Neurology Webcast

July 14, 2020

Forward Looking Language Statement

This presentation includes forward-looking statements regarding our business, financial guidance and the therapeutic and commercial potential of SPINRAZA® (nusinersen) and Ionis' technologies and products in development, including Ionis' neurology franchise. Any statement describing Ionis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, including those related to the impact COVID-19 could have on our business, and including but not limited to those related to our commercial products and the medicines in our pipeline, and particularly those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. Ionis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' annual report on Form 10-K for the year ended December 31, 2019 and our most recent Form 10-Q quarterly filing, 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's Presenters

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

C. Frank Bennett, Ph.D.
Chief Scientific Officer
Ionis Pharmaceuticals

Holly Kordasiewicz, Ph.D.
VP, Neurology Research
Ionis Pharmaceuticals

Frank Rigo, Ph.D.
VP, Functional Genomics & Drug Discovery
Ionis Pharmaceuticals

Today's Agenda

Welcome and Introductions	Wade Walke
Ionis – The Leader in RNA-targeted Drug Discovery and Development	Brett Monia
Ionis – The Leader in Targeting Neurological Diseases	Frank Bennett
Amyotrophic Lateral Sclerosis	Frank Bennett & Frank Rigo
Alzheimer's Disease and Dementia	Holly Kordasiewicz
Parkinson's Disease and Multiple System Atrophy	Holly Kordasiewicz
Spinocerebellar Ataxias	Holly Kordasiewicz
Ionis-owned Medicines – Prion, Lafora and Alexander's Diseases	Holly Kordasiewicz
Conclusion	Brett Monia
Q&A	All

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Ionis – The Leader in RNA-targeted Drug Discovery and Development

Brett Monia

IONIS™

Where We Are Today

Our leadership position in RNA-targeted therapeutics **continues to grow** as our technology advances

We have a **large, diverse, expanding, and mature pipeline** that continues to perform exceptionally well

The Ionis-owned pipeline is a key priority, will expand substantially, and investments are underway to enhance our commercial capabilities

We have the **financial strength** to continue advancing our technology and deliver on our pipeline

Vision	**To become the innovation leader in biotech providing hope and transformational benefit to millions of patients living with severe diseases**

Ionis Delivering Medicines for Most Major Severe Diseases

NEUROLOGICAL

NEUROMUSCULAR

CARDIOVASCULAR

Ultra-rare to Common Diseases

CANCER

HEMATOLOGICAL

KIDNEY

OPHTHALMOLOGY

INFECTIOUS DISEASE

IONIS™

The Ionis Neurological Disease Pipeline

CRACKING THE CODE

Validated platform
- Proof of mechanism
- Proof of efficacy
- Proof of safety
- Commercial success

A rapidly expanding premier pipeline
tackling the most severe diseases

Continued technology advancement
- Greater efficacy
- Less frequent dosing
- Systemic applications (e.g. neuromuscular)

IONIS™

Ionis is Cracking the Code in Neurological Diseases

SPINRAZA
Spinal muscular atrophy

ATTR amyloidosis
TEGSEDI for hATTR polyneuropathy
AKCEA-TTR-L_{Rx} for all major forms

Huntington's disease
Tominersen (IONIS-HTT_{Rx})

Alzheimer's disease
IONIS-$MAPT_{Rx}$

Amyotrophic lateral sclerosis
Tofersen (IONIS-$SOD1_{Rx}$), IONIS-$C9_{Rx}$,
ION541 (Sporadic), ION363 (FUS)

Parkinson's disease
ION859

Centronuclear myopathy
IONIS-DNM2-2.5$_{Rx}$

Alexander disease
ION373

Prion disease
ION716

Lafora disease
ION283

Multiple System Atrophy
ION464

Angelman syndrome
ION581

Severe epilepsies
Multiple Programs

Leukodystrophies

Myotonic dystrophy

Spinocerebellar ataxias

Spinal and Bulbar muscle atrophy

Charcot-Marie-Tooth

Multiple sclerosis

Severe pain

And many more in research stage

IONIS™

Ionis is Cracking the Code in Neurological Diseases

Ionis-owned Neurological Programs

SPINRAZA
Spinal muscular atrophy

ATTR amyloidosis
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Multiple sclerosis

Severe pain

And many more in research stage

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Ionis – The Leader in Targeting Neurological Diseases

Frank Bennett

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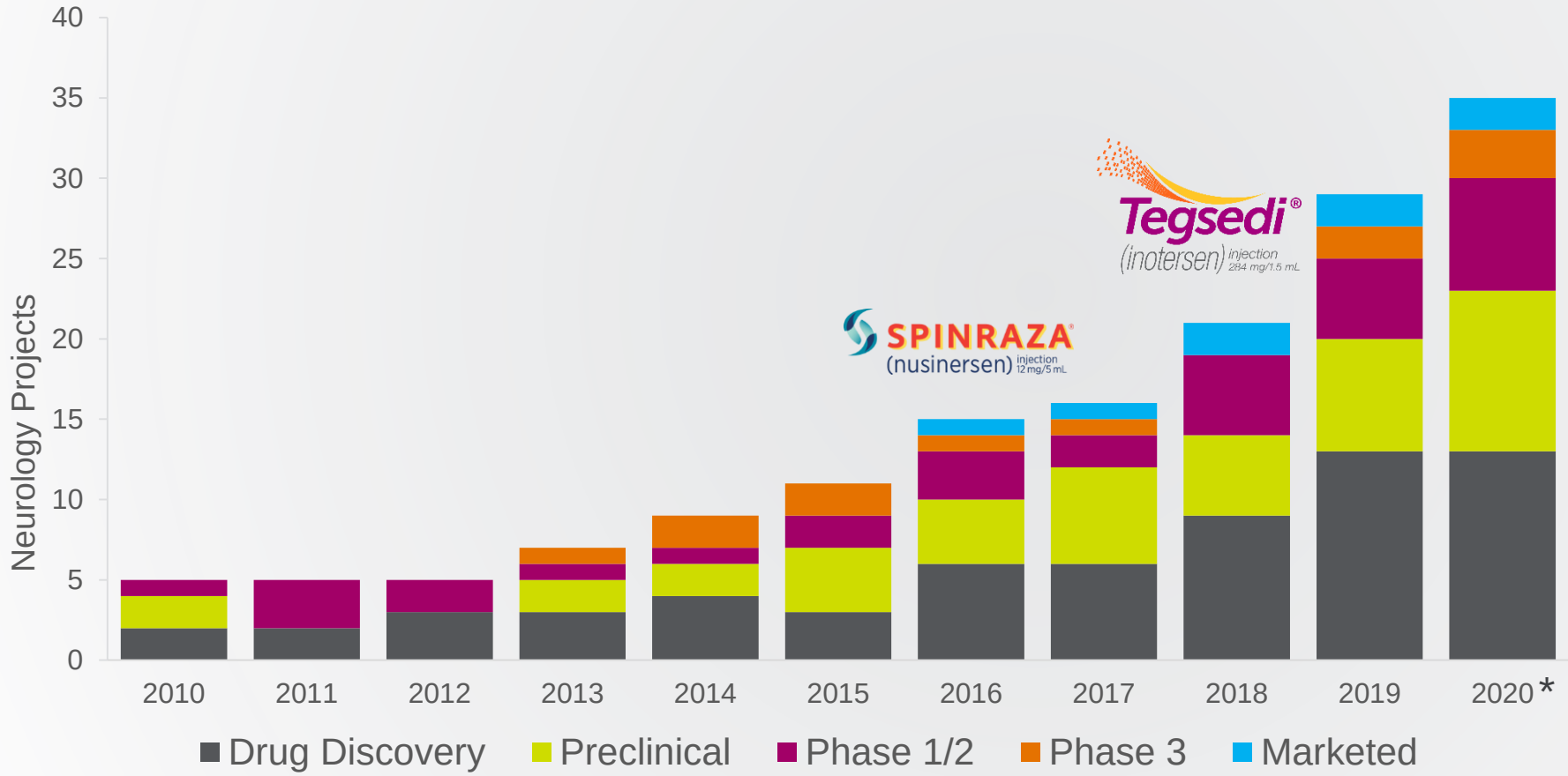
Advancing and Expanding Ionis' Neurology Pipeline



Pre-clinical and Clinical Development Programs*

- Tominersen (HD)
- Tofersen (ALS)
- TTR-L_{Rx} (ATTR)
- IONIS-$MAPT_{Rx}$ (AD)
- IONIS-$C9_{Rx}$ (ALS)
- ION859 (PD)
- IONIS-DNM2-2.5_{Rx} (Centronuclear Myopathy)
- ION373 (AxD)
- ION464 (MSA)
- ION541 (ALS)
- ION363 (ALS)

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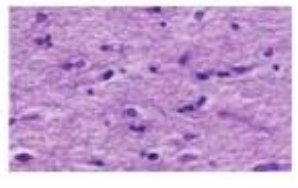
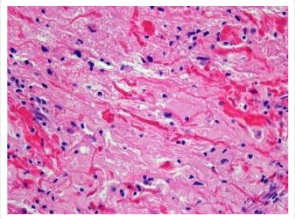
* Projected by year-end 2020

Many Neurodegenerative Diseases are Caused by Toxic Proteins Expressed in Different Brain Regions

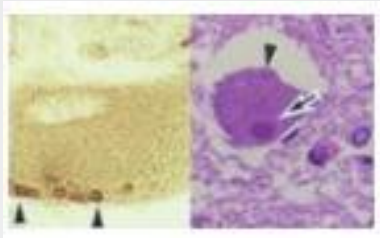
Huntington's disease
Whole brain atrophy
HTT protein aggregates

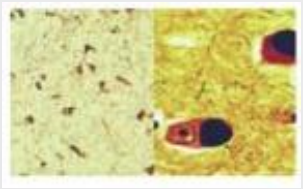


Alexander's disease
Loss of myelin predominantly in frontal lobe
Rosenthal fibers-**GFAP deposits**

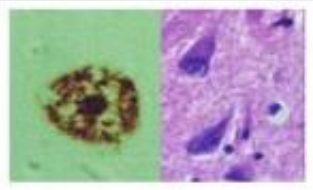


Amyotrophic lateral sclerosis
Atrophy of motor neurons and muscles
Sporadic: **TDP43 inclusions**
SOD1 Patients: **Misfolded SOD1**
C9 Patients: **Dipeptide repeats and RNA foci**

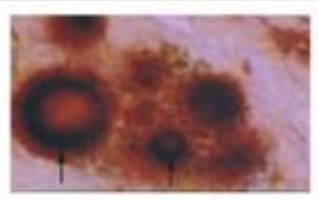




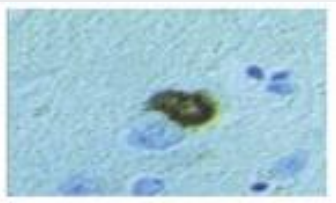
Frontotemporal dementia
Cerebral atrophy
Misfolded TAU



Alzheimer's disease
Cerebral and hippocampal atrophy
Aβ plaques, TAU tangles



Parkinson's disease
Loss of dopamine neurons in substantia nigra and cortical atrophy
Lewy bodies: **alpha-synuclein**



