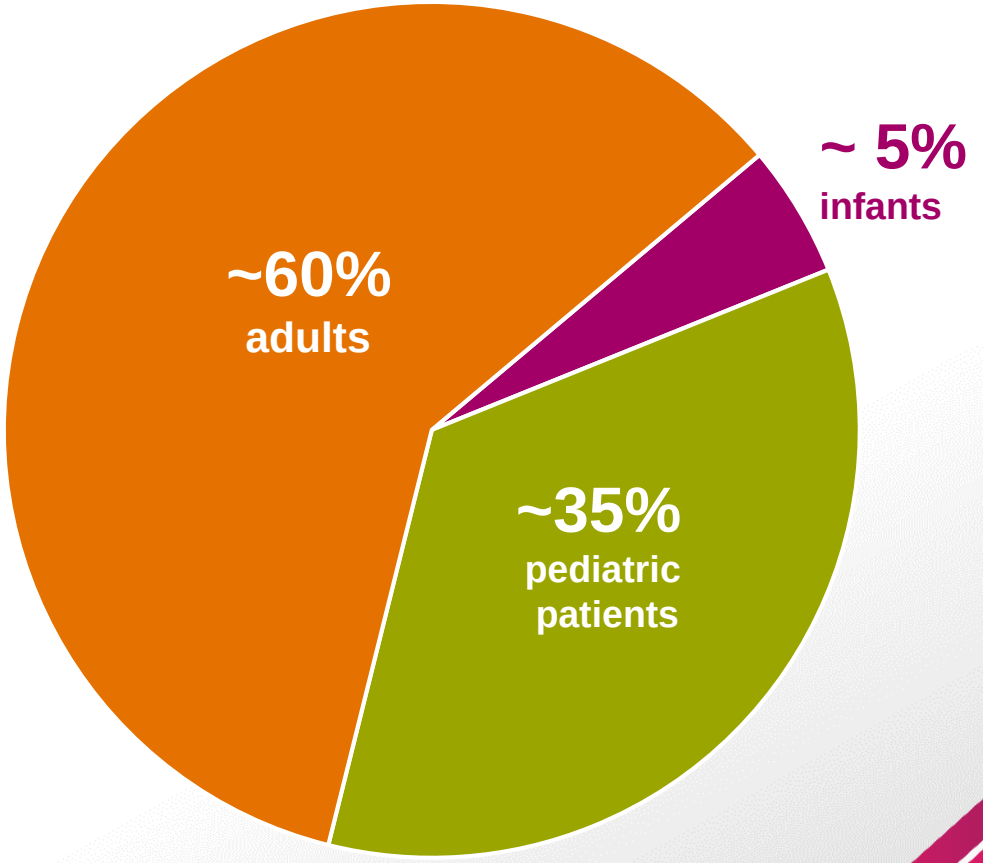
SPINRAZA approved in over 40 countries

- Formal reimbursement in place in **30** countries^
- **> 7,500** patients now on therapy worldwide*

Biogen has continued to increase the number of SMA patients on therapy

- **~50%** of infant and pediatric patients on therapy in the U.S.
- In Q1 2019, **~50%** of new starts were adult (18+) SMA patients, the largest patient segment in the U.S.^

SMA Historical Prevalence



Source: Biogen Q1 2019 Financial Results and Business Update, Results as of March 31, 2019 unless noted otherwise, *Includes patients in commercial setting, EAP and clinical trials, ^As of April 19, 2019

SPINRAZA Continues to Demonstrate Benefit in Infantile Onset SMA

nurture

To determine the **benefits** of treating **pre-symptomatic** infants with SPINRAZA

Pre-symptomatic treatment results in vast **majority** of patients achieving motor milestones more consistent with **normal development**

Favorable safety profile observed with long-term* treatment

shine

To determine the long-term **benefits** of **SPINRAZA**

Up to 6 years of data and **continued improvement** in motor function observed in infantile-onset SMA

Favorable safety profile observed with **long-term** treatment

IONIS

* At a median age of 26 months at last visit

NURTURE Study: Many Infants Treated Pre-Symptomatically Achieving Motor Milestones in Timeframes Consistent with Normal Development

Durable Improvement in Patients*

Study of SPINRAZA in pre-symptomatic infants

100%
Alive

NONE
Required tracheostomy or permanent ventilation

100%
Able to sit without support

88%
Able to walk either with assistance or independently

*NUTURE study interim analysis data cutoff date: May 15, 2018 (~35 months)

SPINRAZA Continues to Demonstrate Benefit in Infantile Onset SMA

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IONIS

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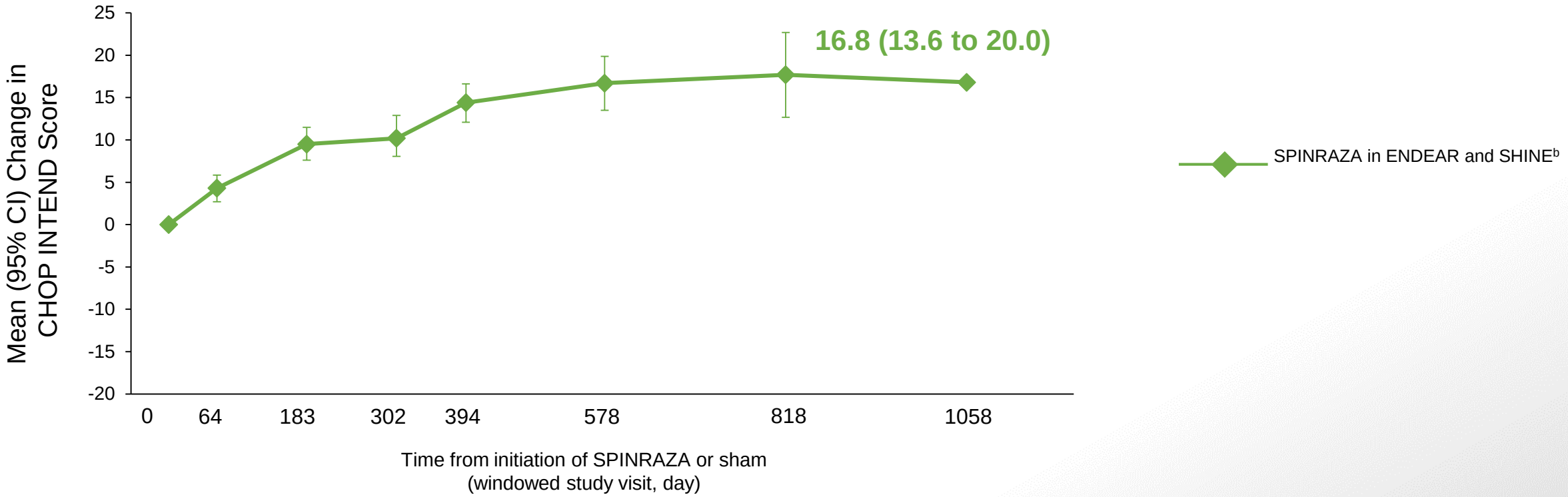
SHINE Study: Long-Term Evaluation of SPINRAZA Continues to Demonstrate Substantial and Increasing Benefit in Infants with SMA

Substantial and Durable Improvements in Strength and Function Demonstrated Regardless of Age at Treatment Initiation



[b] In the ENDEAR end of study analysis, at Day 394, SPINRAZA-treated participants had a mean improvement in CHOP INTEND score of 13.73.

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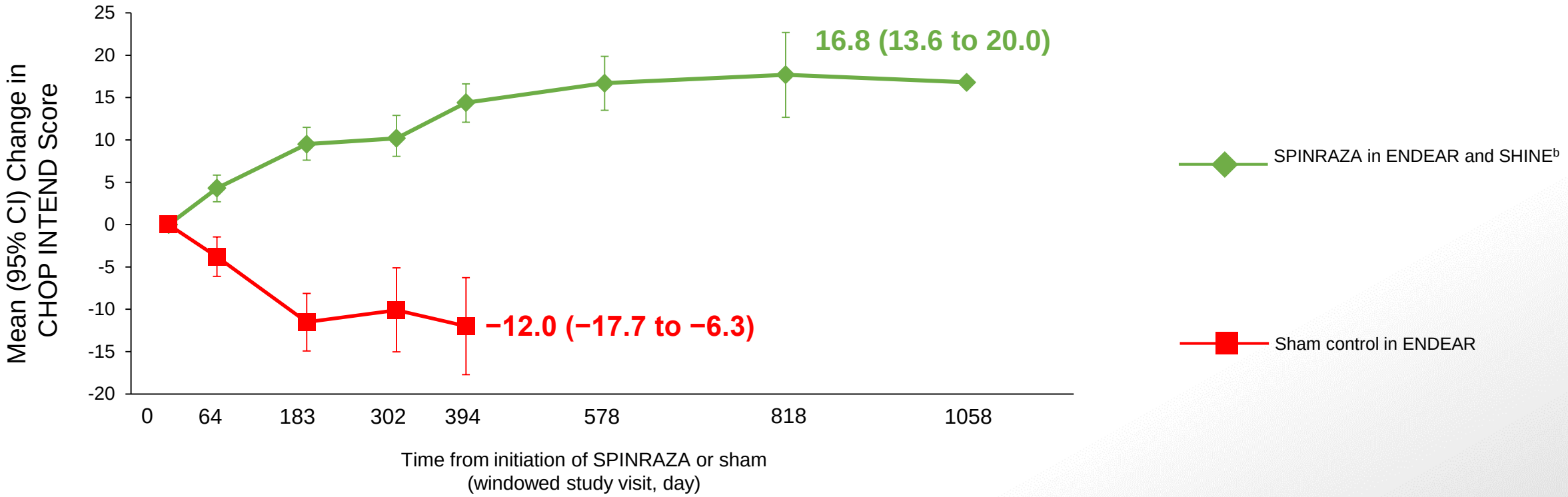

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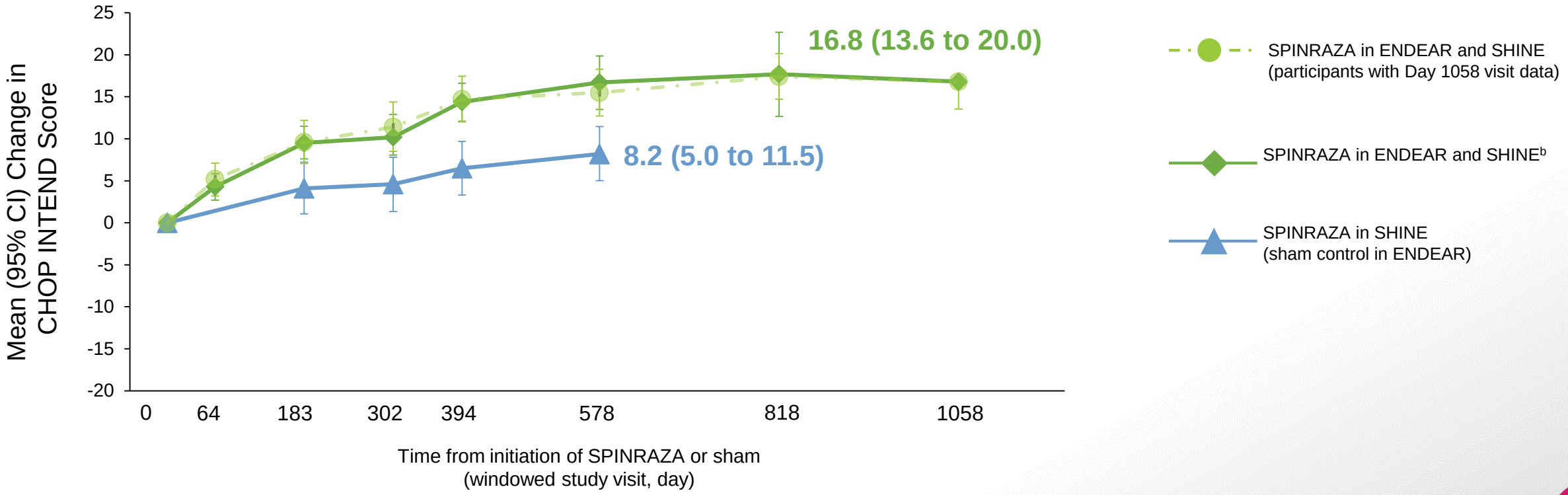

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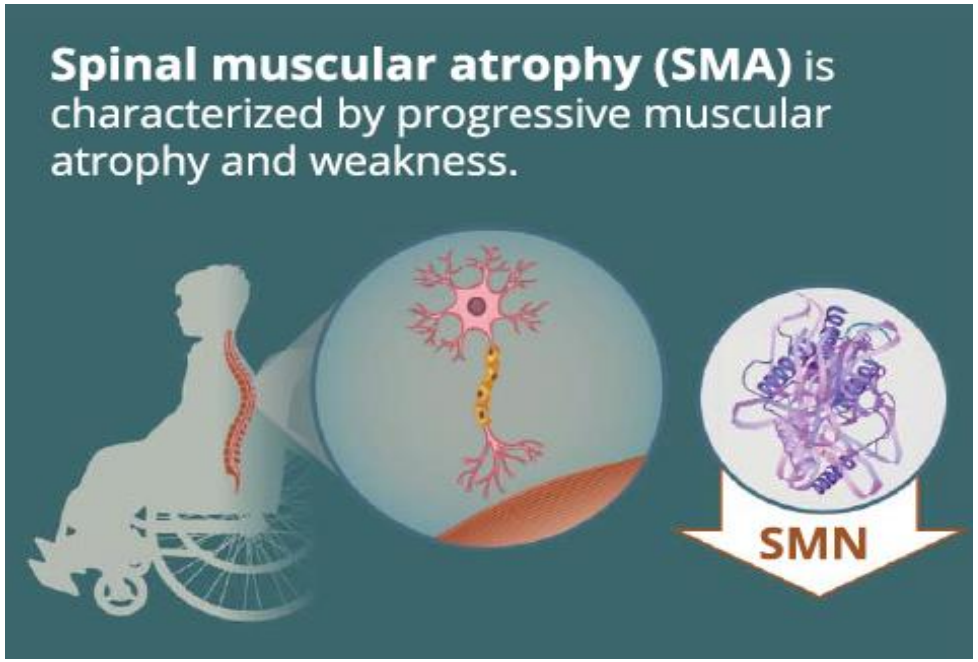
Long-Term SPINRAZA Treatment Improved Motor Function and Stabilized Disease in Children with Later-Onset SMA

AMERICAN ACADEMY OF NEUROLOGY®

Nusinersen in later-onset spinal muscular atrophy

Long-term results from the phase 1/2 studies

Basil T. Darras, MD, Claudia A. Chiriboga, MD, MPH, Susan T. Iannaccone, MD, Kathryn J. Swoboda, MD, FACMG, Jacqueline Montes, PT, EdD, NCS, Laurence Mignon, PhD, Shuting Xia, MS, C. Frank Bennett, PhD, Kathie M. Bishop, PhD, Jeremy M. Shefner, MD, PhD, Allison M. Green, PhD, Peng Sun, PhD, Ishir Bhan, MD, MPH, Sarah Gheuens, MD, PhD, Eugene Schneider, MD, Wildon Farwell, MD, MPH, and Darryl C. De Vivo, MD, on behalf of the ISIS-396443-CS2/ISIS-396443-CS12 Study Groups



Mean change from baseline over ~3 years of treatment

Motor assesment	SMA Type II	SMA Type III
Hammersmith Functional Motor Scale–Expanded score	+10.8 points	+1.8 points
Upper Limb Module score	+4.0 points	NR*
Six-Minute Walk Test distance	NR*	+92.0 points

No children discontinued treatment due to adverse events.

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The First Choice and Trusted Leader in SMA Therapy

SMA BEFORE SPINRAZA

Most common genetic cause of infant death

SMA AFTER SPINRAZA
The Standard-of-Care

Most babies achieving normal milestones with pre-symptomatic treatment

The First Choice and Trusted Leader in SMA Therapy

SMA BEFORE SPINRAZA	SMA AFTER SPINRAZA The Standard-of-Care
Most common genetic cause of infant death	Most babies achieving normal milestones with pre-symptomatic treatment
Progressive and irreversible disease	Patients gaining strength and improved quality of life

The First Choice and Trusted Leader in SMA Therapy

SMA BEFORE SPINRAZA	SMA AFTER SPINRAZA The Standard-of-Care
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Delayed diagnosis	Newborn screening beginning to provide earlier diagnosis and treatment

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Most common genetic cause of infant death	Most babies achieving normal milestones with pre-symptomatic treatment
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Continuing to Generate Data Further Validating SPINRAZA is Transforming SMA

TEGSEDI™: A Transformative Medicine for the Treatment of Patients with hATTR Amyloidosis with Polyneuropathy

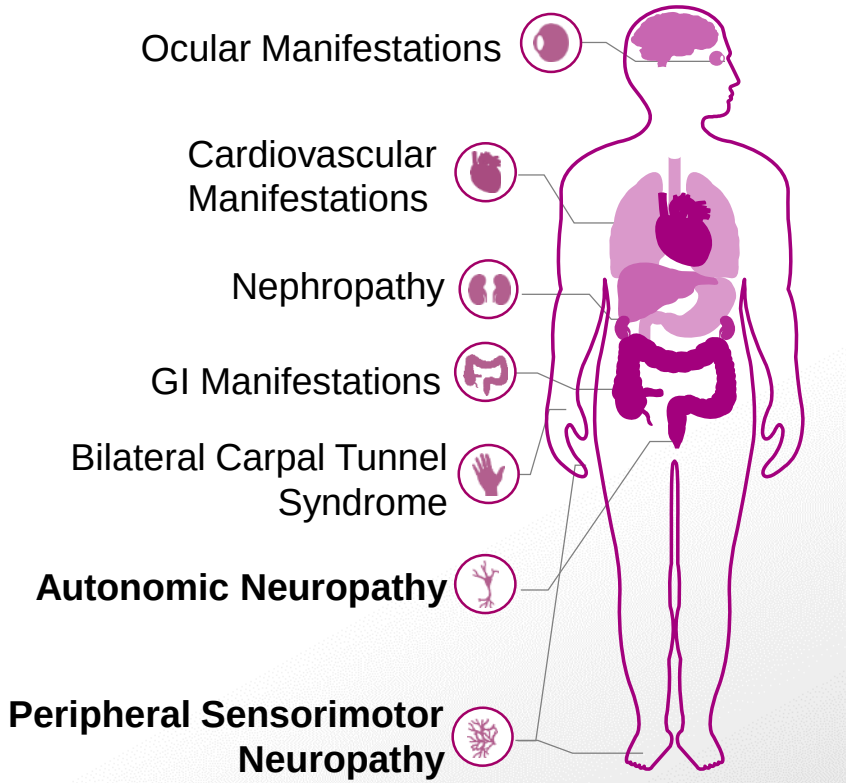
Brett Monia, Ph.D.

Chief Operating Officer

Hereditary Transthyretin (hATTR) Amyloidosis Can Cause Peripheral Sensorimotor and Autonomic Neuropathy

- hATTR amyloidosis is a rare, progressive, and fatal disease that results from buildup of misfolded transthyretin (TTR) protein in major organs and organ systems[1,2]
- Patients typically live 3–15 years[3], but with cardiac involvement only 2–5 years[4]
- Patients experience significant disease burden, morbidity, and a rapid decline in quality of life; symptoms impact multiple aspects of daily life[5-8]

hATTR amyloidosis affects many organ systems[1,9]



GI, gastrointestinal.

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. Coelho T et al. *Muscle Nerve*. 2017;55(3):323-332. 6. Adams D et al. *Orphanet J Rare Dis*. 2015;10(suppl 1):P58. 7. Amyloidosis Foundation. http://www.amyloidosissupport.org/support_groups/fam_isabell_attr.pdf. Accessed November 15, 2018. 8. Stewart M et al. *Neurol Ther*. 2018;7:349-364. 9. Sperry B et al. *J Am Coll Cardiol*. 2018;72:2040-2050.

Launched in the U.S. and EU

- World's first RNA-targeted therapeutic for patients with hereditary transthyretin amyloidosis (hATTR) with polyneuropathy
- The only RNA-targeted therapeutic that offers the convenience of a once per week self administered subcutaneous injection
- Multi-country launch going well
  - Treated patients from early access and open label extension programs, as well as naïve patients
  - Received reimbursement from both public and private payers in the U.S.

Tegsedi™ (inotersen) injection 284 mg/1.5 mL

TEGSEDI was discovered and developed by Ionis and licensed to Akcea in 2018

Showing Substantial Benefit to Patients Across a Wide Range of Clinical Studies

CLINICAL STUDIES					
Phase/Study	**Phase I**	**Phase III (NEURO-TTR)**	**NEURO-TTR OLE**	**Phase II Investigator Study (M. Benson, M.D.)**	**Phase II Investigator Study (R. Falk, M.D.)**
Patients	Healthy Volunteers (n=65)	hATTR-PN (n=172)	hATTR-PN (n=135)	ATTR-CM (n=<=45)	ATTR-CM (n~50)
Design	SAD/MAD Dose-Escalation	15 mo. PBO CTL (2:1)	All patients from NEURO-TTR (Open Label) up to 5 years	Open-Label up to 5 years	Open-Label up to 3 years
Key Endpoints	Safety/Tolerability TTR Reduction	mNIS+7/Norfolk QOL (co-1°)	Long-Term Safety/Efficacy	Safety/Tolerability Efficacy vs NH Data	Safety/Tolerability Efficacy vs Patient History & Disease NH
Status	Complete	Complete	Ongoing	Ongoing	Ongoing
Outcome	Good Safety/Tolerability Robust TTR Reductions	Highly Positive Marketing Approved	Long-Term Safety/Efficacy demonstrated	Long-Term Safety demonstrated w/ Evidence of Efficacy	Just initiated

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Status	Complete	Complete	**Ongoing**	Ongoing	Ongoing
Outcome	Good Safety/Tolerability Robust TTR Reductions	Highly Positive Marketing Approved	**Long-Term Safety/Efficacy demonstrated**	Long-Term Safety demonstrated w/ Evidence of Efficacy	Just initiated

TEGSEDI Treatment Produces Durable Benefit in NEURO-TTR OLE Study – Key Messages from Two Year Update

- **Long-term** treatment resulted in continued **efficacy** as measured by both neurological disease progression and **quality** of **life**
- Treatment of patients previously treated with placebo resulted in **rapid** and **sustained** disease **stabilization**
- **Earlier** treatment results in better **efficacy** outcomes
- **Favorable** benefit risk profile with exposure >5 years
  - No new **safety** concerns observed

Tegsedi™ (inotersen) injection 284 mg/1.5 mL

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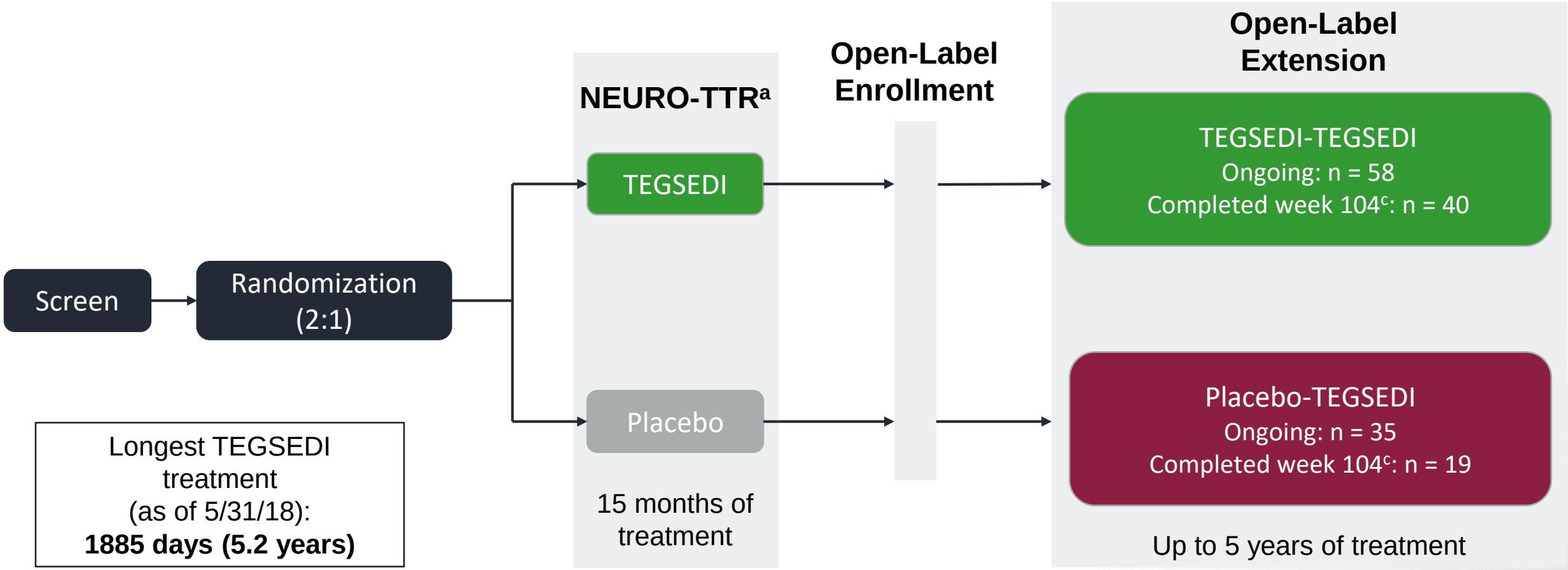
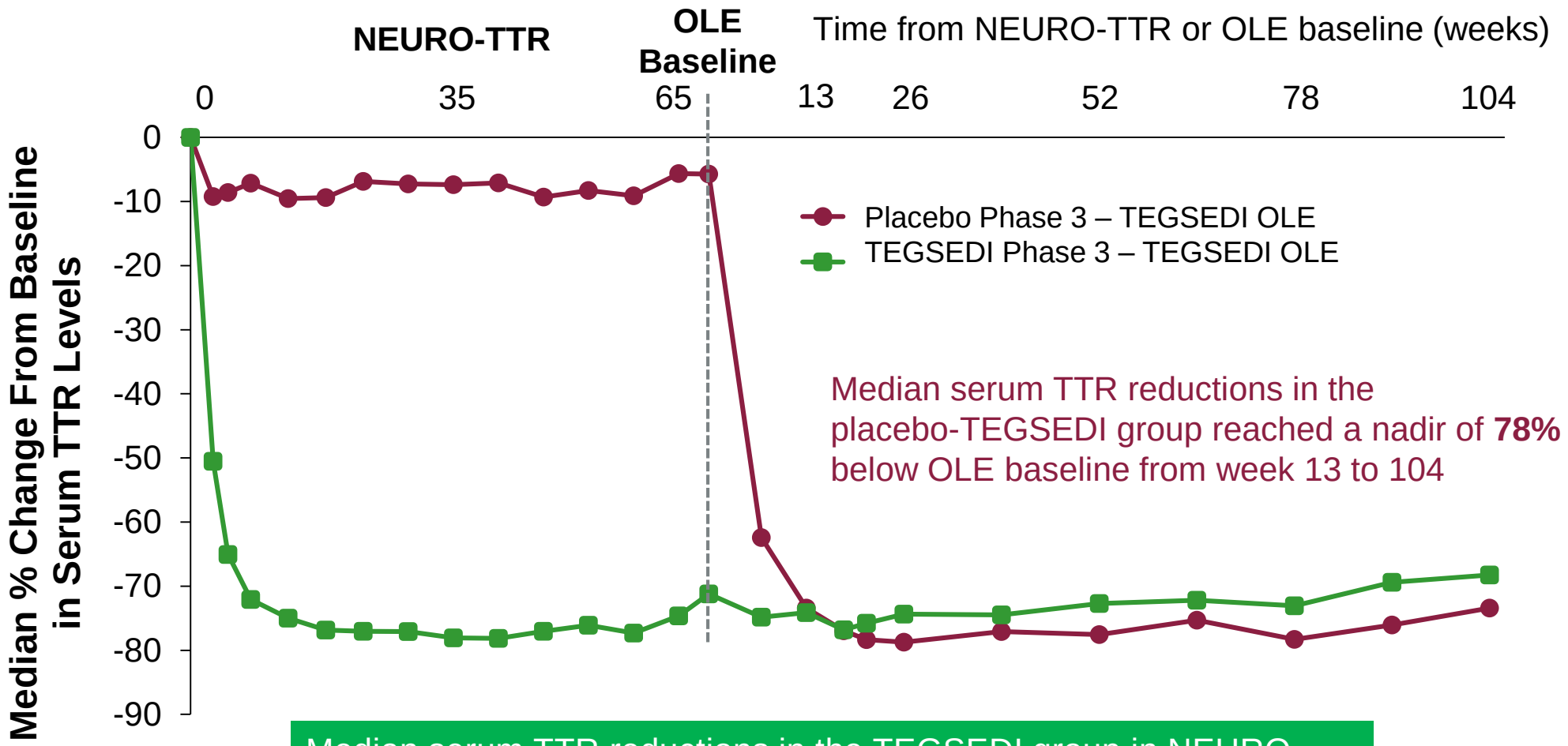
TEGSEDI was discovered and developed by Ionis and licensed to Akcea in 2018

NEURO-TTR and OLE Study Design (as of May 31, 2018 – Two Year Update)



OLE, open-label extension; TTR, transthyretin.
[a]The n values for NEURO-TTR represent the number of patients randomized and treated. Overall, 139 patients (80.3%) completed the NEURO-TTR study, and >95% of patients who completed dosing participated in the OLE. [b]Not all patients had completed 2 years in the OLE as of May 31, 2018.
Benson MD et al. *N Engl J Med*. 2018;379(1):22-31.

TEGSEDI Induced Rapid and Substantial Reduction in Serum TTR Levels



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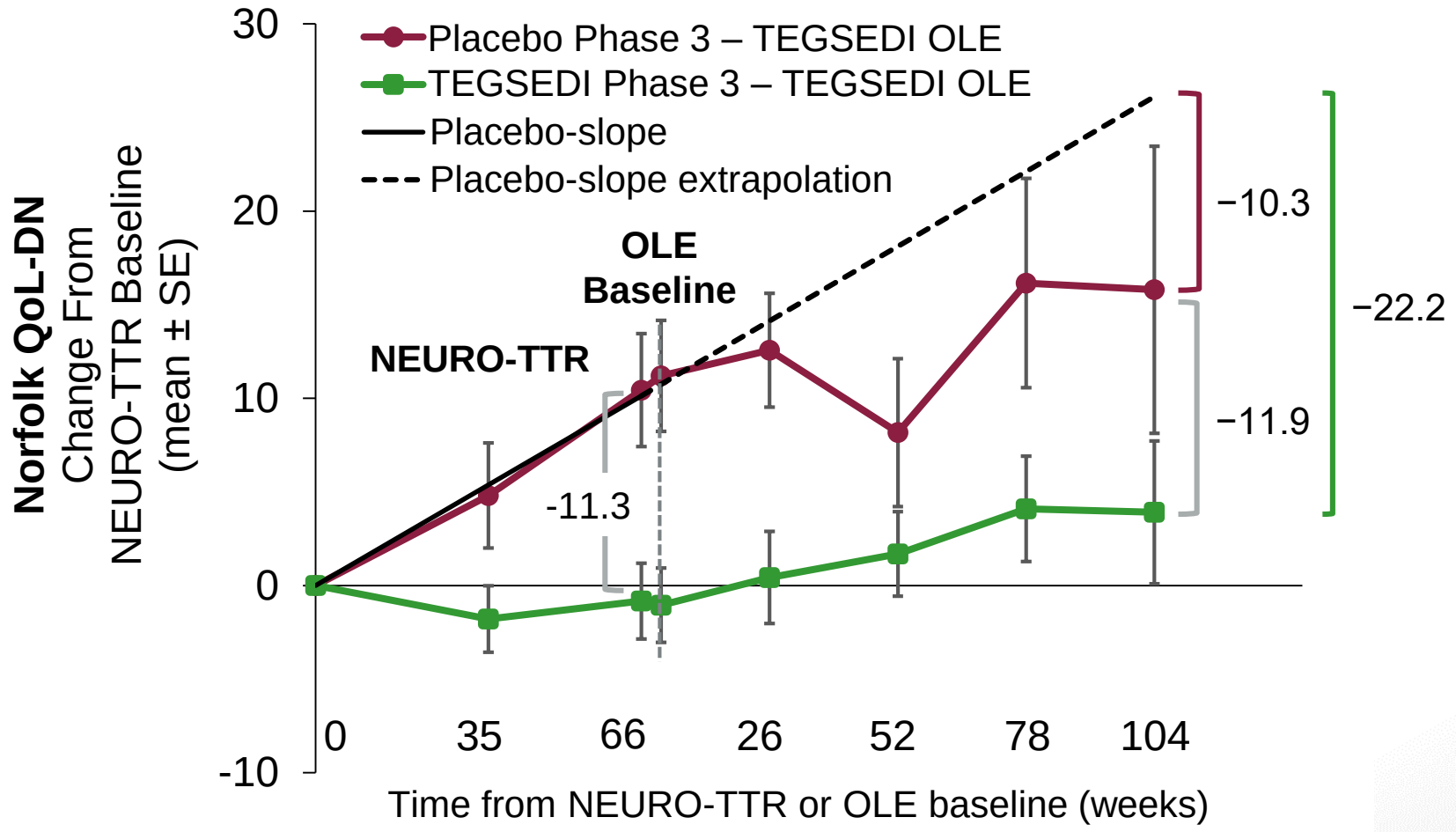
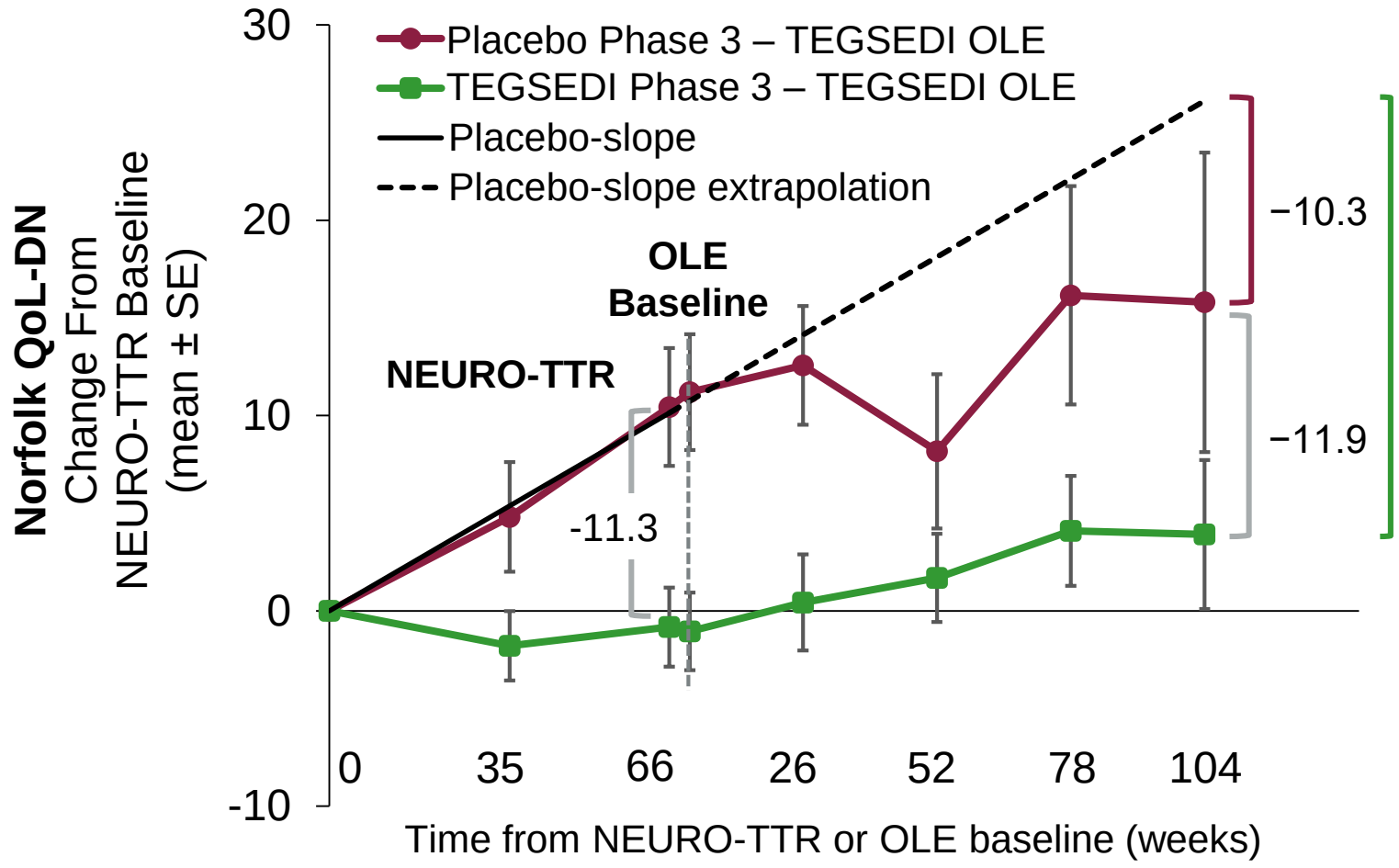
1. Benson MD et al. *N Engl J Med*. 2018;379(1):22-31.