Lewy body disease
Cerebral atrophy
Lewy bodies: **alpha-synuclein**

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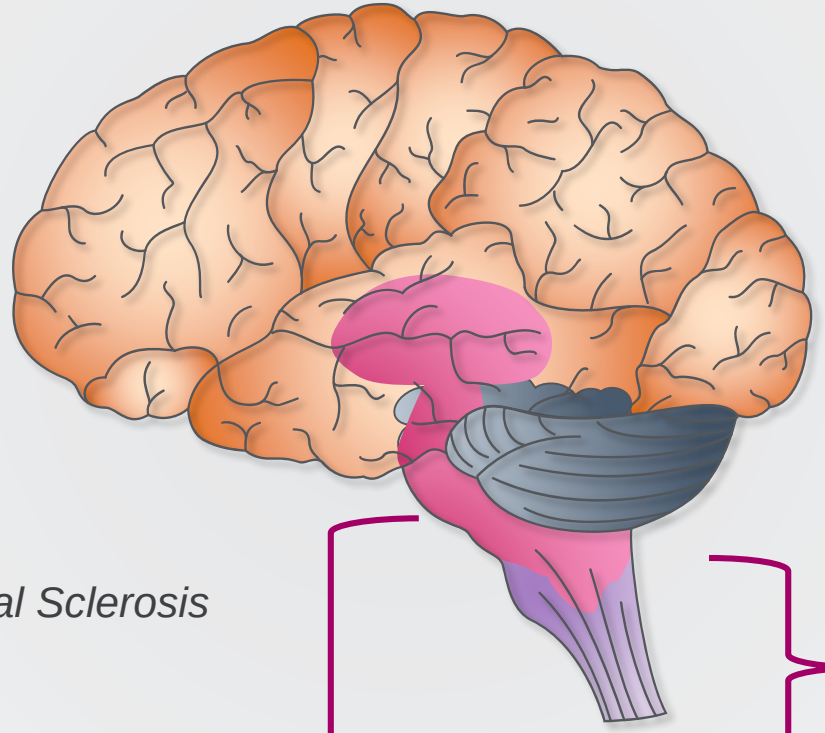
Ionis' Neurological Pipeline Targets All Major Brain Regions



Tofersen

SOD1-Amyotrophic Lateral Sclerosis

SPINRAZA® (nusinersen) injection 12 mg/5 mL

Spinal muscular atrophy

IONIS™

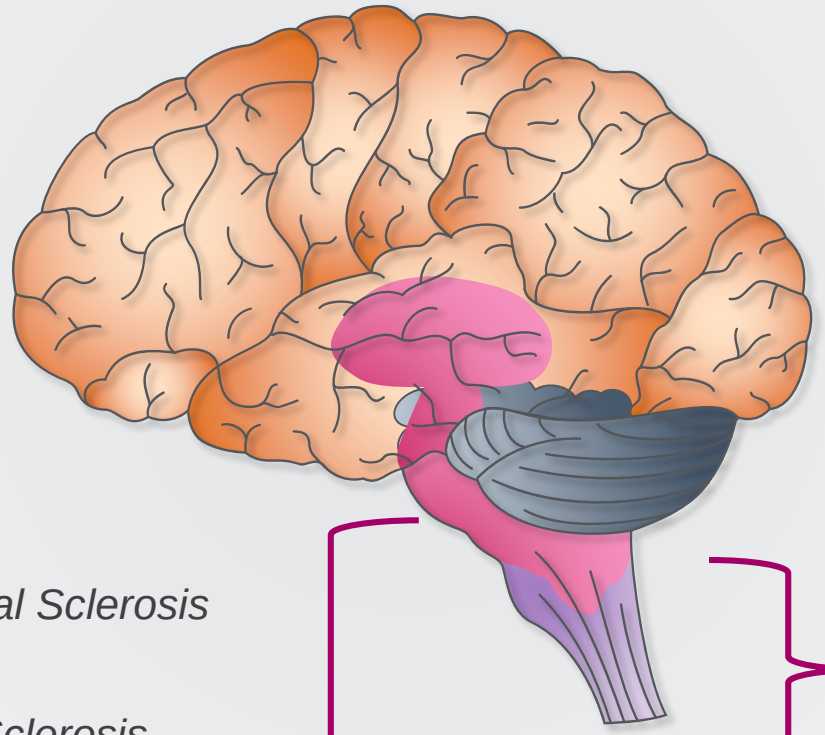
Ionis' Neurological Pipeline Targets All Major Brain Regions

Tominersen
Huntington's Disease

ION373
Alexander Disease

ION716
Prion Disease

ION283
Lafora Disease



IONIS-MAPT$_{Rx}$
Alzheimer's Disease and Tauopathies

ION859
Parkinson's Disease

ION464
Parkinson's Disease and synucleinopathies

Tofersen
SOD1-Amyotrophic Lateral Sclerosis

IONIS-C9$_{Rx}$
C9-Amyotrophic Lateral Sclerosis

ION541
Sporadic-Amyotrophic Lateral Sclerosis

ION363
FUS-Amyotrophic Lateral Sclerosis

SPINRAZA® (nusinersen) injection 12 mg/5 mL
Spinal muscular atrophy

IONIS™

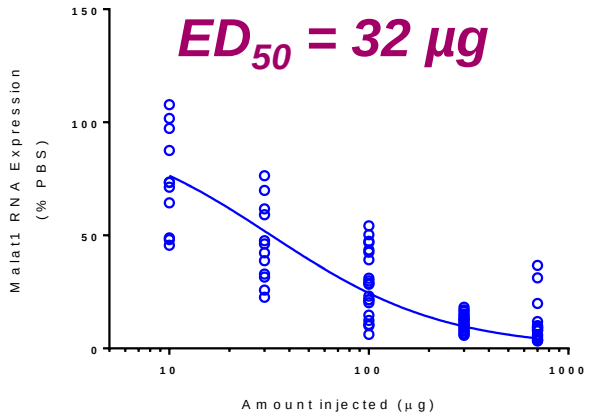
Phase 3
Phase 1/2
Preclinical

Antisense Targets All CNS Cell Types

- Wild type (normal) mice
- Intracerebroventricular (ICV) bolus injection of Malat1 antisense drug at a single dose
- Analyzed at 2 weeks after the dose by cell sorting with antibody and qPCR

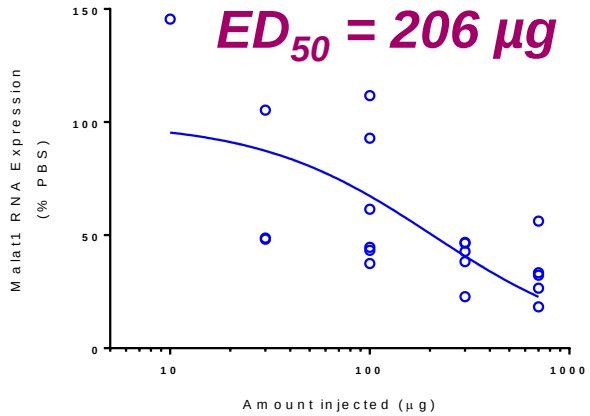
Total cortex RNA

ED_{50} = 32 µg



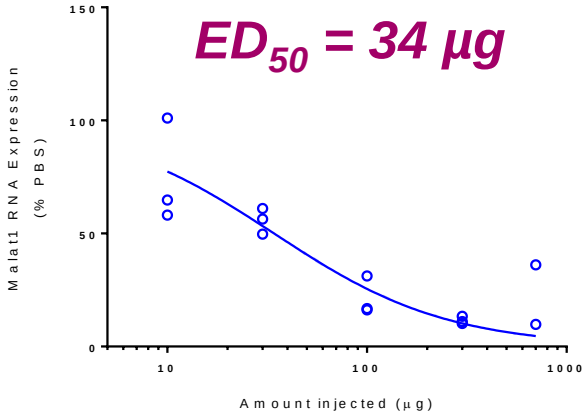
Neurons

ED_{50} = 206 µg



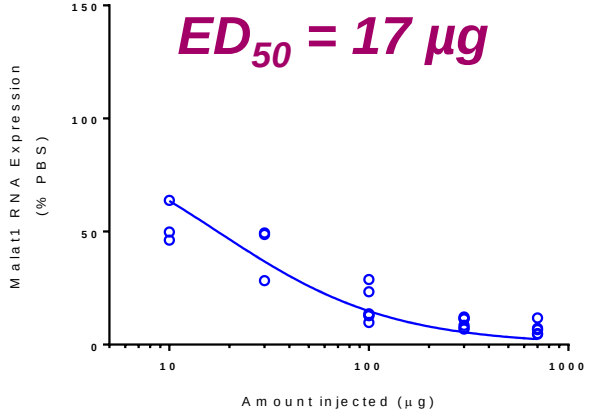
Oligodendrocytes

ED_{50} = 34 µg



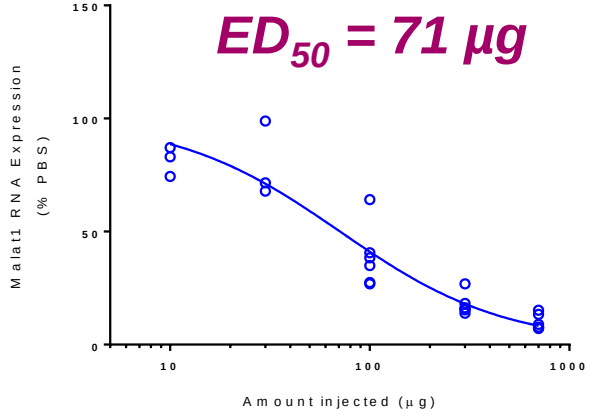
Astrocytes

ED_{50} = 17 µg



Microglia

ED_{50} = 71 µg



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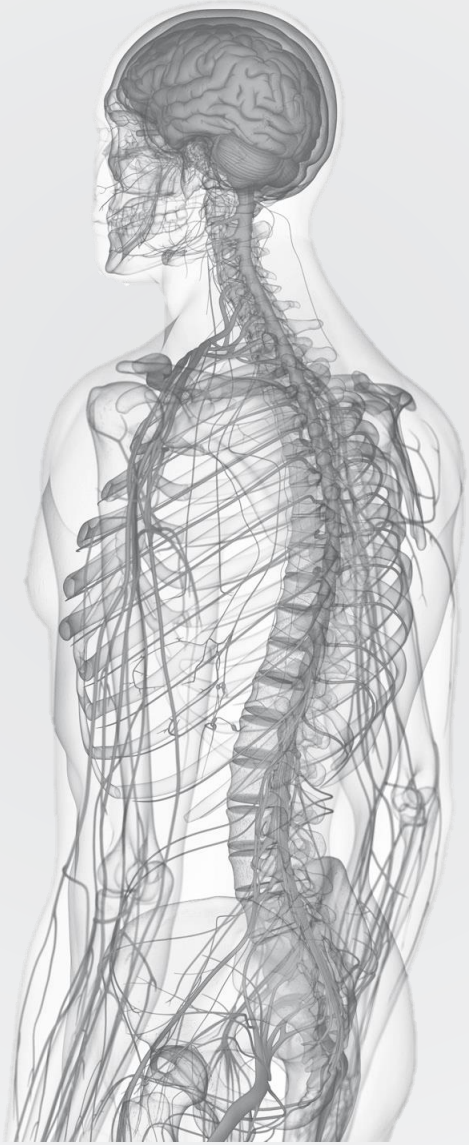
The ED_{50} is the dose that produces a 50% reduction in the target RNA

Ionis' Neurological Pipeline Also Targets the Peripheral Nervous System and Muscle

Tegsedi® (inotersen) injection 284 mg/1.5 mL

Polyneuropathy caused by hereditary transthyretin-mediated amyloidosis



AKCEA-TTR-L$_{Rx}$
All major forms of TTR amyloidosis

IONIS-DNM2-2.5$_{Rx}$
Centronuclear myopathy

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Ionis' Neurological Disease Pipeline