Patients Who Switched From Placebo to TEGSEDI Demonstrated Stabilization of Neuropathy-Related QoL



Norfolk QoL-DN, Norfolk Quality of Life–Diabetic Neuropathy questionnaire total score; OLE, open-label extension; QoL, quality of life; SD, standard deviation; SE, standard error.
[a]At OLE baseline, mean (SD) Norfolk QoL-DN scores were 60.1 (32.0) and 48.2 (29.2) for placebo-inotersen (n = 49) and inotersen-inotersen (n = 78), respectively.
[b]At NEURO-TTR baseline, mean (SD) Norfolk QoL-DN scores were 49.0 (26.9) and 49.3 (27.0) for placebo-inotersen (n = 50) and inotersen-inotersen (n = 80), respectively.

Patients Who Switched From Placebo to TEGSEDI Demonstrated Stabilization of Neuropathy-Related QoL



46% of TEGSEDI-TEGSEDI patients had a <0 point score change from NEURO-TTR baseline[b] to OLE week 104

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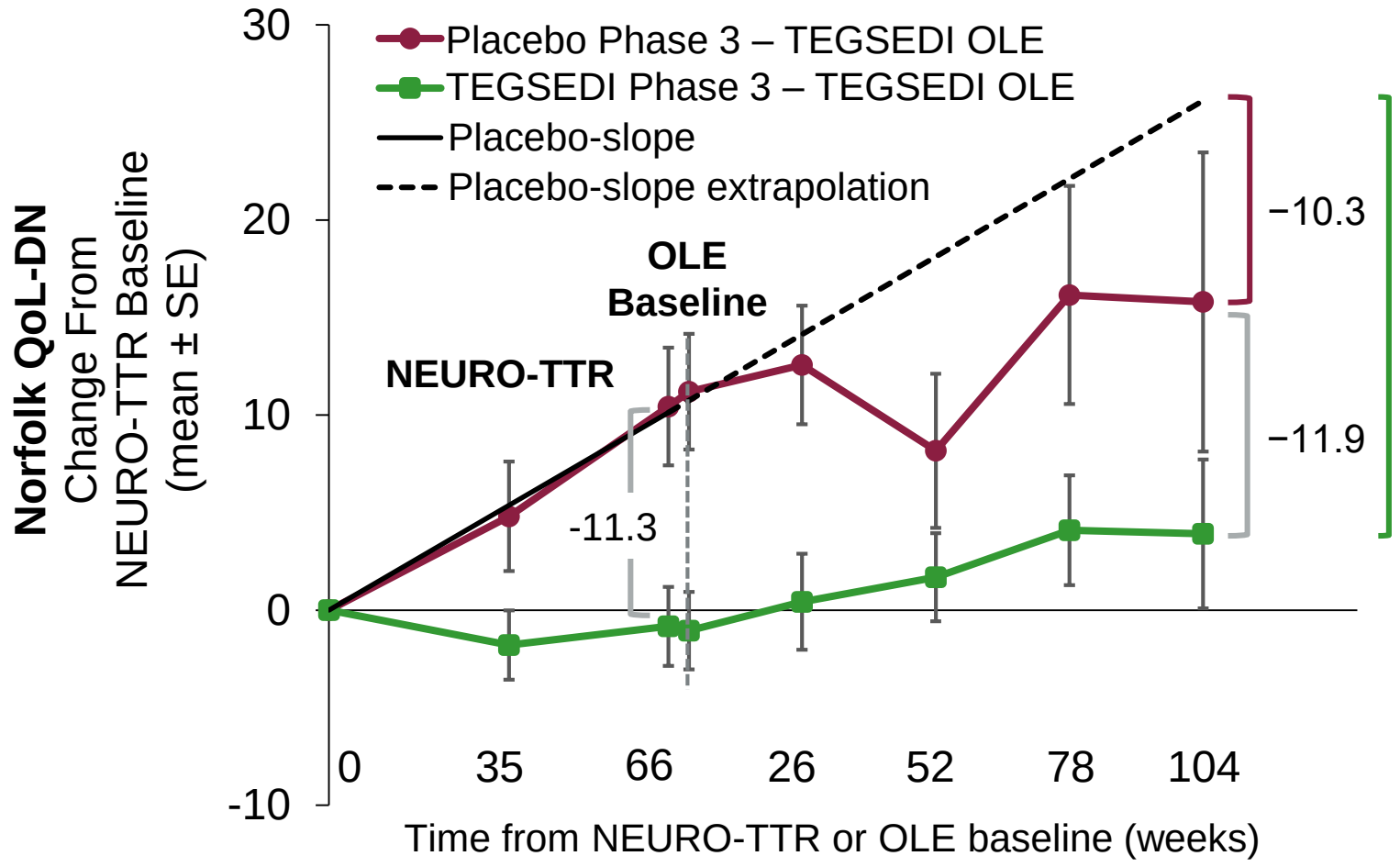
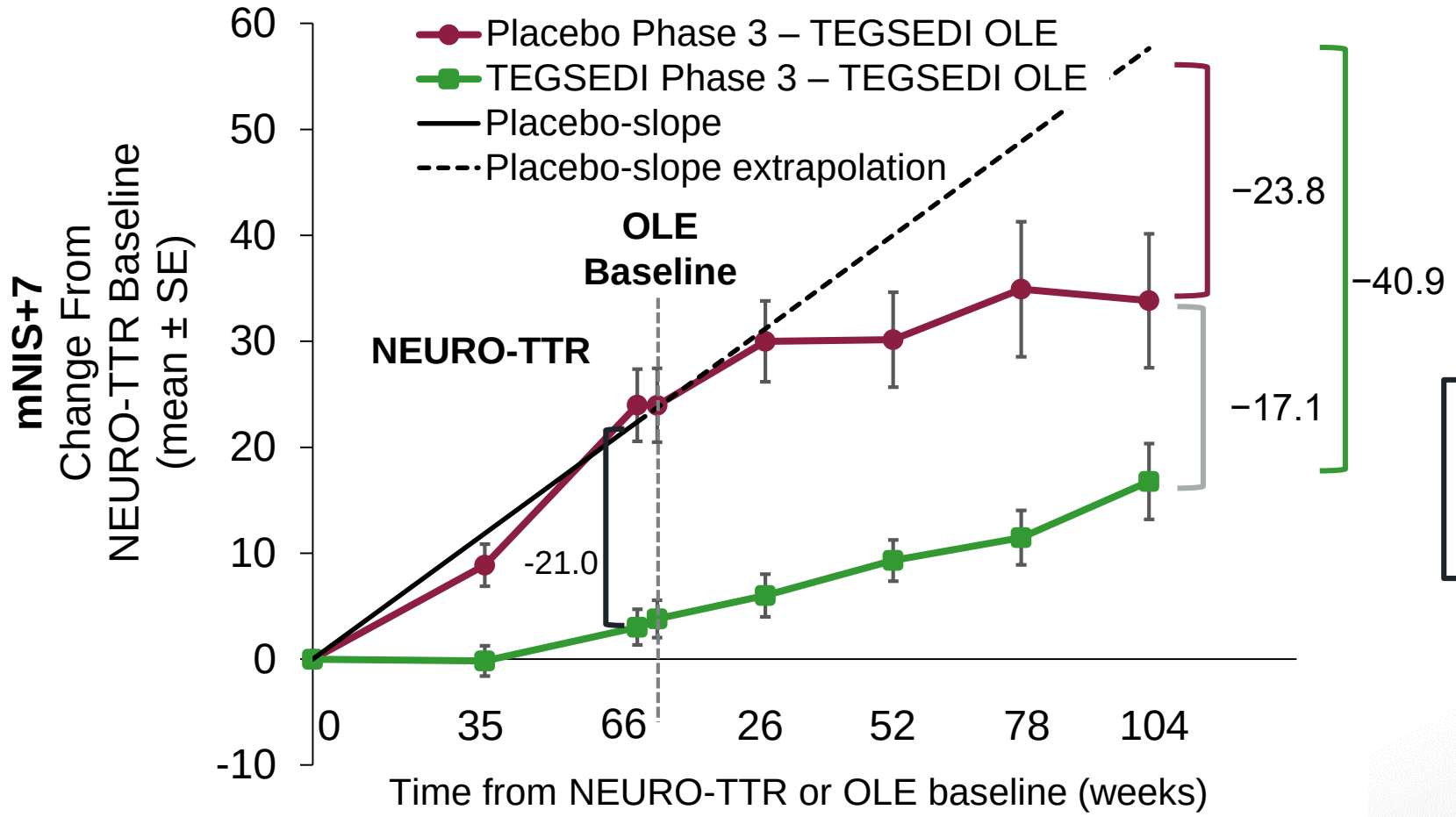


42% of placebo-TEGSEDI patients had a <0 point score change from OLE baseline[a] to week 104

46% of TEGSEDI-TEGSEDI patients had a <0 point score change from NEURO-TTR baseline[b] to OLE week 104

Norfolk QoL-DN, Norfolk Quality of Life–Diabetic Neuropathy questionnaire total score; OLE, open-label extension; QoL, quality of life; SD, standard deviation; SE, standard error.
[a]At OLE baseline, mean (SD) Norfolk QoL-DN scores were 60.1 (32.0) and 48.2 (29.2) for placebo-inotersen (n = 49) and inotersen-inotersen (n = 78), respectively.
[b]At NEURO-TTR baseline, mean (SD) Norfolk QoL-DN scores were 49.0 (26.9) and 49.3 (27.0) for placebo-inotersen (n = 50) and inotersen-inotersen (n = 80), respectively.

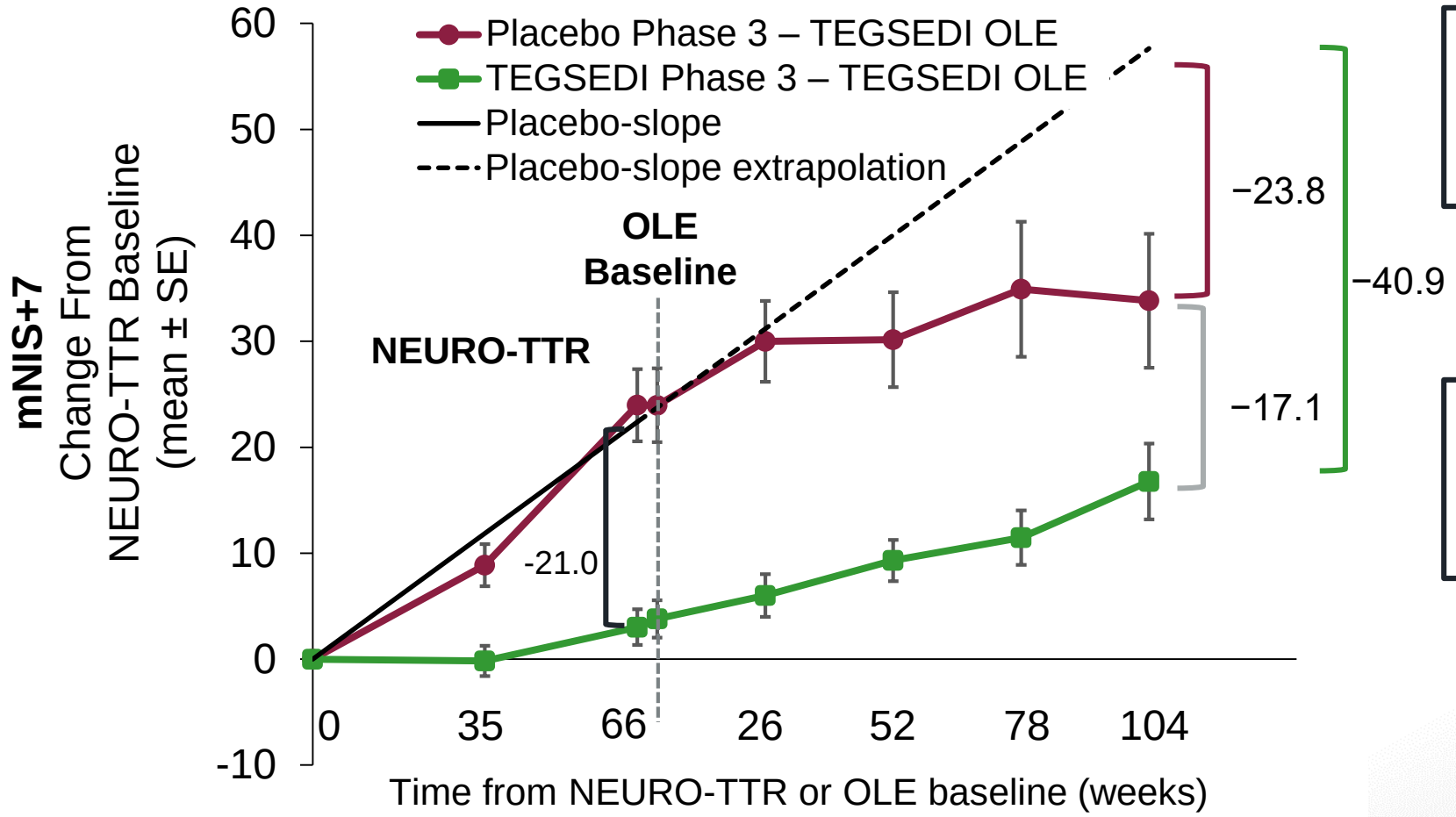
Patients Who Switched From Placebo to TEGSEDI Showed Sustained Reduction in Neuropathy Progression



24% of TEGSEDI-TEGSEDI patients had a <0 point score change from NEURO-TTR baseline[b] to OLE week 104[a]

mNIS+7, modified Neuropathy Impairment Score +7 neurophysiologic tests composite score; OLE, open-label extension; SD, standard deviation; SE, standard error.
[a]At OLE baseline, mean (SD) mNIS+7 scores were 98.7 (51.1) and 85.8 (41.1) for placebo-inotersen (n = 49) and inotersen-inotersen (n = 80), respectively.
[b]At NEURO-TTR baseline, mean (SD) mNIS+7 scores were 74.4 (40.1) and 81.8 (38.0) for placebo-inotersen (n = 50) and inotersen-inotersen (n = 81), respectively

Patients Who Switched From Placebo to TEGSEDI Showed Sustained Reduction in Neuropathy Progression



47% of placebo-TEGSEDI patients had a <0 point score change from OLE baseline[a] to week 104

24% of TEGSEDI-TEGSEDI patients had a <0 point score change from NEURO-TTR baseline[b] to OLE week 104[a]

mNIS+7, modified Neuropathy Impairment Score +7 neurophysiologic tests composite score; OLE, open-label extension; SD, standard deviation; SE, standard error.
[a]At OLE baseline, mean (SD) mNIS+7 scores were 98.7 (51.1) and 85.8 (41.1) for placebo-inotersen (n = 49) and inotersen-inotersen (n = 80), respectively.
[b]At NEURO-TTR baseline, mean (SD) mNIS+7 scores were 74.4 (40.1) and 81.8 (38.0) for placebo-inotersen (n = 50) and inotersen-inotersen (n = 81), respectively

Showing Substantial Benefit to Patients Across a Wide Range of Clinical Studies

CLINICAL STUDIES					
Phase/Study	**Phase I**	**Phase III (NEURO-TTR)**	**NEURO-TTR OLE**	**Phase II Investigator Study (M. Benson, M.D.)**	**Phase II Investigator Study (R. Falk, M.D.)**
Patients	Healthy Volunteers (n=65)	hATTR-PN (n=172)	hATTR-PN (n=135)	ATTR-CM (n=<=45)	ATTR-CM (n~50)
Design	SAD/MAD Dose-Escalation	15 mo. PBO CTL (2:1)	All patients from NEURO-TTR (Open Label) up to 5 years	Open-Label up to 5 years	Open-Label up to 3 years
Key Endpoints	Safety/Tolerability TTR Reduction	mNIS+7/Norfolk QOL (co-1°)	Long-Term Safety/Efficacy	Safety/Tolerability Efficacy vs NH Data	Safety/Tolerability Efficacy vs Patient History & Disease NH
Status	Complete	Complete	Ongoing	Ongoing	Ongoing
Outcome	Good Safety/Tolerability Robust TTR Reductions	Highly Positive Marketing Approved	Long-Term Safety/Efficacy demonstrated	Long-Term Safety demonstrated w/ Evidence of Efficacy	Just initiated

Showing Substantial Benefit to Patients Across a Wide Range of Clinical Studies

CLINICAL STUDIES					
Phase/Study	**Phase I**	**Phase III (NEURO-TTR)**	**NEURO-TTR OLE**	**Phase II Investigator Study (M. Benson, M.D.)**	**Phase II Investigator Study (R. Falk, M.D.)**
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Design	SAD/MAD Dose-Escalation	15 mo. PBO CTL (2:1)	All patients from NEURO-TTR (Open Label) up to 5 years	**Open-Label up to 5 years**	Open-Label up to 3 years
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Outcome	Good Safety/Tolerability Robust TTR Reductions	Highly Positive Marketing Approved	Long-Term Safety/Efficacy demonstrated	**Long-Term Safety demonstrated w/ Evidence of Efficacy**	Just initiated

TEGSEDI in Patients with TTR Cardiomyopathy

Benson & Dasgupta Investigator Initiated Study (Indiana University School of Medicine)

Single center, investigator trial in 33 patients (as of 10/18) with TTR cardiomyopathy

- Wild-type and hereditary ATTR-CM
- Open-label design
- Up to 5 years of treatment

Objective is to evaluate long-term safety and clinical efficacy (vs NH data) in patients with ATTR cardiomyopathy

Main inclusion criteria:

- Biopsy-proven ATTR cardiomyopathy with clinical CHF symptoms (hereditary or wild type)
- LVW thickness ≥ 1.3 cm on transthoracic echocardiography

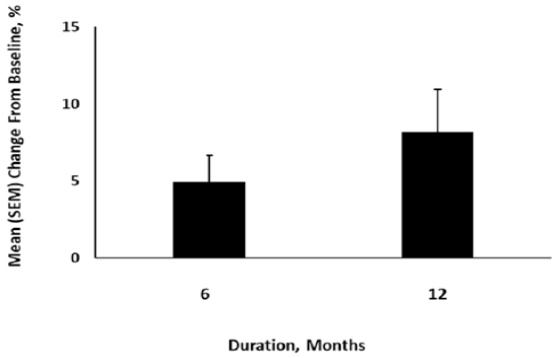
TEGSEDI 300 mg SQ weekly (No Loading Dose)

IONIS

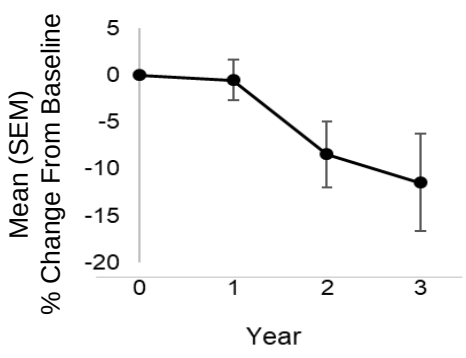
Phase 2 Investigator Study of TEGSEDI Demonstrates Stabilization or Improvements of TTR Cardiomyopathy

Decrease in LV Mass

Natural History Data[1]
(hereditary amyloidosis, n=9)



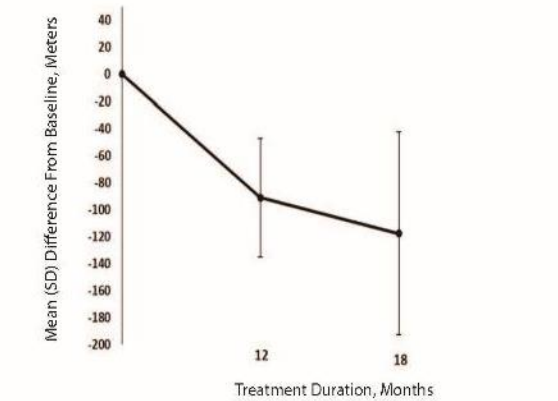
TEGSEDI
(WT and hereditary, n=10)



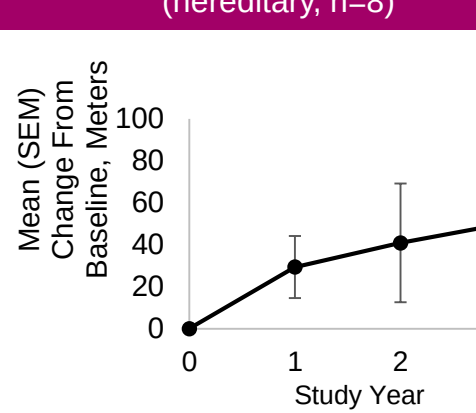
1. Benson MD, et. al., (2011) *Am J Cardiol* 108(2) 285-9. Benson, M.D., AAN.

Improved 6MWT

Natural History Data[2]



TEGSEDI
(hereditary, n=8)



2. Ruberg et al. (2012) *Am Heart J*. 64:222-228.e1. Benson, M.D., AAN.

Patients treated for more than 3 years

TEGSEDI is Well Tolerated and Demonstrates Stabilization and Improvements in TTR Cardiomyopathy Investigator Study

No severe thrombocytopenia or drug-related renal adverse events

- Drug-related side effects included mild injection site reactions and mild flu-like symptoms after injection

13 of 14 patients (93%) completed 2 years of therapy and are alive

- One non-drug related death after surgery due to cardiac arrest

Strong evidence of efficacy at 2 years of therapy compared to natural history

- Improved 6 minute walk distance
- Reduced left ventricular mass
- Decrease in mean BNP compared to baseline

IONIS

A Comprehensive Therapeutic Franchise to Treat All Forms of Transthyretin Amyloidosis

TEGSEDI demonstrated substantial benefit with manageable safety in Phase 3 NEURO-TTR study

- First-approved RNA-targeted therapeutic for hATTR-PN
- Published in *New England Journal of Medicine (Benson, M.D. et al. 2018; 379: 22-31)*
- Multi-country launch going well

NEURO-TTR OLE demonstrating **long-term benefit** with no new safety concerns with long-term treatment

- Patients previously on placebo experiencing disease stabilization
- Disease improvement achieved in many patients
- Earlier treatment results in better outcomes

Long-term **safety** with **strong** evidence of clinical **efficacy** in patients with **wild type** and **hereditary TTR cardiomyopathy** *(Dasgupta, N.R., Benson, MD; ACC, 2019)*

Development of LICA **follow-on** medicine (AKCEA-TTR-L_{Rx}) for all forms of ATTR **underway**

- Phase I study in healthy volunteer nearly complete
- Phase III pivotal studies in hATTR-PN & ATTR-CM to initiate in 2H 2019

Late-Stage Neurological Medicines

Amyotrophic Lateral Sclerosis (ALS)

C. Frank Bennett, Ph.D.

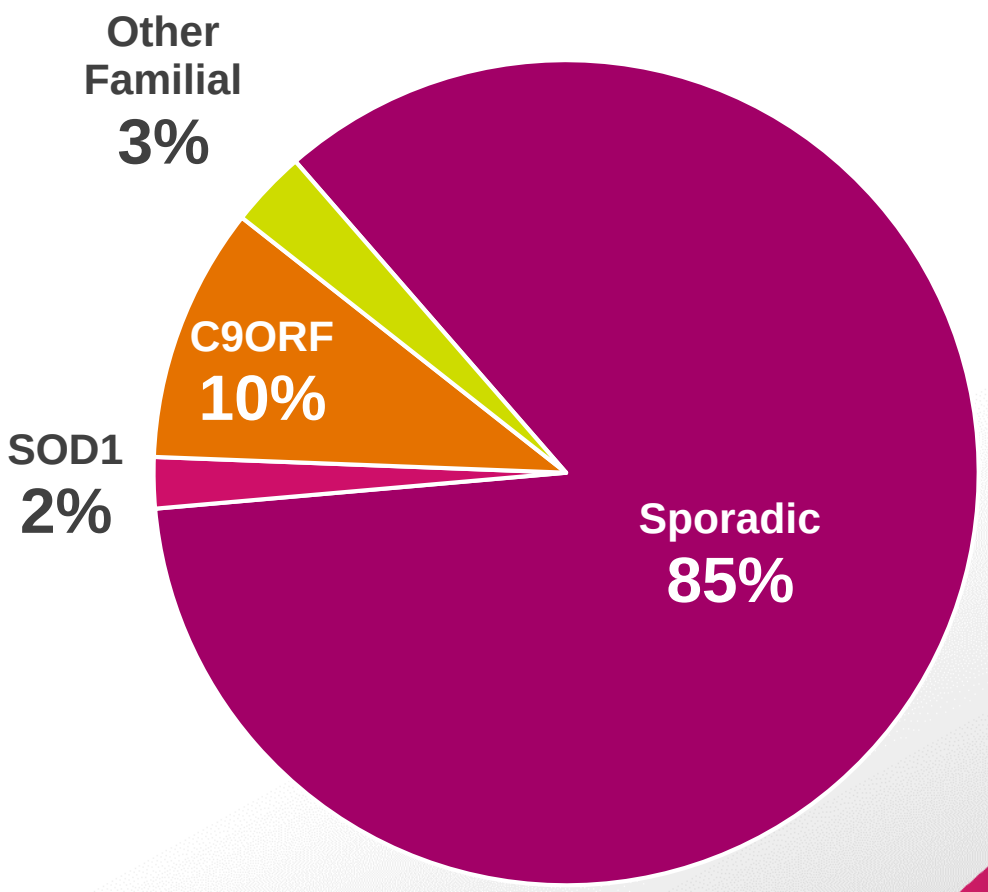
Senior Vice President of Research

ALS is a Fatal Disease with a Tremendous Unmet Medical Need

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

- Approximately 15% of ALS cases have genetic causes
- 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

Breakdown of ALS



IONIS

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

Mutant **SOD1** causes ALS through **toxic** gain of function in neurons and glia

Tofersen directly **targets** a **genetic** cause of **ALS** and is currently in a Phase 3 VALOR study*

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 3 study

IONIS

*Biogen is collaborating with regulators to further define the scope of the clinical data package required to support the registration of Tofersen
** Based on preclinical data

Phase 1/2 Study Design for Tofersen

Single Ascending Dose[a]

Cohort 1: Tofersen 10 mg or placebo

Cohort 2: Tofersen 20 mg or placebo

Cohort 3: Tofersen 40 mg or placebo

Cohort 4: Tofersen 60 mg or placebo

Multiple Ascending Dose

Cohort 1: Tofersen 20 mg or placebo

Cohort 2: Tofersen 40 mg or placebo

Cohort 3: Tofersen 60 mg or placebo

Cohort 4: Tofersen 100 mg or placebo

Endpoints

Primary

- Safety and tolerability
- PK measures of tofersen (plasma and CSF)

Secondary

- Change from baseline in CSF levels of SOD1 protein

Exploratory endpoints include*

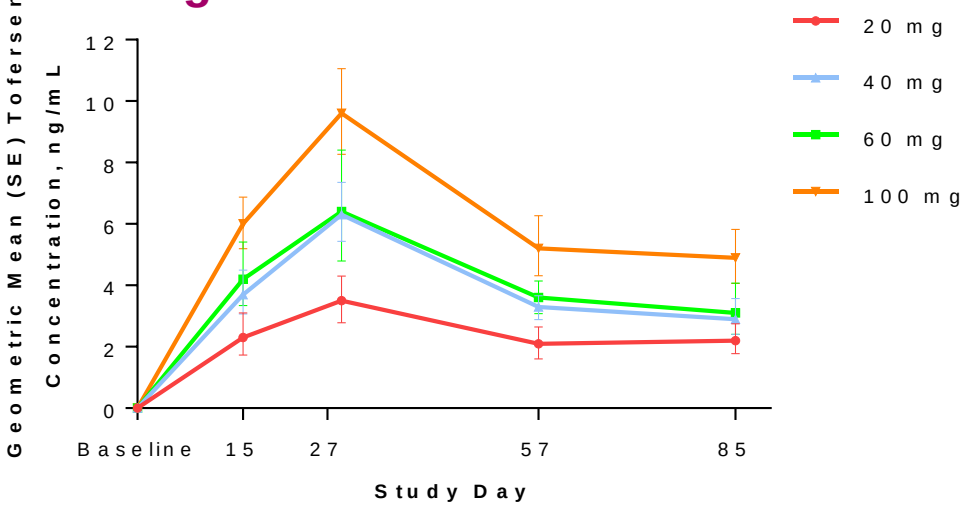
- Changes from baseline of clinical function measures: ALSFRS-R scores, SVC, and HHD

*Only exploratory endpoints discussed in this presentation. Data presented are from an interim analysis. [a]A single ascending dose study (SAD) was done first. Two participants in MAD received an initial dose in SAD and enrolled in MAD after a washout period. ALS = amyotrophic lateral sclerosis; ALSFRS-R = ALS Functional Rating Scale–Revised; CSF = cerebrospinal fluid; PK = pharmacokinetics; SVC = slow vital capacity, Clinicaltrials.gov, NCT02623699; EudraCT, 2015-004098-33

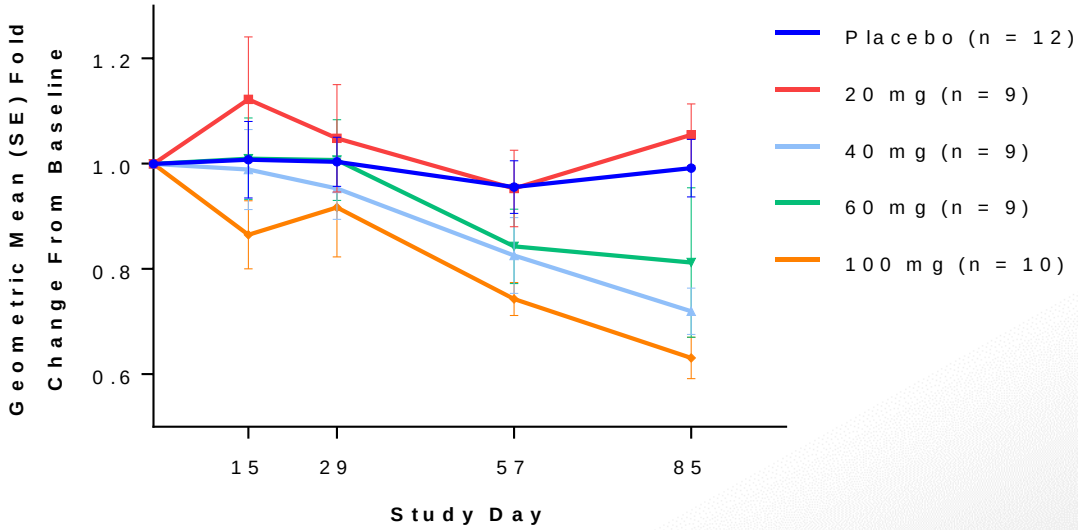
Phase 1/2 Study: Treatment With Tofersen Demonstrated Robust SOD1 Reductions in the CSF