MEDICINES	INDICATION	PARTNER	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3
Tominersen (IONIS-HTT$_{Rx}$)	Huntington's disease	Roche				
Tofersen (IONIS-SOD1$_{Rx}$)	ALS	Biogen				
TTR-L$_{Rx}$	TTR Amyloidosis	Ionis				
IONIS-MAPT$_{Rx}$	Alzheimer's disease	Biogen				
IONIS-C9$_{Rx}$	ALS	Biogen				
ION859	Parkinson's disease	Biogen				
IONIS-DNM2-2.5$_{Rx}$	Centronuclear myopathy	Dynacure				
ION464	Multiple System Atrophy	Biogen				
ION541	ALS	Biogen				
ION581	Angelman syndrome	Biogen				
ION260	Undisclosed	Biogen				
ION363	ALS	Ionis				
ION716	Prion diseases	Ionis				
ION373	Alexander disease	Ionis				
ION283	Lafora disease	Ionis				
Numerous development candidates						

Ionis' Neurological Disease Pipeline

MEDICINES	INDICATION	PARTNER	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3
Tominersen (IONIS-HTT$_{Rx}$)	Huntington's disease	Roche				
Tofersen (IONIS-SOD1$_{Rx}$)	ALS	Biogen				
TTR-L$_{Rx}$	TTR Amyloidosis	Ionis				
IONIS-MAPT$_{Rx}$	Alzheimer's disease	Biogen				
IONIS-C9$_{Rx}$	ALS	Biogen				
ION859	Parkinson's disease	Biogen				
IONIS-DNM2-2.5$_{Rx}$	Centronuclear myopathy	Dynacure				
ION464	Multiple System Atrophy	Biogen				
ION541	ALS	Biogen				
ION581	Angelman syndrome	Biogen				
ION260	Undisclosed	Biogen				
ION363	ALS	Ionis				
ION716	Prion diseases	Ionis				
ION373	Alexander disease	Ionis				
ION283	Lafora disease	Ionis				
Numerous development candidates						

SPINRAZA

Creating new futures for SMA patients and their families

- Transformational therapy with over 10,000 patients on SPINRAZA therapy worldwide and 2019 revenue of $2.1B*
- Continued opportunities for growth in 2020 and beyond
- Committed to expanding our SMA franchise with new innovative technologies for SMA patients

* Commercialized by Biogen

IONIS™

NURTURE Study

Infants treated presymptomatically enables survival and gains in motor function consistent with normal development

Nusinersen continued to impact disease course in children who initiated treatment in the presymptomatic stage of SMA

- All children were alive, and 84% have never required any ventilation support
- Children continued to make gains in motor function
- Children are developing in a manner more consistent with normal development than that expected for children with 2 and 3 *SMN2* gene copies[1,2]

Many motor milestones were achieved within normal limits, and there was no loss of major motor milestones

Lower pNF-H levels on treatment significantly correlated with future HINE-2 total motor milestone score and earlier achievement of walking alone

No new safety concerns were identified

DATA TIME

These data demonstrate the durability of effect over a median of 3.8 years of follow-up, with children aged 2.8–4.8 years at last visit

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NURTURE study interim analysis data cutoff date: 19 February 2020

1. Finkel RS, et al. *Neurology*. 2014;83(9):810-817. 2. Kolb SJ, et al; NeuroNEXT Clinical Trial Network on behalf of the NN101 SMA Biomarker Investigators. *Ann Neurol*. 2017;82(6):883-891.

SPINRAZA Treatment Demonstrated Improved Motor Function and Disease Stabilization in Adult SMA Patients

THE LANCET
Neurology
Volume 19, Issue 4, April 2020, Pages 317-325

Articles

Nusinersen in adults with 5q spinal muscular atrophy: a non-interventional, multicentre, observational cohort study

Tim Hagenacker MD [a*], Claudia D Wurster MD [e*], René Günther MD [f, r*], Olivia Schreiber-Katz MD [g], Alma Osmanovic MD [g], Prof Susanne Petri MD [g], Markus Weiler MD [h], Andreas Ziegler MD [i], Josua Kuttler MD [j], Jan C Koch MD [j], Ilka Schneider MD [k], Gilbert Wunderlich MD [l, m], Natalie Schloss MD [l], Prof Helmar C Lehmann MD [l], Isabell Cordts MD [n], Prof Marcus Deschauer MD [n], Prof Paul Lingor MD [n], Christoph Kamm MD [o] ... Prof Christoph Kleinschnitz MD [a]

Demonstrated meaningful improvements in motor function in a real-world cohort

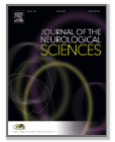
J Neurol. 2020 May 2. doi: 10.1007/s00415-020-09847-8. Online ahead of print.

Treatment Expectations and Patient-Reported Outcomes of Nusinersen Therapy in Adult Spinal Muscular Atrophy

Alma Osmanovic [1], Gresa Ranxha [2], Mareike Kumpe [2], Lars Müschen [2], Camilla Binz [2], Flavia Wiehler [2], Lejla Paracka [2], Sonja Körner [2], Katja Kollewe [2], Susanne Petri [2], Olivia Schreiber-Katz [2]

Spinraza demonstrated treatment effect, which had never occurred in this patient population

ELSEVIER
Journal of the Neurological Sciences
Volume 415, 15 August 2020, 116901



Letter to the Editor

Elderly patient with 5q spinal muscular atrophy type 4 markedly improved by Nusinersen

Teruya Morizumi [a, 1], Akihiro Ueno [a, b, 1], Ken Takasone [a], Kazuki Ozawa [a], Tsuneaki Yoshinaga [a], Katsuya Nakamura [a, c], Yoshiki Sekijima [a]

The oldest patient (71) treated with Spinraza demonstrated marked improvement in motor functions

J Neuromuscul Dis. 2020;7(3):257-268. doi: 10.3233/JND-190453.

Prospective Cohort Study of Nusinersen Treatment in Adults With Spinal Muscular Atrophy

Crystal Jing Jing Yeo [1 2 3], Sarah D Simeone [1], Elise L Townsend [1 4], Ren Zhe Zhang [1], Kathryn J Swoboda [1]

Disease stabilization or improvements in motor function demonstrated in SMA adult patients

IONIS™

SPINRAZA

The SMA foundation of care for SMA patients of all ages

Logan, living with SMA

- Transformational therapy with over 10,000 patients on SPINRAZA therapy*
- Unprecedented efficacy demonstrated across all forms of SMA
- Favorable safety and tolerability profile
- Potential to achieve even greater efficacy with a higher dose in the DEVOTE Phase 2/3 study
- SPINRAZA next generation product – potential improvement in convenience and efficacy

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* Patients on therapy across the pos-marketing setting the EAP and clinical trials

Huntington's Disease

A rare, genetic, fatal neurological disease

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Huntington's Disease

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 40,000 symptomatic patients in the U.S.*

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*Yohrling, G. et al. (November 2019). *Prevalence of Huntington's disease in the U.S.* Poster session, Huntington Society Group.

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

For patients with Huntington's disease

- Phase 3 study for Huntington's disease
- First and only late-stage medicine targeting the cause of Huntington's disease
- Fully enrolled, data expected in 2022
- Granted Orphan designation by FDA and EMA, and PRIME designation by EMA

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Tominersen

A comprehensive program targeting the cause of Huntington's disease

Phase I/IIa[1] N=46
- First-in-human study
- Safety, tolerability, PK and PD
- Early manifest HD patients

Open-Label Extension N=46[2]
- Long-term safety, tolerability, PK and PD
- Early manifest HD patients
- 15 months

HD Natural History Study N=95[3]
- Prospective, longitudinal study
- Early manifest HD patients
- 15 months

GENERATION HD1 N=791[4]
- Pivotal, long-term efficacy and safety
- Manifest HD patients
- 25 months (plus follow-up)

GEN-PEAK N=≤20†[6]
- PK/PD in CSF and plasma
- Manifest HD patients
- 7 months including follow-up

GEN-EXTEND[5] (OLE)

Complete

Complete, data expected in 2021

Ongoing, recruitment complete

Ongoing, recruiting

Includes digital monitoring platform

† An additional 8 patients may be included to allow investigation of additional dose levels and repeat doses if necessary. CSF, cerebrospinal fluid; HD, Huntington's disease; OLE, open-label extension; PD, pharmacodynamics; PK, pharmacokinetics. 1. Tabrizi SJ, et al. *N Engl J Med.* 2019; 380:2307–2316; 2. Clinicaltrials.gov/show/NCT03342053 (Accessed February 2020); 3. Clinicaltrials.gov/show/NCT03664804 (Accessed February 2020); 4. Clinicaltrials.gov/show/NCT03761849 (Accessed April 2020); 5. Clinicaltrials.gov/show/NCT03842969 (Accessed February 2020); 6. Clinicaltrials.gov/show/NCT04000594 (Accessed February 2020).

Tominersen

Potential breakthrough medicine for Huntington's disease

- First **disease-modifying medicine** targeting the **cause** of HD
- **Robust** and **sustained reductions** in mutant huntingtin protein (mHTT)* in patients
- **Favorable safety** and **tolerability** profile*
- Granted **Orphan** designation by **FDA** and **EMA**, and **PRIME** designation by **EMA**
- **Long durability** of action (bi-monthly and tri-annual dosing)
- GENERATION HD1 **Phase 3** study **enrollment complete**, data expected in 2022

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**Based on results from open-label extension (OLE) study*

Amyotrophic Lateral Sclerosis

Frank Bennett and Frank Rigo

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Amyotrophic Lateral Sclerosis

A fatal disease with a tremendous unmet medical need

- **Severe disease** characterized by motor neuron degeneration resulting in **paralysis** and **respiratory failure**
- **Rapidly progressive, with average survival of** 3-5 years from diagnosis
- **~55,000 patients diagnosed** in the G7 countries[1]
  - Sporadic ALS: ~90%
  - Familial ALS (e.g. SOD1, C9, FUS): ~10%
- **Familial** and **sporadic ALS** programs underway with Ionis and Biogen

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1. Biogen data on file, G7 countries include the U.S., Germany, the U.K., France, Italy, Spain, and Japan.

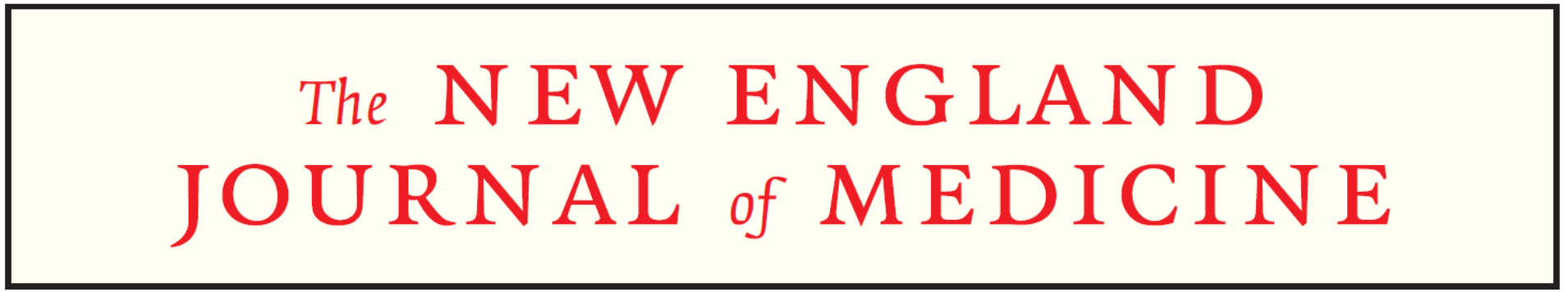
Tofersen (IONIS-SOD1$_{Rx}$)

Targeting SOD1 for patients with SOD1-ALS

- VALOR Phase 3 study for SOD1-ALS ongoing
- Results from the Phase 1/2 study of tofersen* demonstrated a slowing of decline of clinical function
- Data from the VALOR Phase 3 study expected in 2021
- Granted Orphan Drug Designation by the FDA and EMA

* Licensed to Biogen

The New England Journal of Medicine Publishes Positive Final Results from Phase 1/2 Study of Tofersen



Phase 1–2 Trial of Antisense Oligonucleotide Tofersen for *SOD1* ALS

T. Miller, M. Cudkowicz, P.J. Shaw, P.M. Andersen, N. Atassi, R.C. Bucelli, A. Genge, J. Glass, S. Ladha, A.L. Ludolph, N.J. Maragakis, C.J. McDermott, A. Pestronk, J. Ravits, F. Salachas, R. Trudell, P. Van Damme, L. Zinman, C.F. Bennett, R. Lane, A. Sandrock, H. Runz, D. Graham, H. Houshyar, A. McCampbell, I. Nestorov, I. Chang, M. McNeill, L. Fanning, S. Fradette, and T.A. Ferguson

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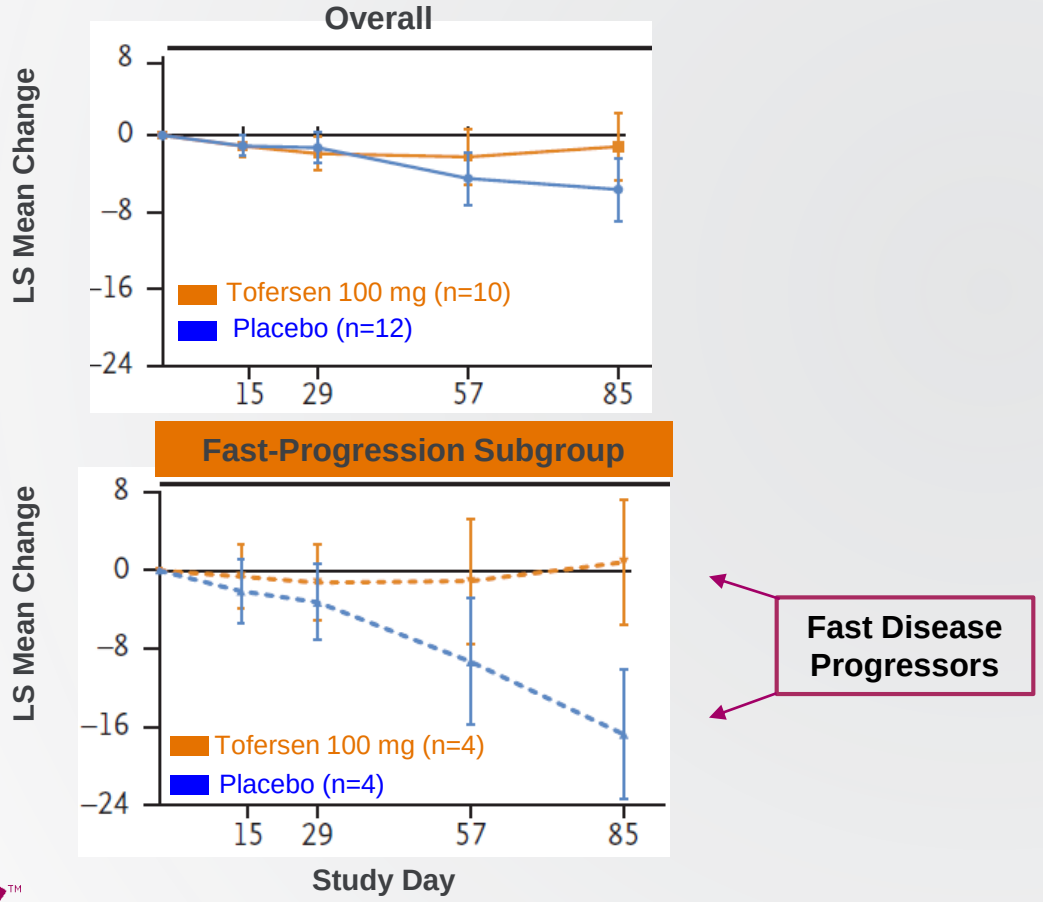
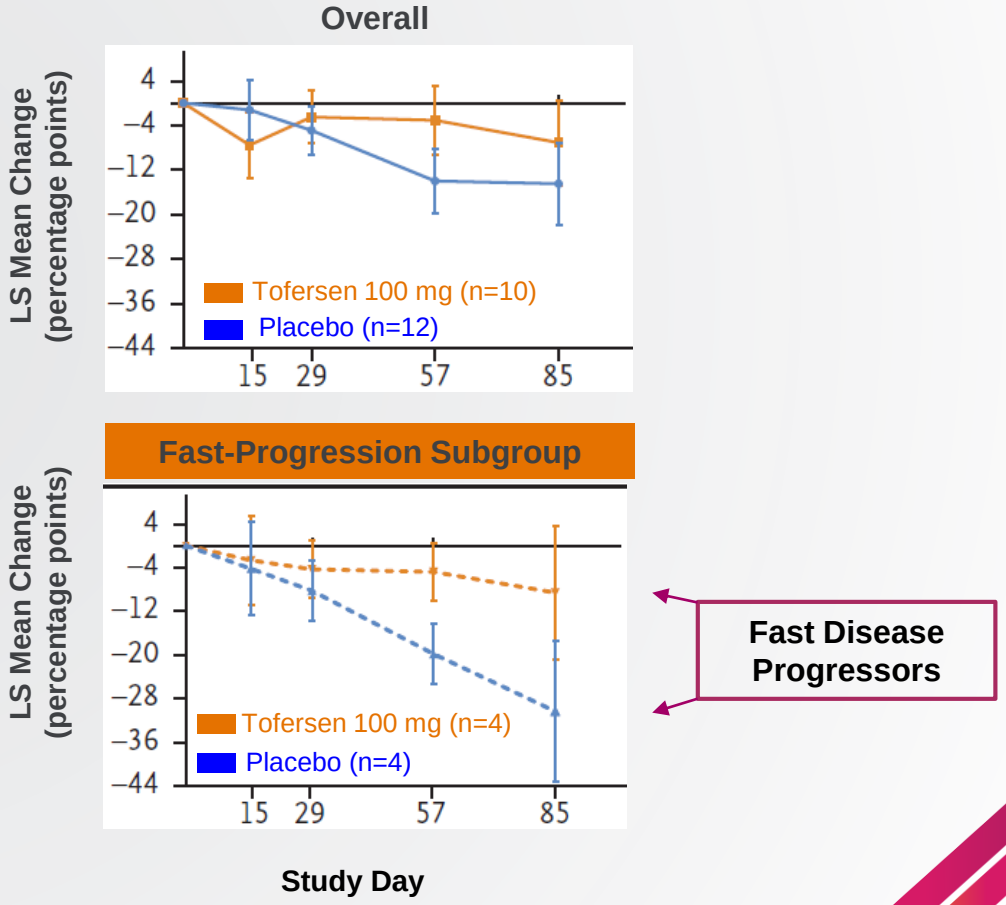
Phase 1/2 Results: Treatment with Tofersen 100 mg Demonstrated a Slowing of Decline of Clinical Function

Clinical Outcome ALSFRS-R



Lung Function % Predicted SVC

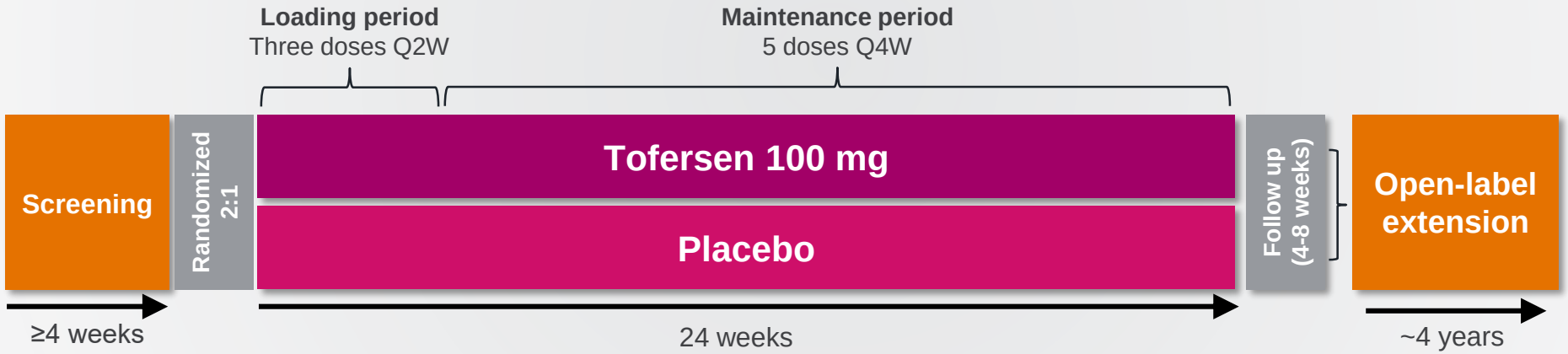


ALSFRS-R = ALS Functional Rating Scale–Revised; SVC = slow vital capacity

Phase 3 VALOR Study of Tofersen

Innovative study design with potential to support registration

- A global, randomized, double-blind, placebo-controlled study in ~ 99 patients with ALS and a confirmed SOD1 mutation, randomized 2:1 to tofersen 100 mg by intrathecal injection or placebo
- Outcome measures:
  - Primary: Change from baseline in ALSFRS-R total score
  - Secondary: Clinical measures, change in SOD1 CSF levels, safety and tolerability



Achieved Orphan Drug Designation
Data expected in 2021

ALS = amyotrophic lateral sclerosis; ALSFRS-R = ALS Functional Rating Scale–Revised; CSF = cerebrospinal fluid; Clinicaltrials.gov, NCT02623699

Tofersen

First investigational medicine to demonstrate clinical benefit in SOD1-ALS patients

- Treatment with tofersen in Phase 1/2 study demonstrated **robust SOD1 reductions** in the CSF
- Trends in slowing of **disease progression** demonstrated in Phase 1/2 study
  - In rapidly progressing patients, tofersen (100 mg) demonstrated **benefit in functional** and **respiratory** measures **after** only **3 months** of treatment
- Generally **well tolerated**
- **VALOR Phase 3 study** in adult ALS patients with SOD1 mutations underway, data expected in 2021

IONIS™

IONIS-C9$_{Rx}$

Frank Rigo

Targeting mutant C9orf72 for patients with C9-ALS

- Ongoing Phase 1/2 for C9orf72-ALS, data expected in 2021
- The first medicine to specifically target mutant C9orf72 mRNA
- Granted Fast Track Designation by the FDA

IONIS-C9$_{Rx}$ (BIIB078): In collaboration with Biogen

IONIS-C9$_{Rx}$

For the treatment of familial Amyotrophic Lateral Sclerosis (ALS)

- A **novel approach** for the treatment of patients with **ALS** who have a mutation in the **chromosome 9 open reading frame 72** (C9orf72) gene, for whom there is **no effective treatment**
  - Highly potent and selective inhibitor of human mutant C9orf72 transcripts
  - Proof of concept obtained in an animal model of C9-ALS
- **Intrathecal** administration allows for direct **access** to **key** affected **regions** of the **central nervous system**
- **Safety**, **tolerability** and **pharmacokinetic** profile of **IONIS-C9$_{Rx}$** in adults with C9orf72-ALS is being **evaluated** in a **Phase 1/2** clinical study conducted by our partner Biogen
- **Data** from the **Phase 1/2** clinical study expected in **2021**