SOD1 concentrations in the CSF were substantially reduced at higher Tofersen doses

Trough CSF Concentration Tofersen



SOD1 CSF Concentration



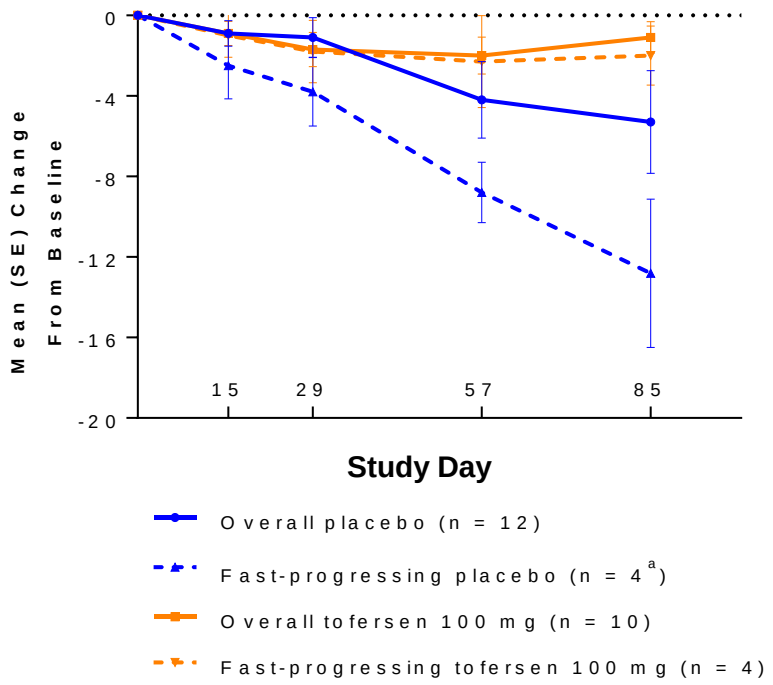
Tofersen was generally well tolerated

Most AEs were mild or moderate in severity

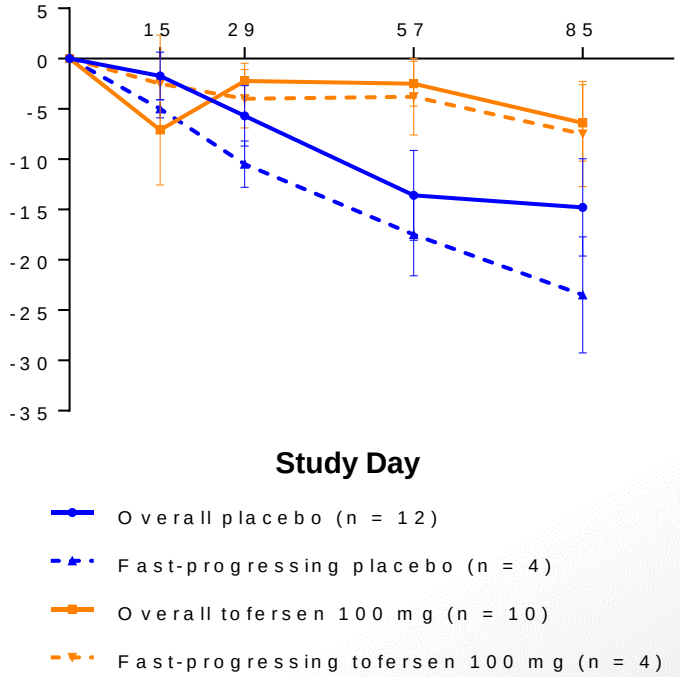
Values below limit of quantitation are set to zero at day 1 predose and set to half of lower limit of quantitation (1 ng/mL) at other time points in calculation.
AE = adverse event, CSF = cerebrospinal fluid; PD = pharmacodynamics; PK = pharmacokinetics; SOD1 = superoxide dismutase 1

Interim Results: Treatment With Tofersen 100 mg Demonstrated a Slowing of Clinical, Functional and Respiratory Function Decline

Clinical Outcome
ALSFRS-R



Lung Function
% Predicted SVC



[a] Missing values due to deaths were imputed using last observation carried forward. ALSFRS-R = ALS Functional Rating Scale–Revised; FP = fast-progressing mutation; SVC = slow vital capacity

Innovative Phase 3 with Potential to Support Rapid Path to Patients

Single Ascending Dose[a]

Cohort 1: Tofersen 10 mg or placebo

Cohort 2: Tofersen 20 mg or placebo

Cohort 3: Tofersen 40 mg or placebo

Cohort 4: Tofersen 60 mg or placebo

Multiple Ascending Dose

Cohort 1: Tofersen 20 mg or placebo

Cohort 2: Tofersen 40 mg or placebo

Cohort 3: Tofersen 60 mg or placebo

Cohort 4: Tofersen 100 mg or placebo

Phase 3 VALOR**

Tofersen 100 mg or placebo

Endpoints

Primary

- Safety and tolerability
- PK measures of tofersen (plasma and CSF)

Secondary

- Change from baseline in CSF levels of SOD1 protein

Exploratory endpoints include*

- Changes from baseline of clinical function measures: ALSFRS-R scores, SVC, and HHD

Primary

- ALSFRS-R score, a validated rating instrument for monitoring the progression of disability in patients with ALS

IONIS

*Only exploratory endpoints discussed in this presentation. Data presented are from an interim analysis. [a]A single ascending dose study (SAD) was done first. ALS = amyotrophic lateral sclerosis; ALSFRS-R = ALS Functional Rating Scale–Revised; CSF = cerebral spinal fluid; PK = pharmacokinetics; SVC = slow vital capacity Clinicaltrials.gov, NCT02623699; EudraCT, 2015-004098-33, **Biogen is collaborating with regulators to further define the scope of the clinical data package required to support the registration of Tofersen

Tofersen (IONIS-SOD1$_{Rx}$) First Investigational Medicine to Demonstrate Significant Lowering of SOD1

- Potential **First-in-Class** and **Best-in-Class** Medicine to Treat SOD1-ALS
- **Significant lowering** of SOD1 in CSF
- Trends in slowing of **disease progression**
- Biogen licensed based on **positive** data from interim analysis of Phase 1/2 data
- **Phase 3 VALOR** study ongoing*

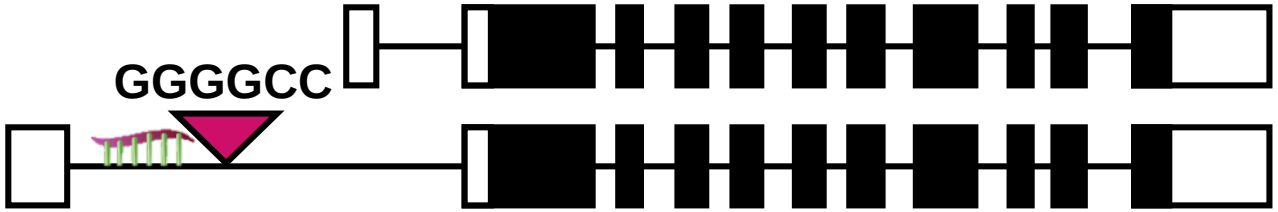
IONIS

*Biogen is collaborating with regulators to further define the scope of the clinical data package required to support the registration of Tofersen

C9ORF72 Molecular Pathology

Mutant C9ORF72 toxic gain of function

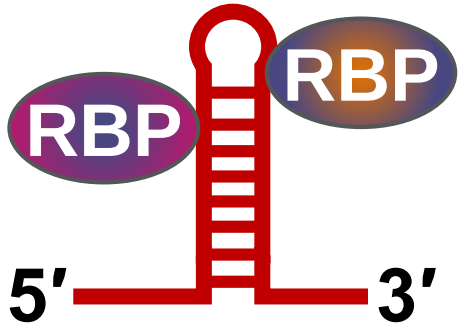
C9ORF72 repeat expansion causes a toxic gain of function leading to rapid progressive loss of motor neurons



Decrease Transcription

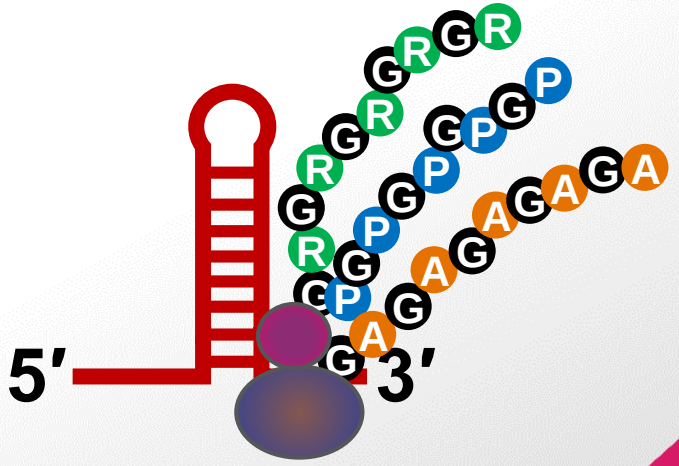
C9orf72 protein

Repeat RNA-mediated toxicity



RBP = RNA Binding Protein

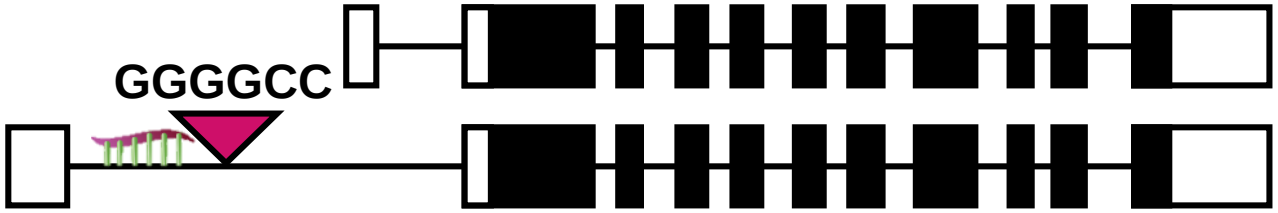
Dipeptide protein toxicity



C9ORF72 Molecular Pathology

Mutant C9ORF72 toxic gain of function

In preclinical studies, we showed that we can selectively reduce the toxic C9ORF72 RNA with a C9 antisense oligonucleotide and demonstrated reduced behavioral deficits were sustained

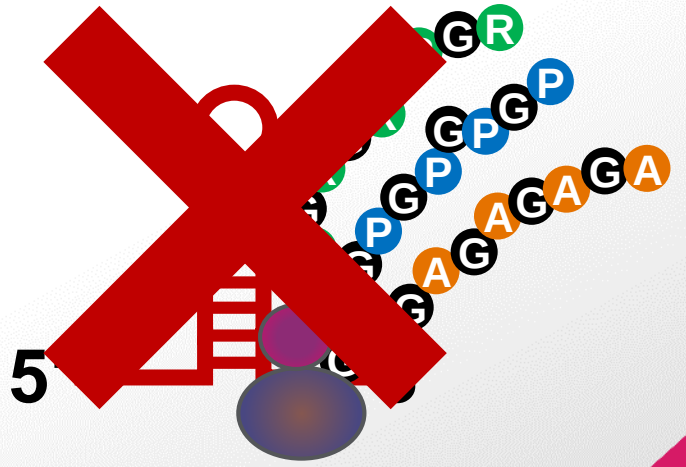


Decrease Transcription

Repeat RNA-mediated toxicity

RBP = RNA Binding Protein

Dipeptide protein toxicity



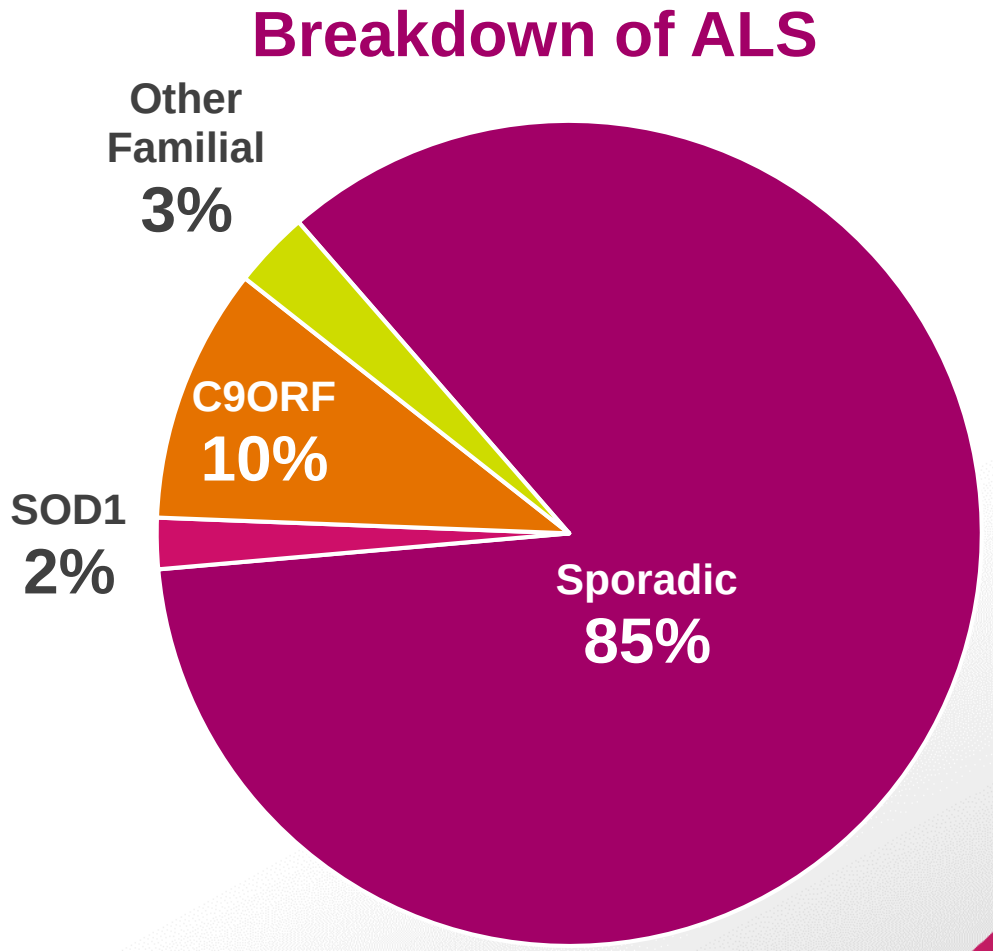
IONIS-C9$_{Rx}$ (BIIB078): Proof of Concept Obtained in Several Preclinical Models of the Disease

- Preclinical **data** show that we can **selectively** inhibit mutant **C9ORF72** transcript
- Phase 1/2 study **ongoing** (initiated Q4 2018)

ALS is a Fatal Disease with a Tremendous Unmet Medical Need

Ionis and Biogen committed to addressing all forms of ALS

- Tofersen: The **first** to demonstrate **significant reductions** in **SOD1** and trends in slowing of disease progression
- IONIS-C9$_{Rx}$: **Phase 1/2 study ongoing** (initiated Q4 2018)
- **New programs** expected to reach development for **sporadic** ALS and **additional** forms of **familial** ALS in the near future



IONIS

Leading the Way in Developing Treatments for Huntington's Disease, Alzheimer's Disease and Frontotemporal Dementia

Holly Kordasiewicz, Ph.D.

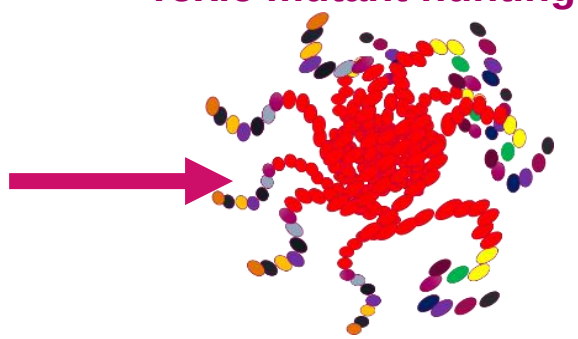
Executive Director,
Neurological Drug Discovery

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

>35 repeats

HD Gene ….CCTTC**CAGCAGCAGCAG**…….CCGCC…

Toxic mutant huntingtin



HEREDITARY — Caused by a toxic gain-of-function triplet repeat (CAG) expansion in the huntingtin gene, 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 & 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.

IONIS

IONIS-HTT$_{Rx}$ (RG6042) Potentially the First Disease Modifying Medicine for Huntington's Disease

- **Phase 1/2** data demonstrated
  - **Robust reductions** in mutant **huntingtin** protein
  - mHTT **reduction** correlated with **improvement** in clinical measures of **HD***
  - Favorable **safety** and **tolerability** profile
- **Phase 3** study **underway** by Roche

IONIS

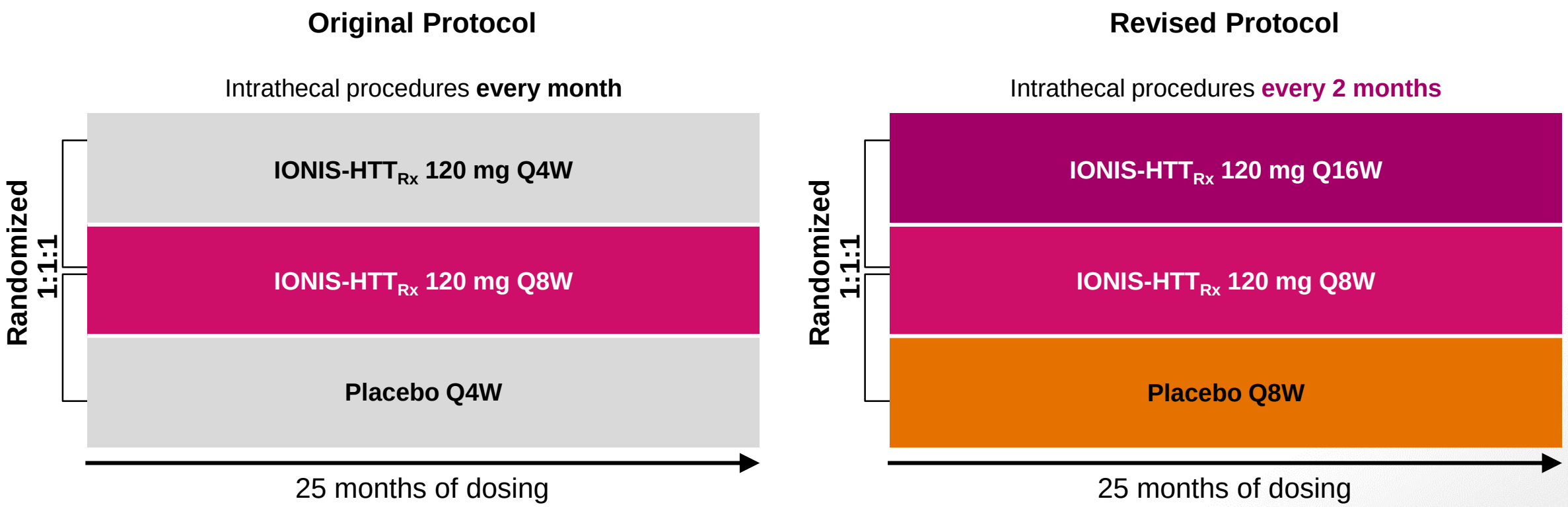
*Based on a post-hoc analysis

IONIS-HTT$_{Rx}$ (RG6042) Demonstrates Robust and Durable Mutant Huntingtin Reductions in the Ongoing OLE Study to Support Less Frequent Dosing

- **Demonstrated** mutant huntingtin (mHTT) reduction with bi-monthly dosing that was robust and durable to support less frequent dosing
- **No overall advantage** to monthly treatment versus bi-monthly, based on the totality of the data, including safety and tolerability
- **Replaced monthly** dosing arm of the pivotal study with a tri-annual (every 4 months) dosing arm
- **Updated pivotal** study design with less frequent dosing is more manageable for patients and physicians
- **Not expected to delay** timing of study completion

IONIS

Phase 3 Study Revised with Less Frequent Dosing



OLE study support the continued development of IONIS-HTT$_{Rx}$ with less frequent dosing regimen

OLE, open-label extension; Q4W, once every month; Q8W, every 2 months; Q16W, every 4 months.

Robust Investment Coupled to a Rapid to Market Strategy

Phase I/IIa[1,2]
(Completed: End 2017)

- First-in-human study
- Safety, tolerability, PK/ PD
- Early manifest HD patients
- N=46

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Targeting Huntingtin Expression in Patients with Huntington's Disease

Sarah J. Tabrizi, M.B., Ch.B., Ph.D., Blair R. Leavitt, M.D., C.M., G. Bernhard Landwehrmeyer, M.D., Edward J. Wild, M.B., B.Chir., Ph.D., Carsten Saft, M.D., Roger A. Barker, M.R.C.P., Ph.D., Nick F. Blair, M.B., B.S.,* David Craufurd, M.B., B.S., F.R.C.Psych., Josef Priller, M.D., Hugh Rickards, M.D., Anne Rosser, M.B., B.Chir., Ph.D., Holly B. Kordasiewicz, Ph.D., Christian Czech, Ph.D., Eric E. Swayze, Ph.D., Daniel A. Norris, Ph.D., Tiffany Baumann, B.S., Irene Gerlach, Ph.D., Scott A. Schobel, M.D., Erika Paz, B.S., Anne V. Smith, Ph.D., C. Frank Bennett, Ph.D., and Roger M. Lane, M.D.

Open-Label Extension[3]
(Q1 2018)

Ongoing studies

HD Natural History Study[4]

GENERATION HD1[5,6]
(Phase III Q1 2019)

GEN-EXTEND[7]*
(OLE)

GEN-PEAK[8] *(Planned)*

IONIS

* There will be a temporary pause in enrolment of new patients to allow for the protocol amendment to be fully approved and in place at a study site. HD, Huntington's disease; OLE, open-label extension; PD, pharmacodynamic; PK, pharmacokinetic; Q4W, once every month; Q8W, every 2 months. 1. Tabrizi SJ, et al. N Engl J Med. 2019; 2. Clinicaltrials.gov/show/NCT03342053 (Accessed March 2019); 3. Clinicaltrials.gov/show/NCT03664804 (Accessed March 2019); 4. Clinicaltrials.gov/show/NCT03761849 (Accessed March 2019); 5. Schobel S, et al. Presented at EHDN plenary meeting 2018; Available at: http://bit.ly/2NhPBAz (Accessed March 2019); 6. Clinicaltrials.gov/show/NCT03842969 (Accessed March 2019); 7. Planned study to commence in 2019. Data on file.

Long-Term Dosing of IONIS-HTT$_{Rx}$ (RG6042) is Well Tolerated at 9-Month Interim Assessment

No acute or serious safety issues identified requiring modification of protocol or program

Bi-monthly dosing has less adverse events than monthly dosing

- 157 adverse events, which were mostly mild to moderate in severity
  - ✓ 4 non-drug related SAEs
  - ✓ 0 possibly drug related

Monthly dosing arm adverse events

- 254 adverse events, which were mostly mild to moderate in severity
  - ✓ 4 non-drug related SAEs*
  - ✓ 3 possibly drug-related SAEs

120 mg IONIS-HTT$_{Rx}$ Q8W appears more suitable for chronic dosing relative to Q4W

IONIS

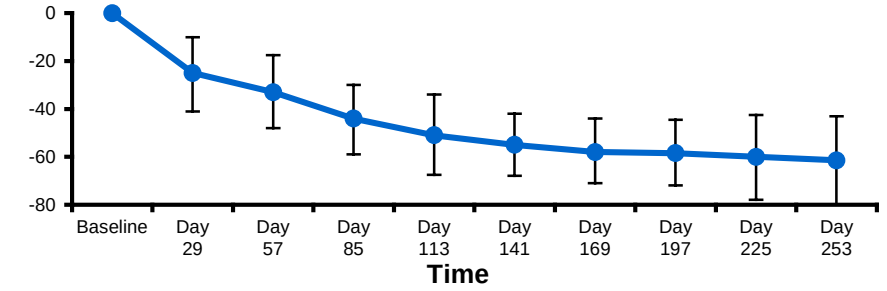
Datacut: January 2019. *One non-drug related death (suicide in patient with a family history of suicide in two members).
AE, adverse event; Q4W, once every month; Q8W, every 2 months; SAE, serious AE.

Demonstrated Robust and Sustained Lowering of mHTT and Transient Changes in Neurofilament at 9-Month Interim Assessment

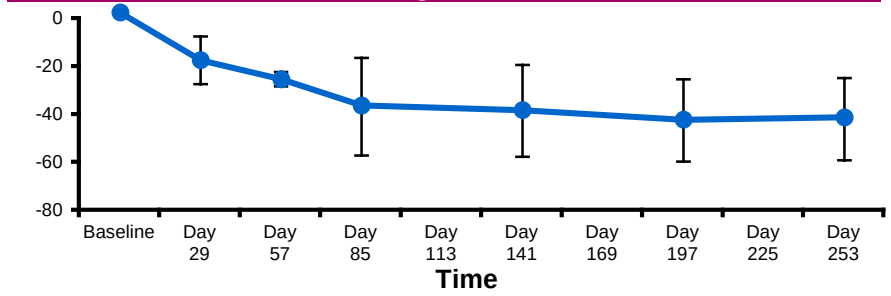
CSF mHTT lowering occurs from first follow-up measurement and is persistent

CSF mHTT % change

Q4W

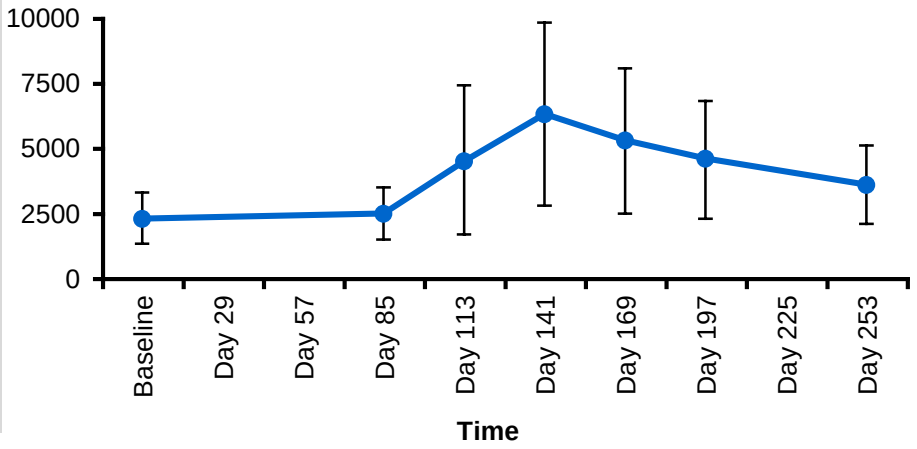


Q8W

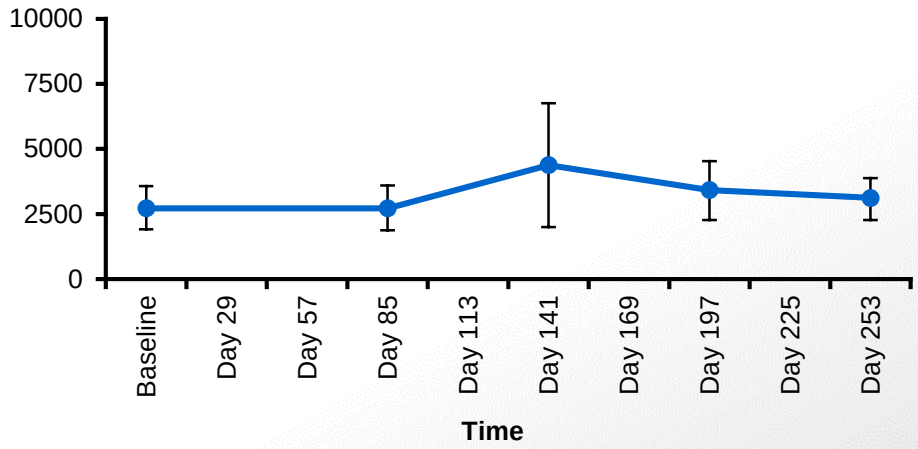


CSF NfL (ng/L)

Q4W



Q8W



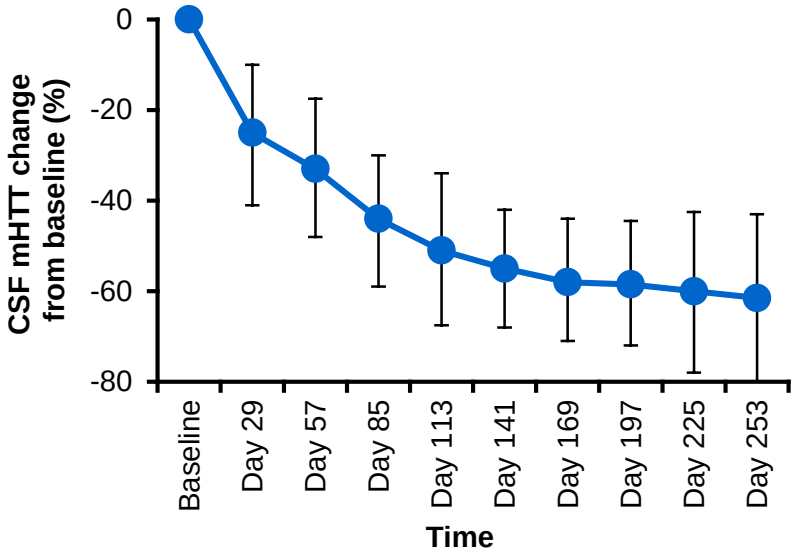
CSF NfL increases at ~month 5 then decreases while on continued treatment

No safety issues associated with transient NfL increase

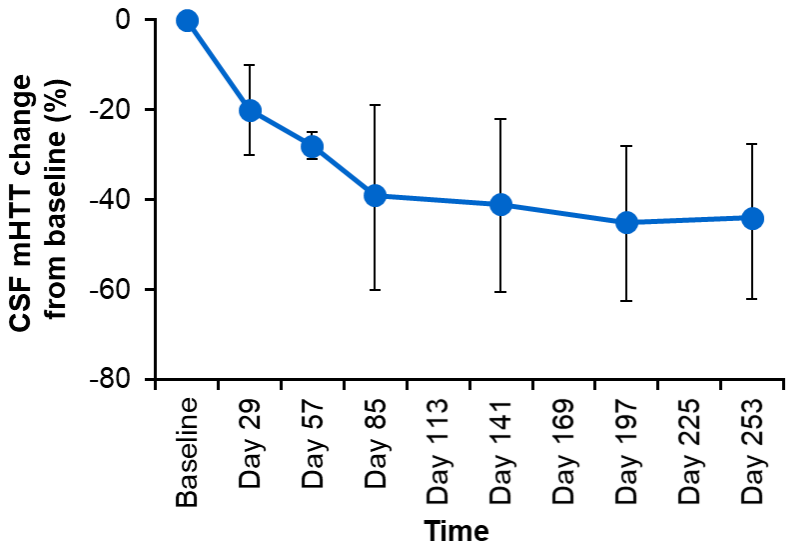
Data points represent mean values and error bars represent standard deviations.
CSF, cerebrospinal fluid; mHTT, mutant huntingtin protein; NfL, neurofilament light chain; OLE, open-label extension; Q4W, once every month; Q8W, every 2 months.

Demonstrated Robust and Sustained Lowering of mHTT at 9-Month Interim Assessment

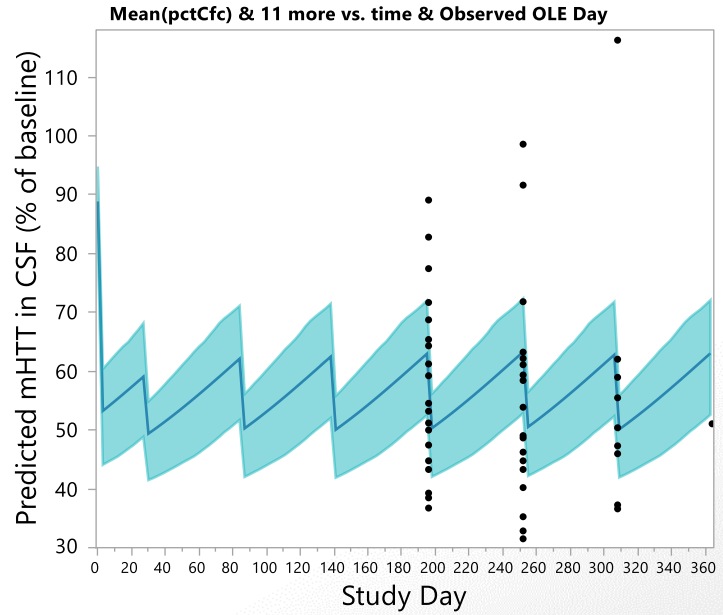
IONIS-HTT$_{Rx}$ Q4W



IONIS-HTT$_{Rx}$ Q8W



Preclinical Model



CSF mHTT lowering is consistent with preclinical model predictions and exceeds our target for the program in both arms

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Demonstrated Robust and Sustained Lowering of mHTT at 9-Month Interim Assessment

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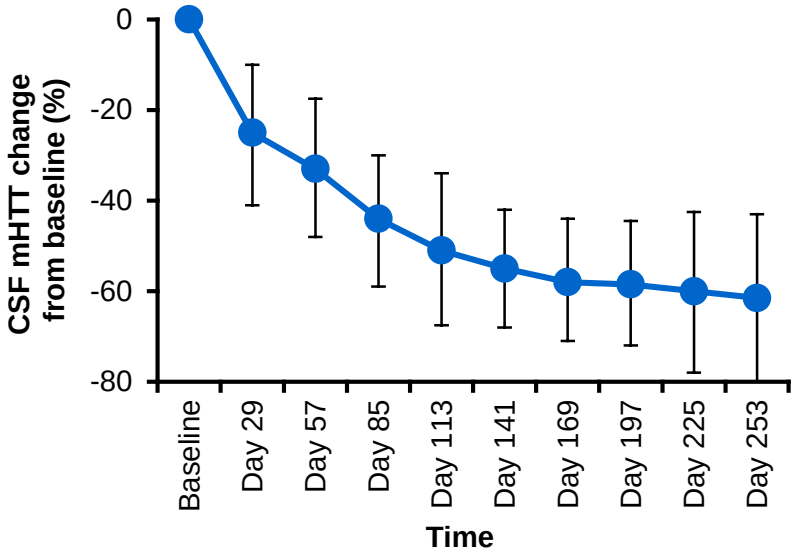
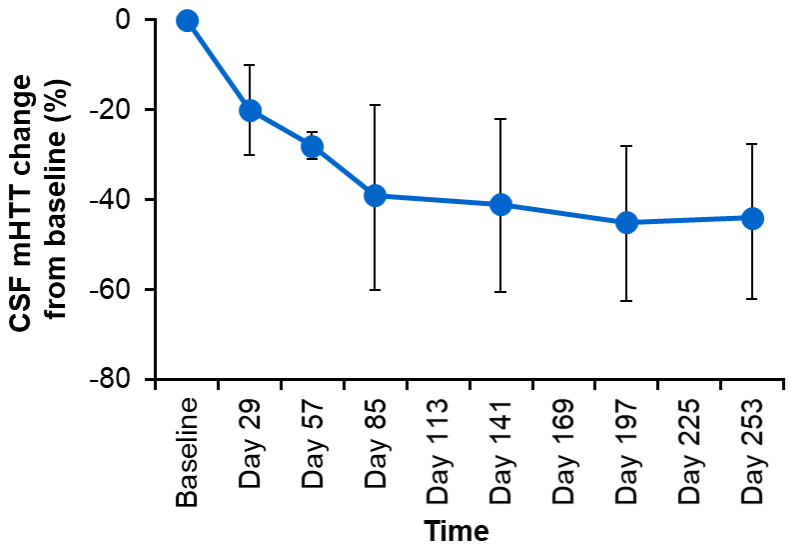


IONIS-HTT$_{Rx}$ Q8W



% CSF HTT KD	% HTT KD in cortex	% HTT KD in caudate
20–30	**30–55**	5–20
40–50	**55–80**	**25–45**

CSF mHTT lowering is consistent with preclinical model predictions and exceeds our target for the program in both arms

Data points represent mean values and error bars represent standard deviations.
CSF, cerebrospinal fluid; mHTT, mutant huntingtin protein; NfL, neurofilament light chain; OLE, open-label extension; Q4W, once every month; Q8W, every 2 months.