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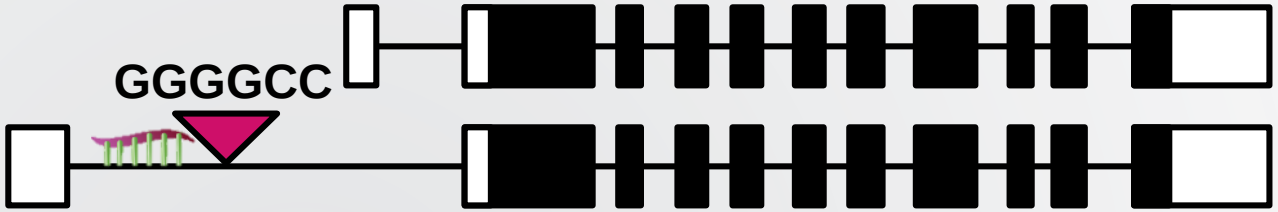
C9orf72 Molecular Pathology

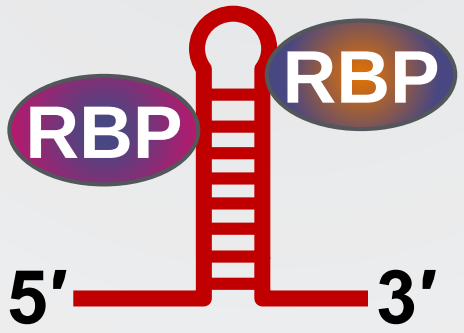
Mutant C9orf72 toxic gain of function

C9orf72 repeat expansion causes a toxic gain of function leading to rapid progressive loss of motor neurons



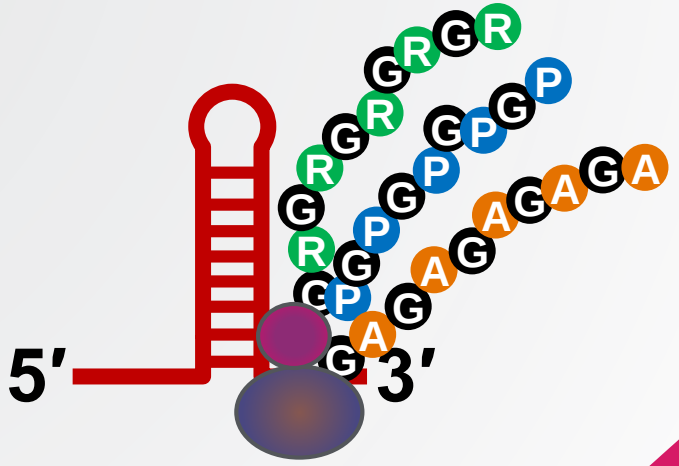
Decrease Transcription

Repeat RNA-mediated toxicity



RBP = RNA Binding Protein

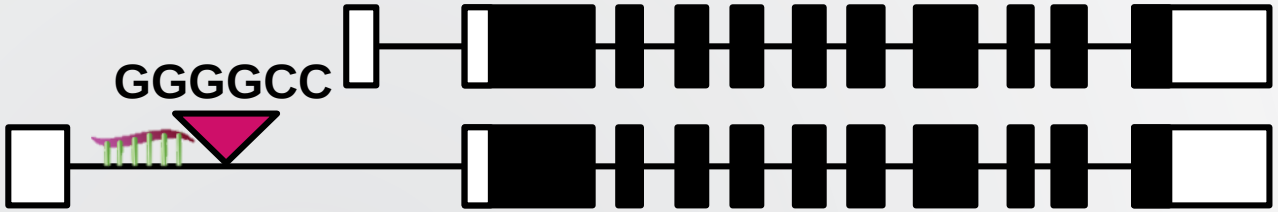
Dipeptide protein toxicity



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



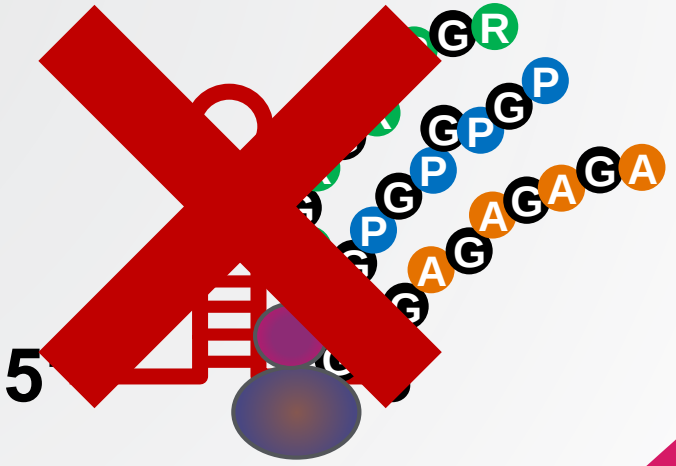
Decrease Transcription

C9orf72 protein

Repeat RNA-mediated toxicity

RBP = RNA Binding Protein

Dipeptide protein toxicity



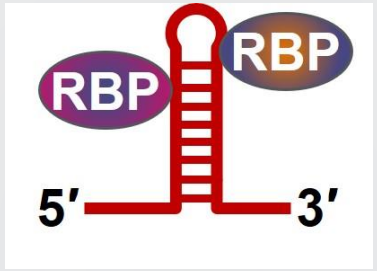
Antisense Suppression of Mutant C9orf72 Transcripts

Reduces repeat RNA & dipeptide protein toxicity in a mouse model of C9orf72-ALS

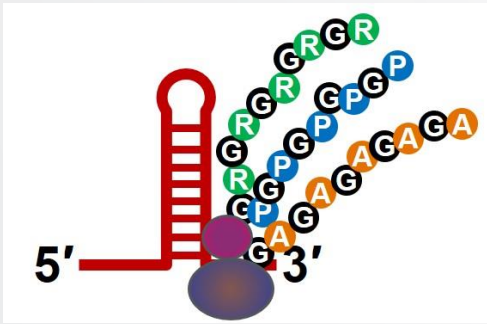
Decreases mutant C9orf72 transcripts w/out affecting total C9orf72 RNA/protein

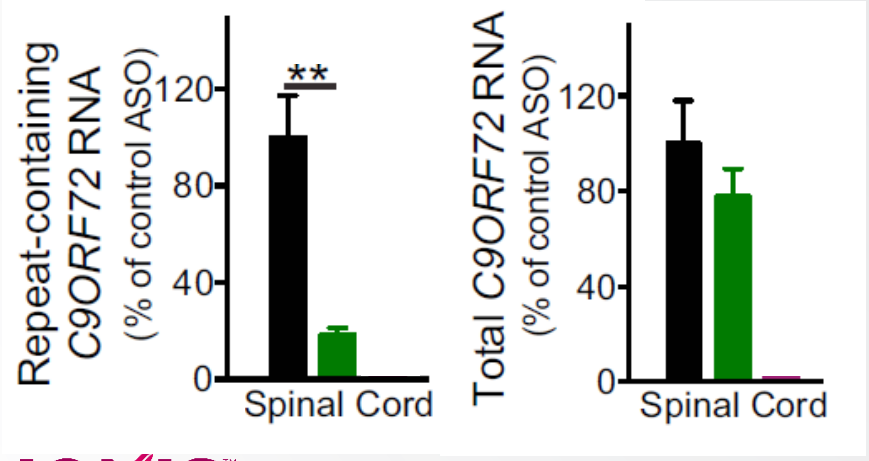
C9orf72 protein

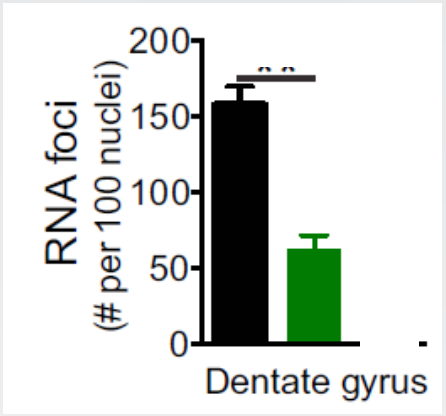
Decreases repeat RNA-mediated toxicity

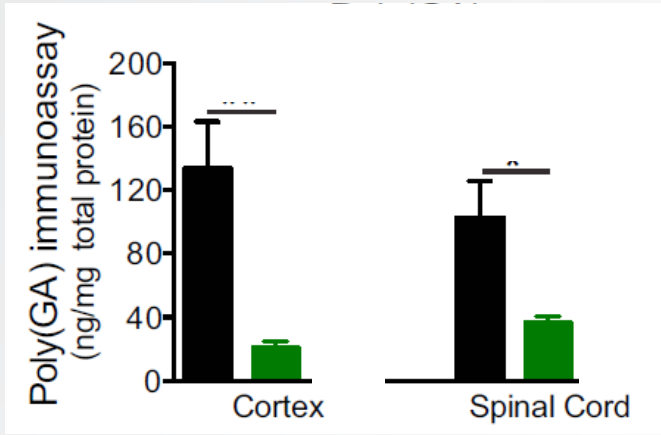


Decreases dipeptide protein toxicity









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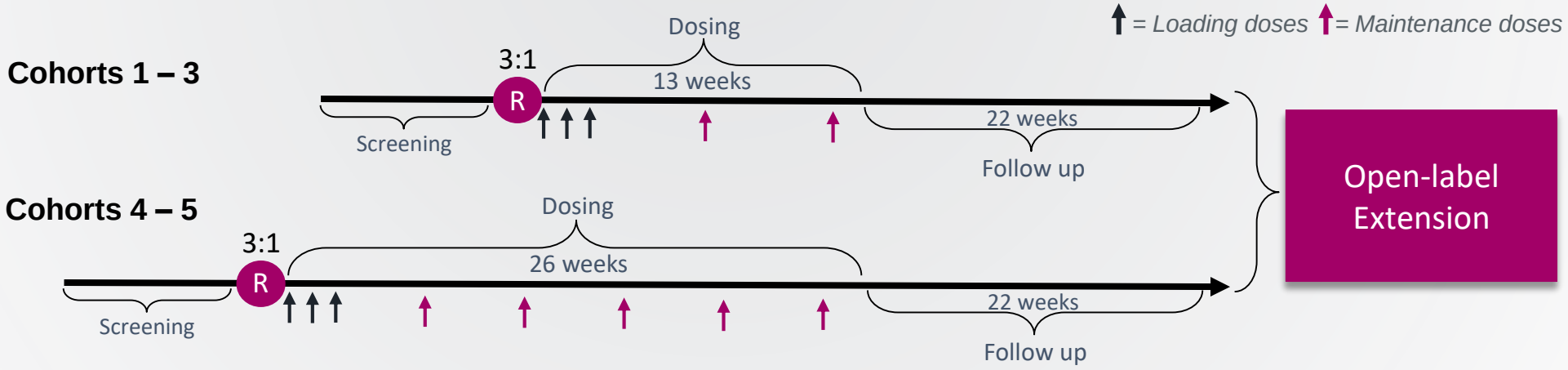
Jiang et al., Neuron 2016.

IONIS-C9$_{Rx}$ Phase 1/2 Study

Study in patients with C9ORF72-ALS (ongoing)

- **Design:** A randomized, double-blind, placebo-controlled, multiple-ascending dose study in up to 90 patients with C9ORF72-ALS
- **Primary Endpoint:** Safety and tolerability of intrathecally administered IONIS-C9$_{Rx}$ compared to placebo
- **Key Secondary Endpoints:**
  - Change from baseline in Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised (ALSFRS-R) scores
  - Percent change from baseline in Predicted Slow Vital Capacity (SVC)
  - Change in muscle strength from baseline as measured using hand-held dynamometry (HHD)
- **Dosing Regimen:** 3 loading doses followed by two maintenance doses for cohorts 1-3 and five maintenance doses for cohorts 4-5



Granted Fast Track Designation
Data Expected in 2021

ION363

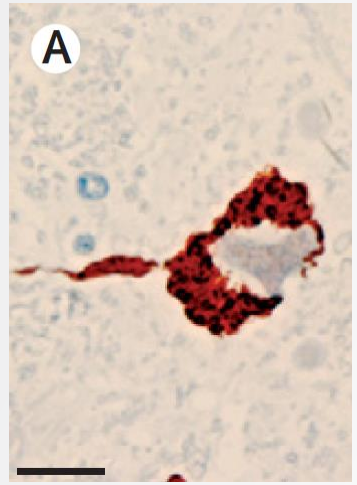
Targeting FUS for patients with FUS-ALS

- The first medicine to target FUS-ALS
- Initiation of Phase 1/2 clinical study on track for the end of 2020/early 2021

FUS-ALS

Caused by mutations in the Fused in Sarcoma (FUS) gene – no effective treatment

- 3rd most common inherited form of ALS
  - ~25% incidence of SOD1-ALS
- Caused by mutations in the Fused in Sarcoma (FUS) gene
- FUS-ALS is generally a predictably fast progressing disease
  - Good genotype-phenotype correlation
- FUS mutations cause motor neuron degeneration through a toxic gain of function mechanism
  - FUS is an RNA binding protein
  - Mutant FUS protein aggregates in the cytoplasm



MacKenzie et al., Lancet Neurology 2010.

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ION363

First medicine targeting FUS-ALS

- Antisense-mediated reduction of mutant FUS protein in a FUS-ALS mouse model prevents motor neuron loss
- We have identified a clinical candidate, ION363, which is designed to selectively reduce the expression of human FUS
- Our FUS medicine has been used by a clinical investigator to treat several ALS patients with FUS mutations under a compassionate use IND
- Initiation of Phase 1/2 study in FUS-ALS patients on track for the end of 2020/early 2021
- Potential for a rapid path to the market

IONIS™

ION541

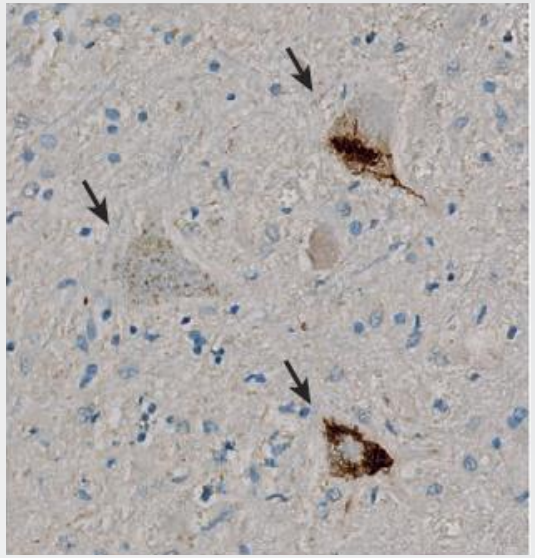
Targeting ATXN2 for patients with sporadic ALS

- Initiation of Phase 1/2 clinical study on track for 2H20
- The first medicine to specifically diminish TDP-43 aggregation, the pathological hallmark of ALS

ION541 (BIIB105): In collaboration with Biogen

Sporadic ALS: TDP-43 Aggregation

- ~90% of ALS is sporadic, with no apparent familial history
- A prominent pathological hallmark found in the neurons of people with sporadic ALS is the aggregation of the RNA binding protein called TDP-43
  - TDP-43 aggregation induces toxicity to motor neurons



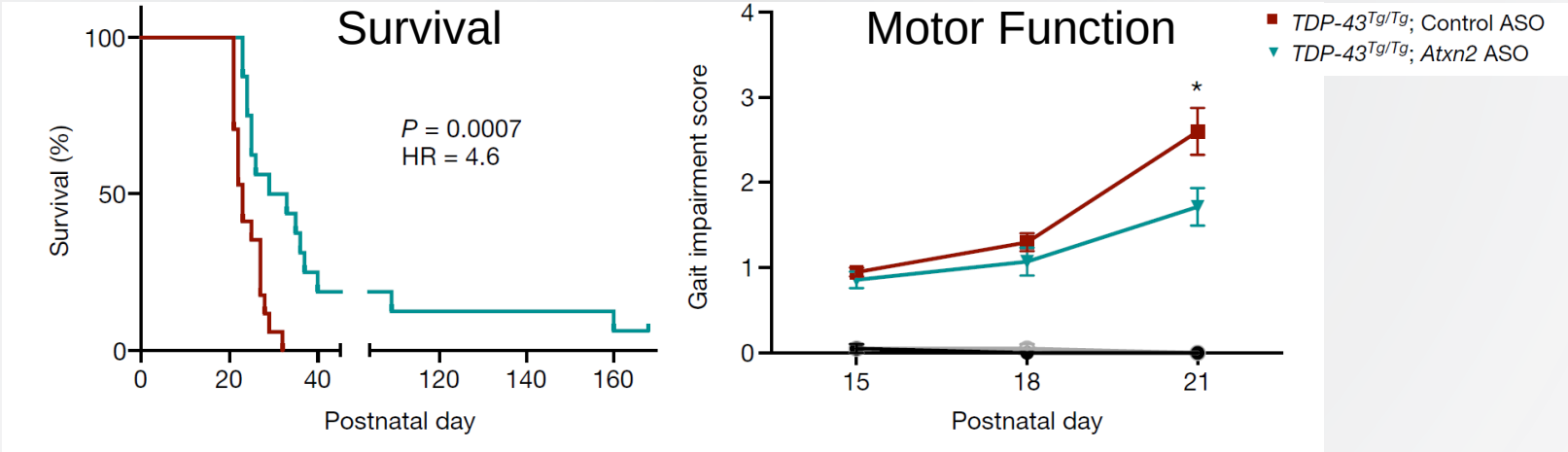
Arrows show
cytoplasmic TDP-43 inclusions in
spinal cord motor neurons

Taylor et al., Nature 2016.

IONIS™

ION541 Targeting Sporadic ALS

- ATXN2 has been shown to play a role in modulating TDP-43 toxicity, and human genetic data validates it as a target for sporadic ALS
- ION541, a highly potent inhibitor of ATXN2 mRNA, is the first gene-targeted medicine designed to diminish the toxicity of TDP-43
  - ASO-mediated reduction of ATXN2 increases survival and motor function in mouse models of TDP-43 toxicity

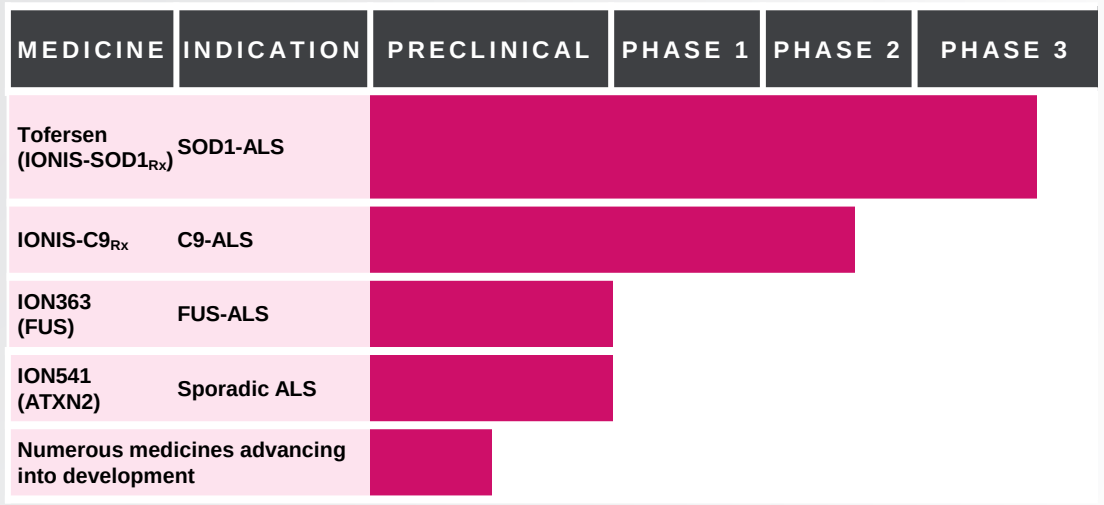


Becker et al., Nature 2017.

We Are Committed to Treating All Forms of ALS

- Tofersen: **Phase 3 VALOR** study underway (data expected 2021)
- IONIS-$C9_{Rx}$: **Phase 1/2 study ongoing in C9-familial ALS** (data expected 2021)
- ION363, **Ionis-owned** targeting **FUS** on track to initiate a Phase 1/2 study in FUS-ALS in late 2020/early 2021
- ION541 targeting **ATXN2** in **sporadic ALS** on track to initiate a Phase 1/2 study in 2H20
- Additional programs advancing focused on **treating all forms of ALS**

Multiple ALS Medicines in Development



Alzheimer's Disease and Dementia

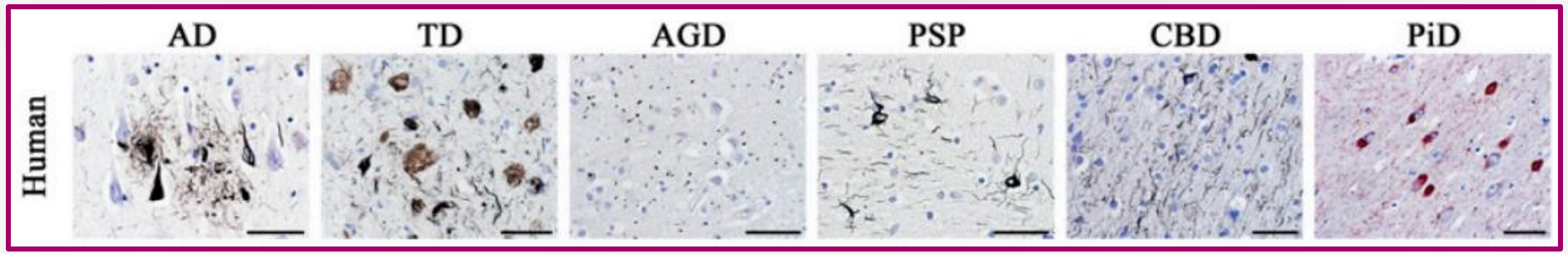
Holly Kordasiewicz

IONIS™

Tauopathies:

A spectrum of fatal, progressive and devastating diseases

- **Tauopathies** are a group of neurodegenerative diseases characterized by **accumulating** intracellular fibrillar tau inclusions, or **tangles**[1]
  - Tangles begin as soluble and monomeric tau protein and develop into hyper-phosphorylated, insoluble and filamentous tau in various disease states
  - Tangled tau proteins result in a toxic-gain-of-function associated with synaptic and neuronal loss[2]
- **Tangles** are the **hallmark** feature of **tauopathies**, including, but not limited to, **Alzheimer's** disease, **frontotemporal degeneration**
- An unmet need exists for a therapy with the ability to delay disease onset and progression in all types of tauopathies



AD: Alzheimer's disease, TD: Tangle-only dementia, AGD: Argyrophilic grain disease, PSP: Progressive supranuclear palsy, CBD: Corticobasal degeneration, PiD: Pick disease. 1. Alonso AC, Zaidi T, Grundke-Iqbal I, Iqbal K. *PNAS* 1994; 91: 5562-5566; 2. Spillantini MG and Goedert M. *Lancet Neurol* 2013; 12: 609-622.