IONIS-HTT$_{Rx}$ (RG6042): First Potential Disease-Modifying Medicine

- **Robust reductions** in mutant huntingtin protein
- mHTT reduction correlated with **improvement** in clinical measures of **HD**
- **Favorable** safety and tolerability profile
- **Phase 3** study **underway** by Roche
- Roche plans to engage with regulators regarding an **accelerated path** to patients

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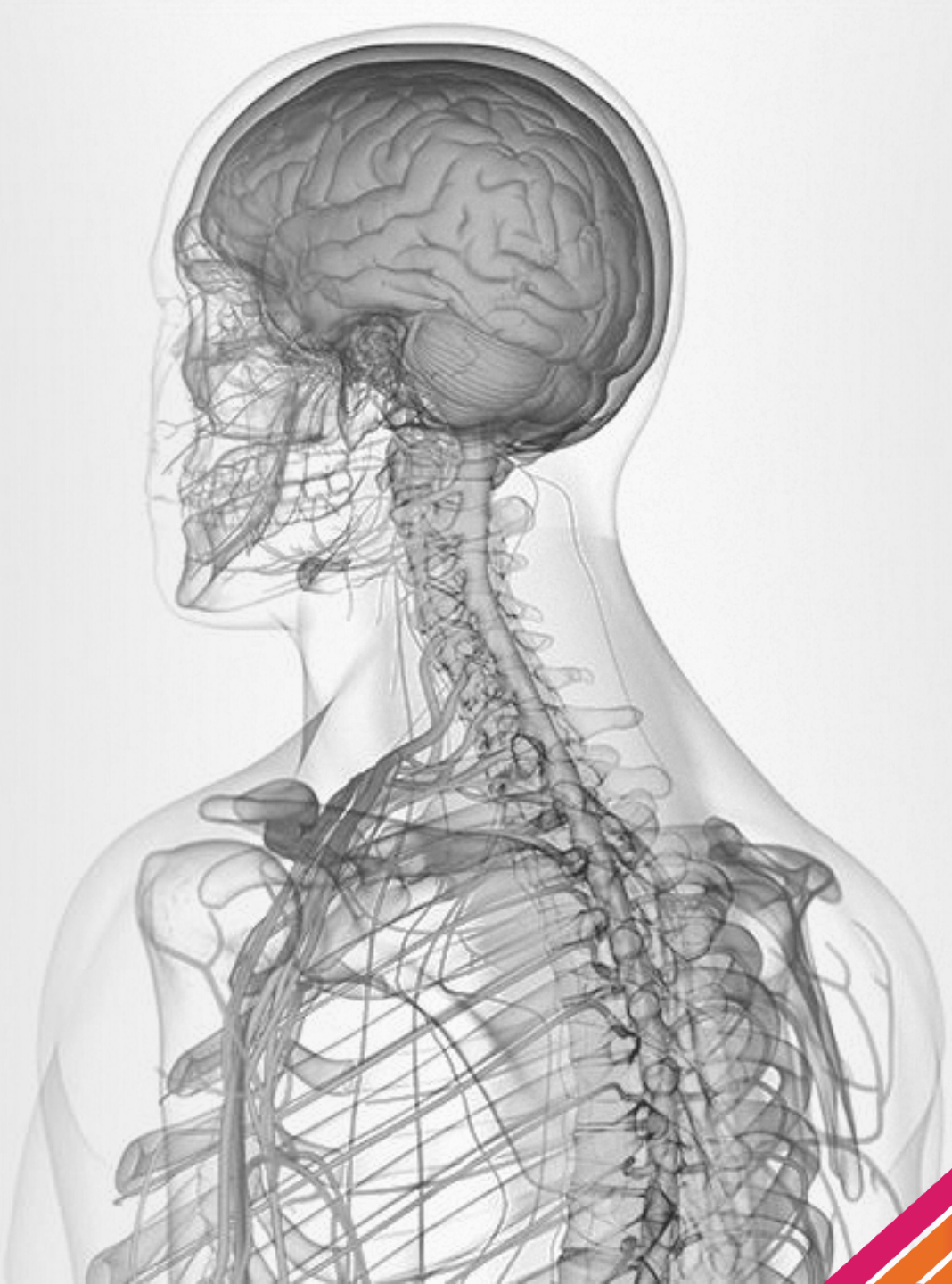
Alzheimer's Disease and Frontotemporal Dementia



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

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

- Accumulation of pathologic tau is an AD pathology and correlates with cognitive decline in AD[1]
- FTD typically occurs following the accumulation of neuronal proteins, including tau

Approximately
5.5 million
people are living
with **AD** in the U.S.[2]

Approximately
50,000 – 60,000
people are affected
by **FTD** in the U.S.[3]

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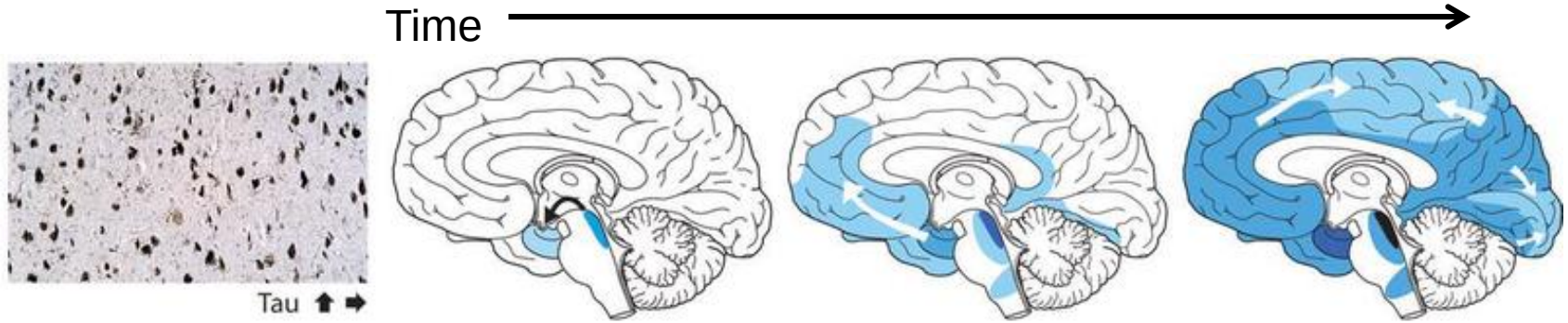
1. Huang Y and Mucke L. Alzheimer mechanisms and therapeutic strategies. Cell 2012; 148(6): 1204-1222; 2. Latest Alzheimer's Facts and Figures. Latest Facts & Figures Report | Alzheimer's Association (2013). Available at: //www.alz.org/facts/overview.asp.; 3. Knopman DS and Roberts RO. Estimating the number of persons with frontotemporal lobar degeneration in the US population. J Mol Neurosci 2011; 45: 330-335

IONIS-MAPT$_{Rx}$ (BIIB080): Designed to Selectively Reduce the Microtubule-Associated Protein Tau (MAPT)*

MAPT, or **tau protein**, is a contributor or cause of certain neurodegenerative diseases, characterized by abnormal tau protein in neurons and non-neuronal cells in the brain



Tau pathology increases in density (darker blue) and spreads throughout the AD brain over time.

MAPT antisense reversed pathology in disease mouse model by reducing tau

Phase 1/2 ongoing in patients with Alzheimer's disease

Phase 2/3 study planned in MAPT-FTD

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*Partnered with Biogen

Advancing Ionis' Neurological Pipeline

Eric Swayze, Ph.D.

Vice President,
Chemistry and Neuro Drug Discovery

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Advancing Ionis Neurological Pipeline Spanning Rare to Common Diseases

SPINRAZA
(Spinal Muscular Atrophy)

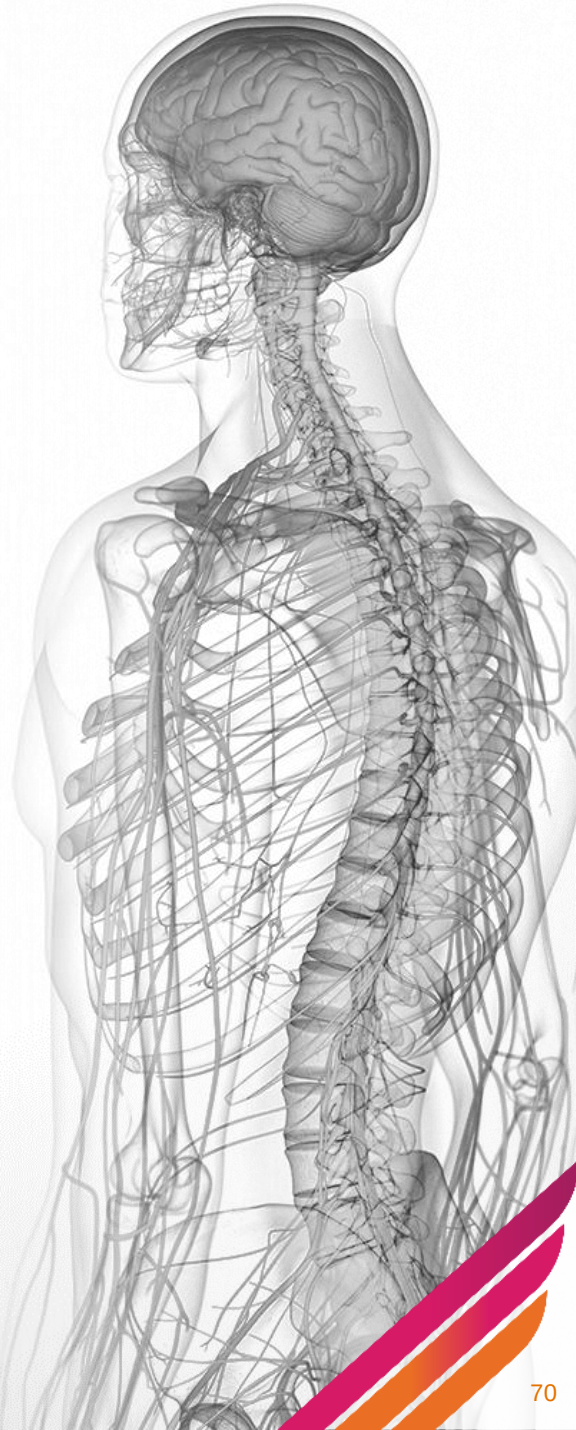
TEGSEDI *(hATTR)*

ATTR Amyloidosis
AKCEA-TTR-L_{Rx}

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

Dementia (Alzheimer and FTD)
IONIS-$MAPT_{Rx}$ (BIIB080)

Amyotrophic Lateral Sclerosis
Tofersen (IONIS-$SOD1_{Rx}$)
IONIS-$C9_{Rx}$(BIIB078)



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Ionis-owned **Partnered**

Advancing Ionis Neurological Pipeline Spanning Rare to Common Diseases

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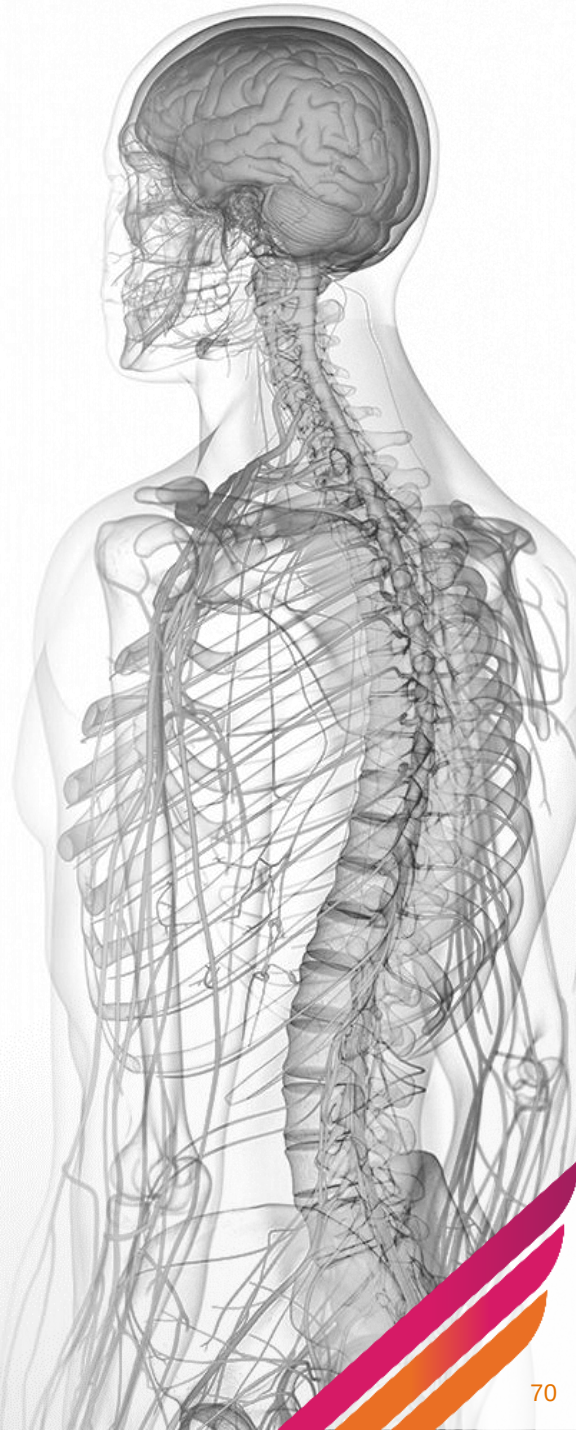
Neurodegenerative Diseases
IONIS-BIIB6$_{Rx}$
IONIS-BIIB7$_{Rx}$
IONIS-BIIB8$_{Rx}$