Alzheimer's Disease and Frontotemporal Degeneration

Severe and progressive neurodegenerative diseases

Alzheimer's disease (AD) and **frontotemporal degeneration** (FTD) are forms of **dementia** characterized by predominant memory impairment and behavioral changes, resulting in progressive loss of independence and eventually death

Mutations in MAPT directly cause some forms of FTD

Approximately

50,000 – 60,000

people are affected by **FTD** in the U.S.[3]

Accumulation of pathologic tau is an AD pathology and correlates with cognitive decline in AD[1]

Approximately

5.5 million

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

IONIS™

1. Huang Y and Mucke L. *Cell* 2012; 148(6): 1204-1222; 2. Latest Alzheimer's Facts and Figures. Alzheimer's Association (2013). www.alz.org/facts/overview.asp.; 3. Knopman DS and Roberts RO. *J Mol Neurosci* 2011; 45: 330-335

IONIS-MAPT$_{Rx}$

For patients with Alzheimer's disease and other tauopathies

- We designed IONIS-MAPT$_{Rx}$* to selectively reduce production of the tau protein in the brain
- A Phase 1/2 study in patients with Alzheimer's disease is ongoing with data expected in 2021

* IONIS-MAPT$_{Rx}$ (BIIB080) Licensed to Biogen

IONIS-MAPT$_{Rx}$

Designed to selectively reduce the microtubule-associated protein tau (MAPT)

- **IONIS-MAPT$_{Rx}$** is an antisense medicine we designed to bind to *MAPT* pre-mRNA, thereby promoting specific degradation of ***MAPT* RNA**
  - Degradation of *MAPT* RNA prevents the translation of tau protein
  - Decreasing production of all isoforms, post-translation modifications and conformations of the tau protein is expected to target the primary mechanism in tauopathies
- In preclinical studies in transgenic rodents, treatment with *MAPT*-targeting antisense medicines **suppressed human tau** and provided evidence for **prevention** of, and **reversal** of existing, **tau pathology**

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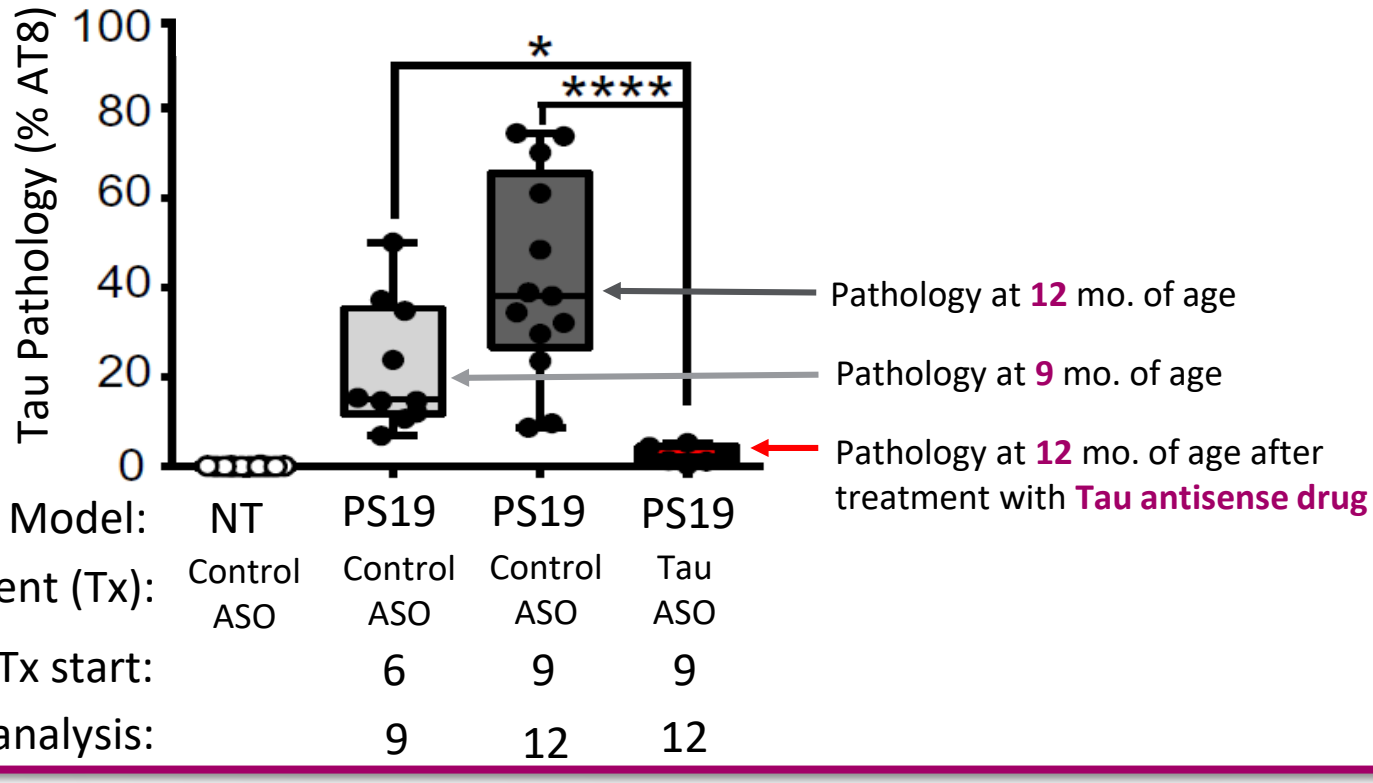
Suppression of Human Tau with *MAPT*-targeting Antisense Medicine ***Reversed*** Disease-state Pathology in Mice

Total AT8 Tau Staining in Hippocampus and Brain of Transgenic Mice



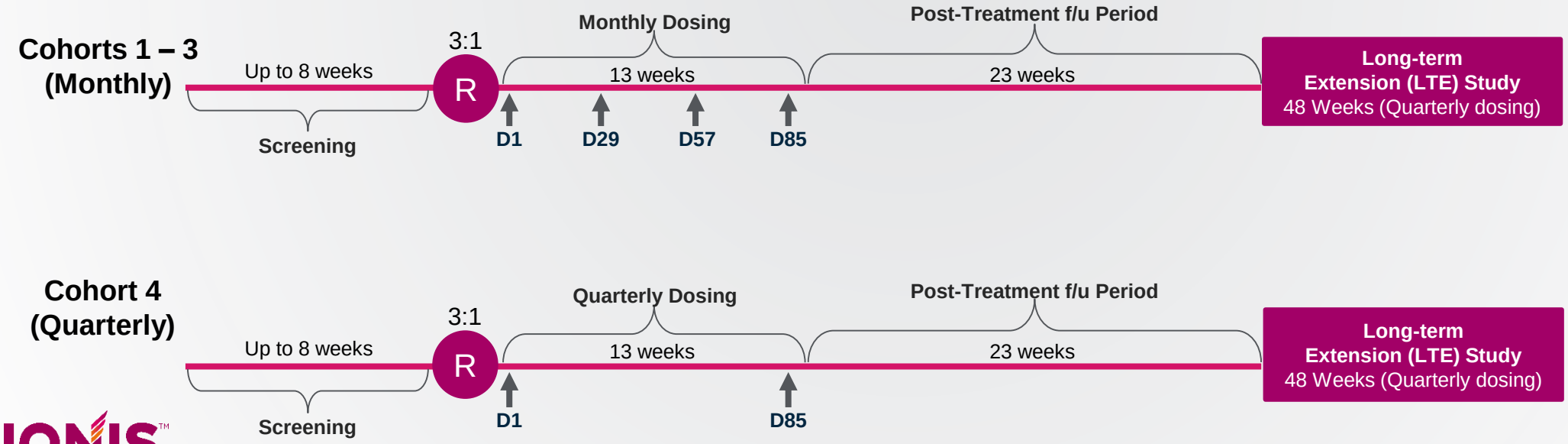
- *MAPT*-targeted antisense treatment reversed pathology in mice with a progressed disease-state
- PS19 mice treated at 9 months with *MAPT*-targeting antisense medicine had less severe pathology at 12 months of age (red) than control PS19 mice at 9 months of age (light gray)

*p < 0.05, ****p < 0.0001; AT8 = Common monoclonal antibody used for detecting tau, NT = Non-transgenic/Negative Control, Control Antisense Drug, PS19 = Transgenic mouse model that expresses human tau carrying the P301S mutation; Note: PS19 mice at 9 months of age were treated with control or MAPT-targeting antisense drugs for one month at 30 µg/day via Alzet osmotic pump for slow infusion; DeVos, S. L. et al. *Sci. Transl. Med.* 9, eaag0481 (2017).

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

Enrollment completed January 2020, data expected 2021

- A double-blind, randomized, placebo-controlled, multiple-ascending dose study in up to 46 patients with mild Alzheimer's disease (AD) delivered by intrathecal bolus administration
- Objectives:
  - Evaluate the safety and tolerability
  - Evaluate CSF pharmacokinetics and pharmacodynamic effects (effects on CSF levels of total tau protein)



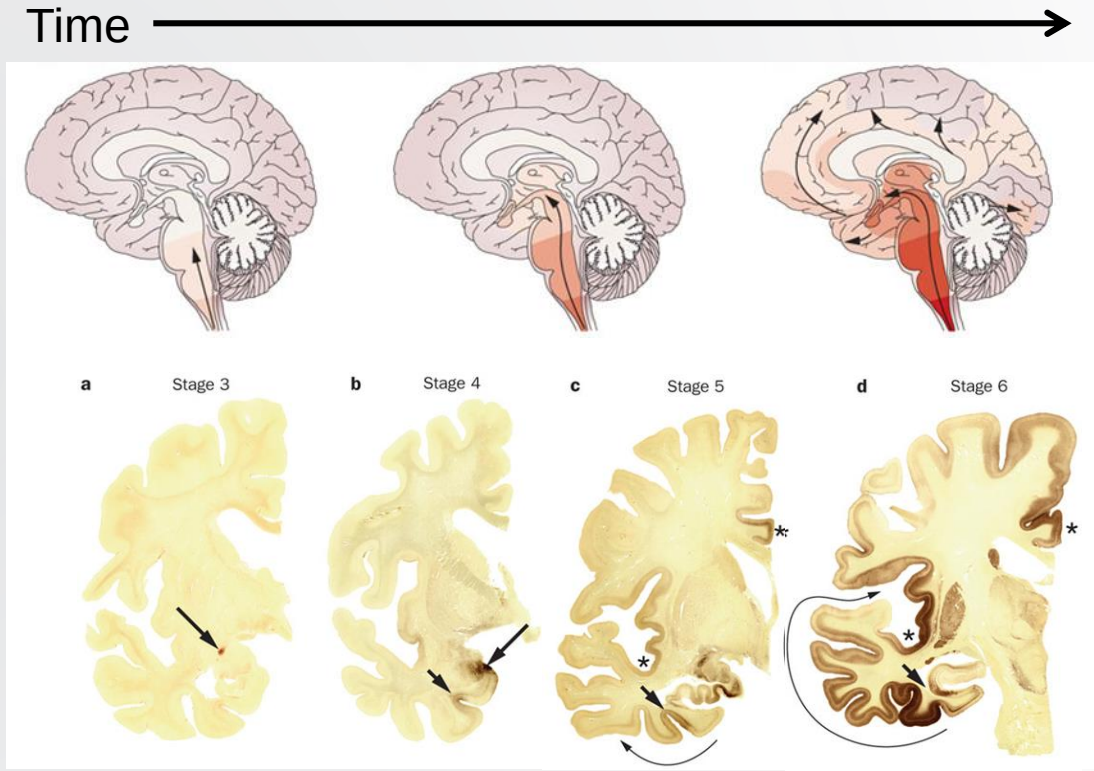
Parkinson's Disease and Multiple System Atrophy