Alexander Disease
IONIS-GFAP$_{Rx}$

Prion Disease

Lafora Disease

Charcot-Marie-Tooth



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Ionis-owned **Partnered**

Projected Ionis Neurological Pipeline

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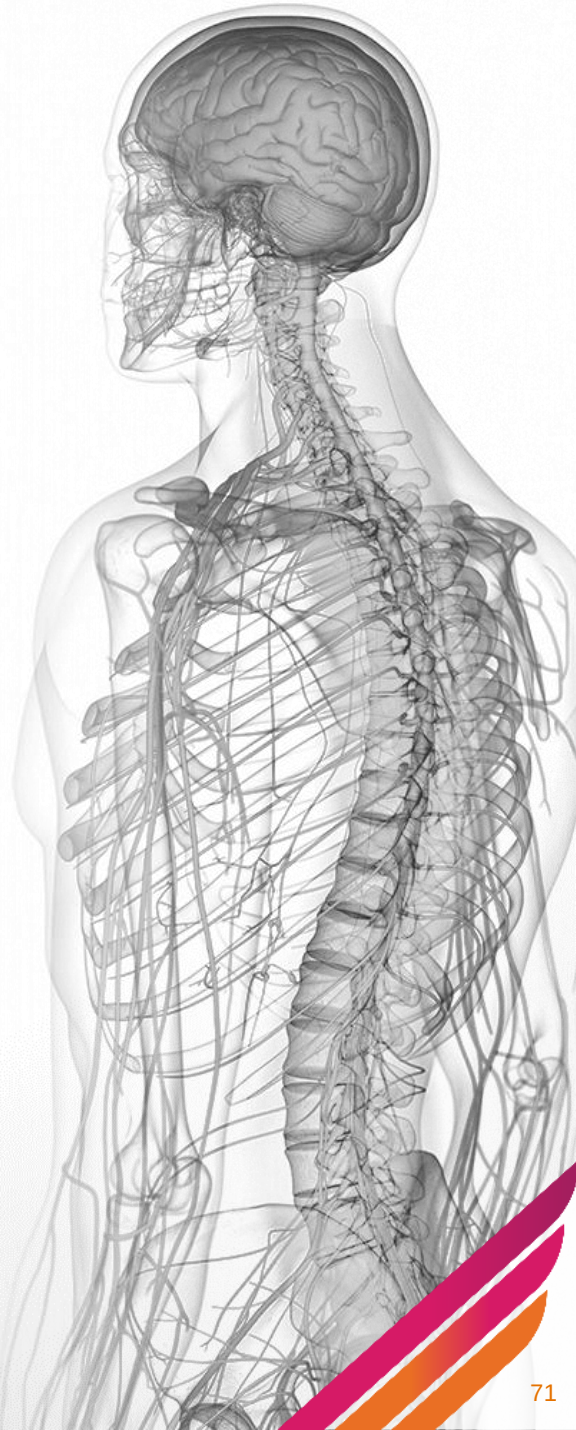

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Ionis-owned **Partnered**

Projected Ionis Neurological Pipeline

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Prion Disease

Lafora Disease

Charcot-Marie-Tooth

Myotonic Dystrophy

Spinocerebellar Ataxias

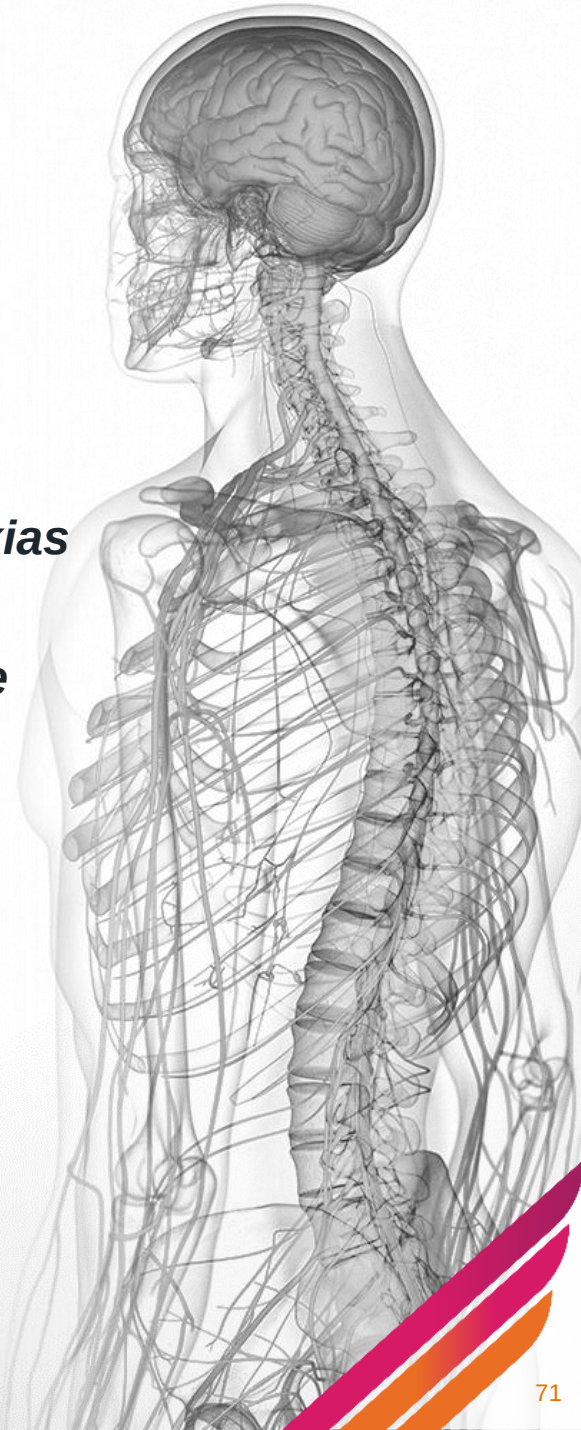
Angelman Syndrome

Multiple Sclerosis

Parkinson's Disease

Alzheimer's Disease

Pain



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Ionis-owned | Partnered | Near-term

IONIS NEUROLOGY PIPELINE – 2019

Stage	Partnered	Ionis
DISCOVERY RESEARCH	BIIB Undisclosed BIIB Undisclosed BIIB Undisclosed BIIB Undisclosed BIIB Undisclosed BIIB Undisclosed BIIB Undisclosed BIIB Undisclosed BIIB Undisclosed BIIB Undisclosed BIIB Undisclosed BIIB Undisclosed	Ionis Undisclosed Ionis Undisclosed Ionis Undisclosed Ionis Undisclosed Ionis Undisclosed Ionis Undisclosed Ionis Undisclosed Ionis Undisclosed Ionis Undisclosed Ionis Undisclosed Ionis Undisclosed
DRUG DISCOVERY	BIIB Undisclosed BIIB Undisclosed BIIB Undisclosed BIIB Undisclosed BIIB Undisclosed BIIB undisclosed SMN-Follow on	Charcot-Marie-Tooth Lafora Disease Prion Disease Ionis Undisclosed Ionis Undisclosed Ionis Undisclosed
PRE-CLINICAL DEV	IONIS- BIIB8 IONIS- BIIB7 IONIS- BIIB6	IONIS-GFAP$_{Rx}$ AxD
PHASE 1/2A	Tofersen* (IONIS-SOD1$_{Rx}$) IONIS-MAPT$_{Rx}$ (BIIB080) IONIS-C9$_{Rx}$ (BIIB078)	AKCEA-TTR-L$_{Rx}$
PHASE 3	IONIS-HTT$_{Rx}$ (RG6042)	
COMMERCIAL	SPINRAZA	TEGSEDI

*Biogen is collaborating with regulators to further define the scope of the clinical data package required to support the registration of Tofersen

Prion: A Fatal Neurodegenerative Disease

- Rare, progressive and **fatal** neurodegenerative disease
- Causative agent: prions, composed of **misfolded PrP protein** (PrP^{Sc})
- Toxic Prp^{Sc} **spreads** throughout the brain by inducing misfolding
- **Prion** antisense **enhanced survival** in preclinical model
- **Development candidate** expected in 2020

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Alexander's: Severe and Typically Fatal Neurodegenerative Disease

- **Severe**, progressive, rare **neurodegenerative** disease and usually **fatal**
  - Patients often experience seizures, loss of body movements and developmental delays
- Caused by autosomal dominant missense **mutation** in glial fibrillary acidic protein (GFAP)
- GFAP **antisense** has been shown to **reverse pathology** and **improve disease** (Hagemann, et al. *Ann. Neurol.* 2018*, 83*, 27-39)
- Phase 1 **initiation** expected in 2020
- **No** current treatment for Alexander's disease

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We Are Applying Pioneering Advances in Antisense to Neurological Disease Drug Development

Focused **medicinal chemistry**

- Enhanced potency via improved affinity to RNA
- Enhanced duration via increased stability

Better Drugs

Increased Patient Convenience

Higher Commercial Value

We Are Applying Pioneering Advances in Antisense to Neurological Disease Drug Development

Focused **medicinal chemistry**

- Enhanced potency via improved affinity to RNA
- Enhanced duration via increased stability

Basic research on antisense **mechanisms**

- Increased therapeutic index
- Enhanced efficiency of platform
- Able to modulate expression up and down

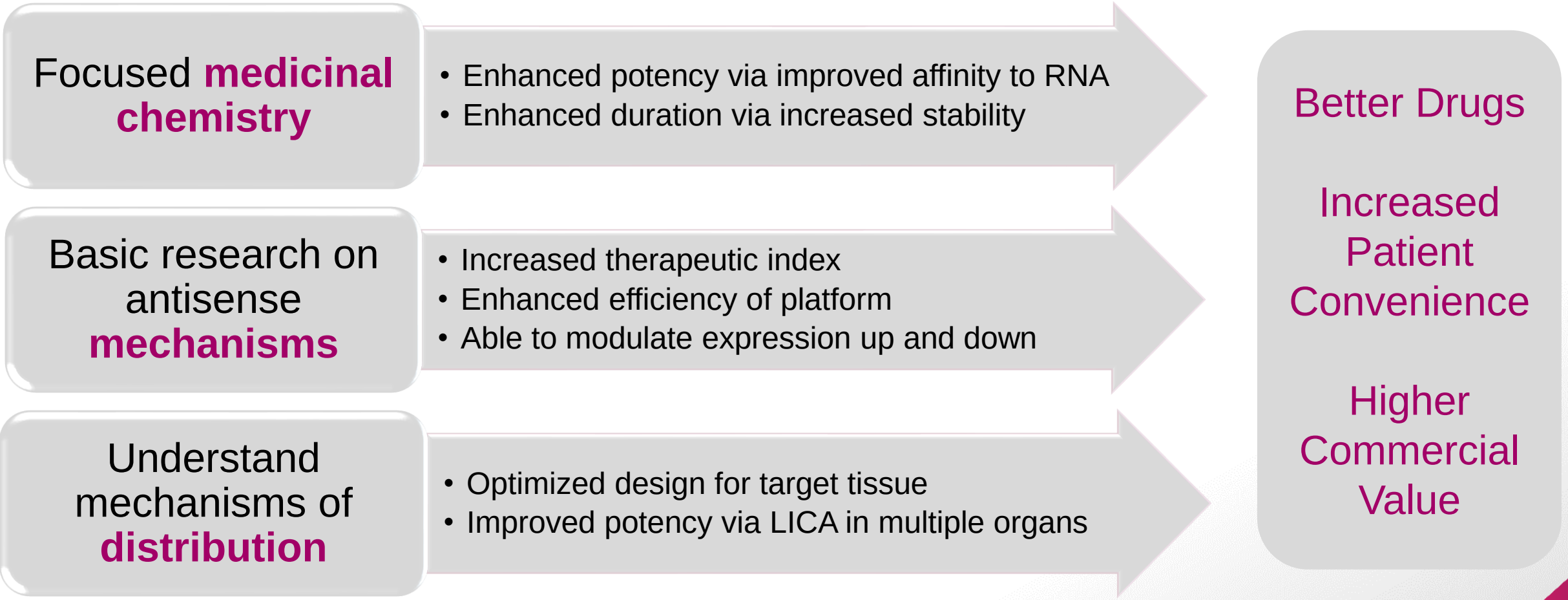
Better Drugs

Increased Patient Convenience

Higher Commercial Value

IONIS™

We Are Applying Pioneering Advances in Antisense to Neurological Disease Drug Development



IONIS™

Ionis: The Leader in RNA-Targeted Therapeutics

Stanley Crooke, M.D., Ph.D.

Chief Executive Officer and Chairman

IONIS

Ionis: The Leader in RNA-Targeted Therapeutics

- **Antisense:** A novel and more efficient drug discovery platform
- **Rapidly** incorporate the advances in the technology into our pipeline
- **Focusing** on bringing maximum value to the patients who need it the most
- **Focus** on the truly novel molecular targets that revolutionize therapy
- **Constantly** expand and advance our pipeline in both rare and common diseases
- **Continuing** to retain an ever greater fraction of commercial revenues

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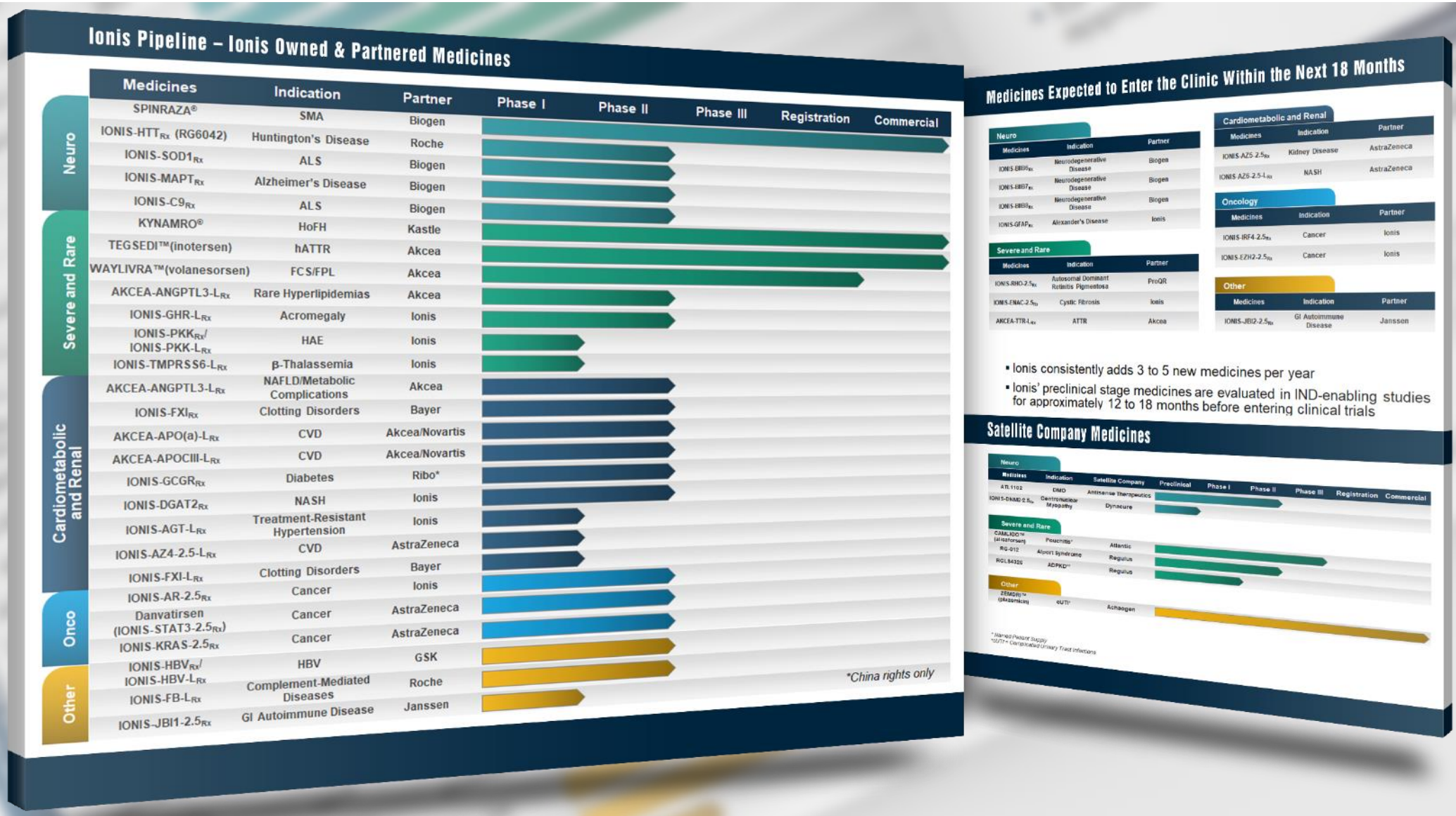
Ionis Today:
Advancing and Growing Pipeline of Over 40 Medicines



Large Late-Stage Pipeline Delivers the Next Transformative Commercial Opportunities

- **First-** or **best-in-class** medicines with transformative potential
- Numerous medicines with **blockbuster** potential
- Spanning **rare** to **common** patient populations
- **10+ medicines** with potential to enter **phase 3** studies in 2 years
- **4+ medicines** planned to enter **phase 3** studies in 2019

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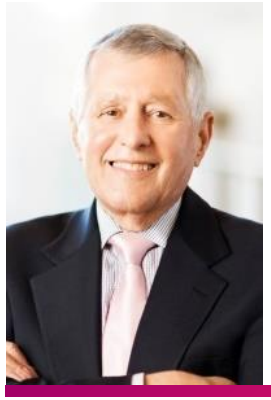
Planned Technology Webcast in 2H 2019

Advances in Antisense Technology

Q&A



Stanley Crooke, M.D., Ph.D.
CEO and Chairman
Ionis Pharmaceuticals

C. Frank Bennett, Ph.D.
SVP Research
Ionis Pharmaceuticals

Brett Monia, Ph.D.
Chief Operating Officer
Ionis Pharmaceuticals

Eric Swayze, Ph.D.
VP, Chemistry & Neurological Drug Discovery
Ionis Pharmaceuticals

Holly Kordasiewicz, Ph.D.
ED, Neurological Drug Discovery
Ionis Pharmaceuticals

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Ionis: A Force for Life