IONIS™

Synucleinopathies:

A Spectrum of terminal, progressive and devastating diseases

- Synucleinopathies are a class of diseases directly linked to accumulation of αsyn[1]
- Synucleinopathies include:
  - Parkinson's disease (PD)
  - Multiple system atrophy (MSA)
  - Diffuse Lewy body disease (DLBD)
  - Dementia with Lewy bodies (DLB)
  - Gaucher disease
- No therapy exists to target the underlying disease pathology in synucelinopathies



αSyn accumulations increase in density (darker red) and spread throughout the PD brain[2]

1. Savicaet al. 2013; 2. Goedert et al., 2013

Parkinson's Disease and Multiple Systems Atrophy

- **Parkinson's disease** (PD) is a progressive **neurodegenerative** disease characterized by **loss** of **neurons** in the **motor system**
  - Patients can experience tremors, loss of balance and coordination, stiffness, slowing of movement, changes in speech and in some cases cognitive decline
  - Parkinson's disease is ultimately fatal, and effects 1% of the population over 60 (~10M WW)
- **Multiple system atrophy** (MSA) is a rare, **fatal**, rapidly progressing neurodegenerative disease
  - Patients with MSA typically experience progressive motor dysfunction, with death often occurring within 5-10 years after symptom onset
  - MSA effects ~15,000 people in the U.S.[1]
- There are currently **no disease modifying** therapies
  - The exact cause is unknown, but it is believed to be a combination of genetics and environmental factors

IONIS™

1. Fanciulli and Wenning. *Multiple-Systems Atrophy*. *NEJM* 2015.

ION464

For patients with Multiple System Atrophy (MSA) and Parkinson's disease (PD)

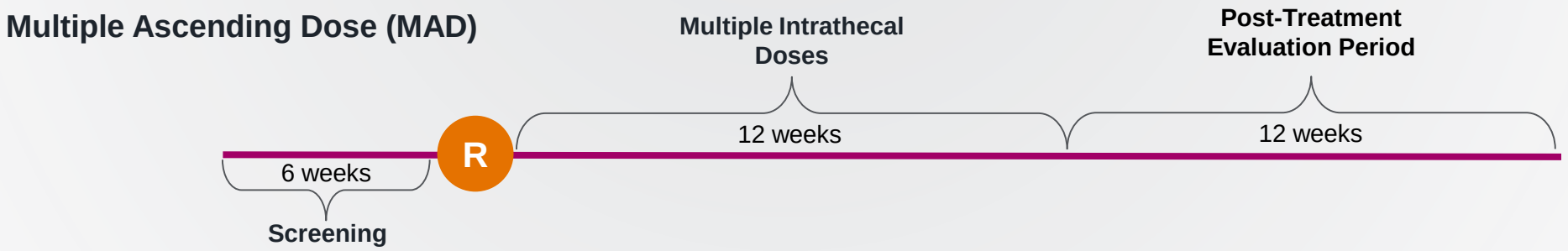
- ION464 targets SNCA mRNA, and prevents the production of alpha-synuclein
- Phase 1/2 study in patients with Multiple System Atrophy initiated

ION464 (BIIB101): In collaboration with Biogen

ION464 Phase 1/2 Study

Study in patients with Multiple Systems Atrophy

- Randomized, triple-blind, placebo-controlled, dose-escalation (MAD) study in up to 34 patients with multiple systems atrophy
  - 3 multiple-ascending dose cohorts
- Objectives:
  - Safety and tolerability
  - Evaluate pharmacokinetic profile



ION859

For patients with Parkinson’s disease (PD)

- ION859* targeting LRRK2
- Phase 1/2 study in patients with Parkinson’s disease ongoing

* ION859 (BIIB094) In collaboration with Biogen

ION859 Targets LRRK2

The most common genetic cause of Parkinson's disease

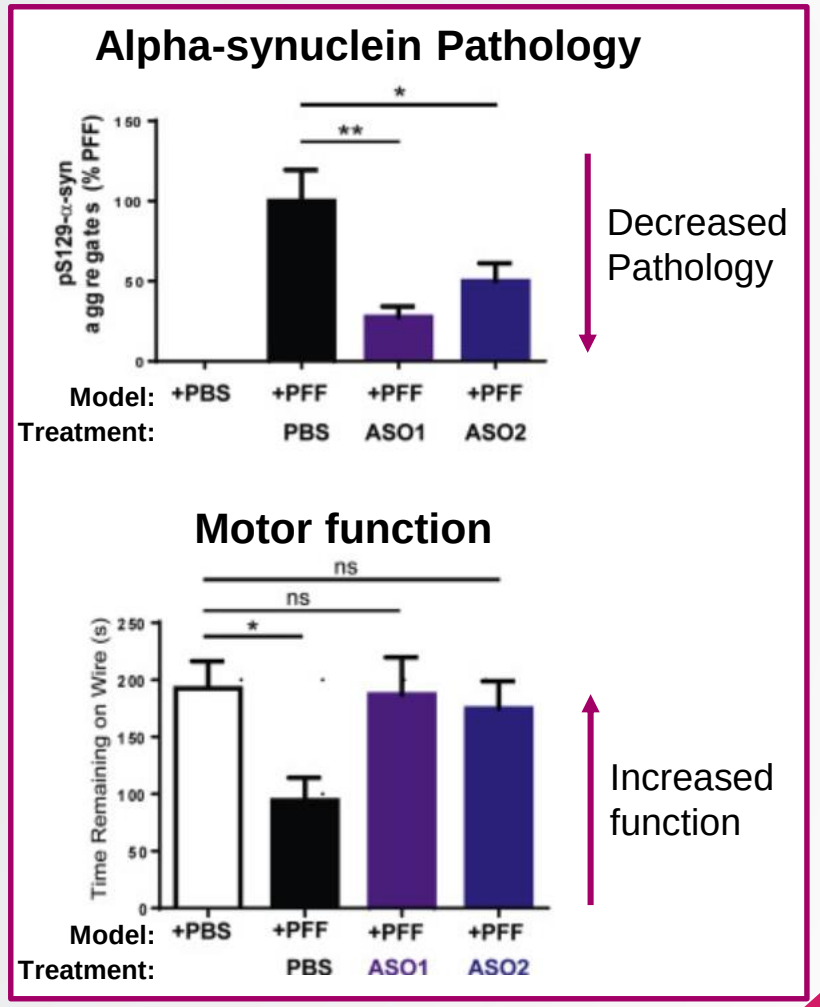
- ION859 is an antisense medicine we designed to inhibit the production of LRRK2 protein and is being developed as a potential therapy for Parkinson's disease
- The most common dominantly inherited mutations in PD cases are found in the LRRK2 gene
  - Increased LRRK2 protein activity may be one of the key drivers of PD pathogenesis
- Reduction of LRRK2 mRNA and, subsequently, reduced synthesis of LRRK2 protein, may ameliorate the toxic effects of gain-of-function mutations as well as the primary pathology in PD patients without the LRRK2 mutation

First patient dosed 3Q19
Data Expected 2022

IONIS™

ION859 Targeting Leucine Rich Repeat Kinase 2 (LRRK2) for Patients with Parkinson's Disease (PD)

- LRRK2 is a member of a family of LRRKs composed of functional GTPase and kinase domains flanked by multiple protein-protein interaction domains[1]
  - Dominantly inherited gain-of-function mutations in the LRRK2 gene cause Parkinson's disease[3]
- LRRK2 protein is increased in sporadic PD and in LRRK2 mutation carriers[4]
- Suppression of LRRK2 in models of sporadic PD is beneficial[5]
- There are advantages to centrally delivered LRRK2 ASOs over small molecule kinase inhibitors, as ASOs do not suppress lung LRRK2[5]

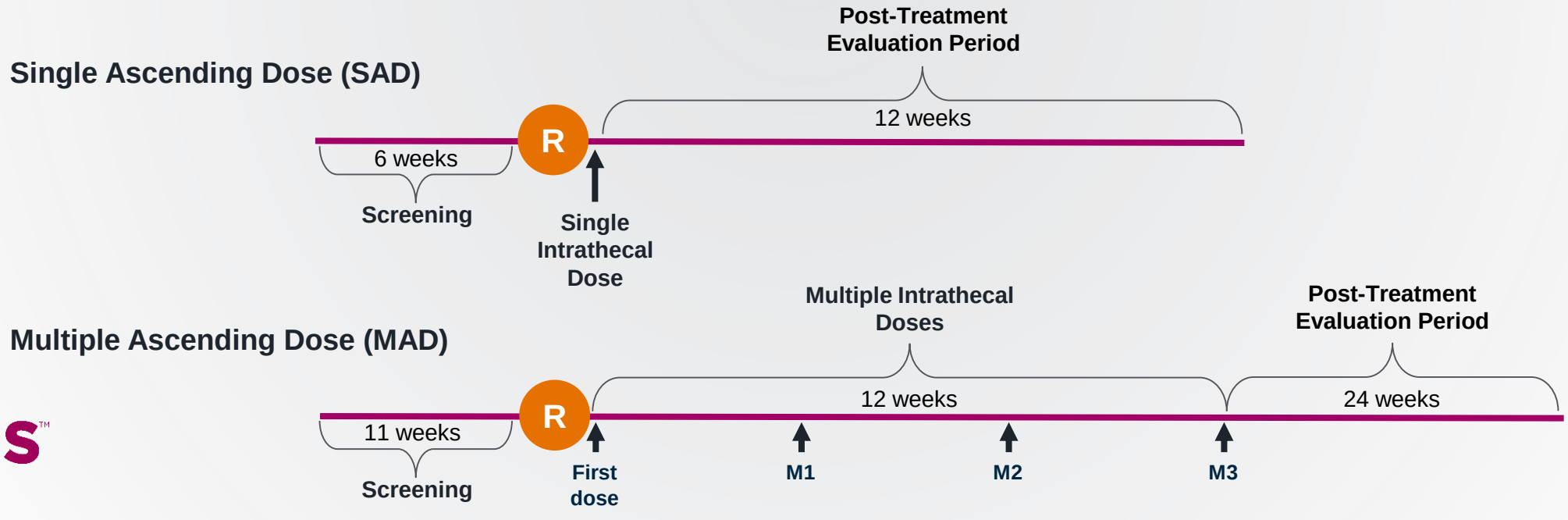


1. MacLeod et al. Neuron 2006, Matta et al. Neuron 2012, Beilina et al. PNAS 2014, Gillardon et al J Neurochem 2009, for review see Rudenko et al Neurotherapeutics 2014; 2. Berg et al. 2005, Healy et al. 2008, Paisan-Ruiz et al. 2004, Zimbrick et al. 2004; 3. Cho et al. 2013, Guerreiro et al. 2013, Mabrouk et al.; 4. Zhao et al. 2017.

ION859 Phase 1/2 REASON Study

Ongoing study in patients with Parkinson's disease

- Randomized, double-blind, placebo-controlled, dose-escalation (SAD/MAD) study in up to 62 patients with Parkinson's disease (PD) caused by a LRRK2 mutation as well as patients with sporadic PD and no verified PD-related genetic mutation
  - 4 single-ascending dose cohorts (SAD) and 3 multiple-ascending dose cohorts (MAD)
  - MAD dose cohorts include PD patients with verified LRRK2 mutation and sporadic PD patients
- Objectives: Evaluate the safety and tolerability and pharmacokinetic profile of multiple doses of ION859



Spinocerebellar Ataxias

- Class of rare diseases
- Patients often experience loss of balance and motor dysfunction
- No cure for spinocerebellar ataxias

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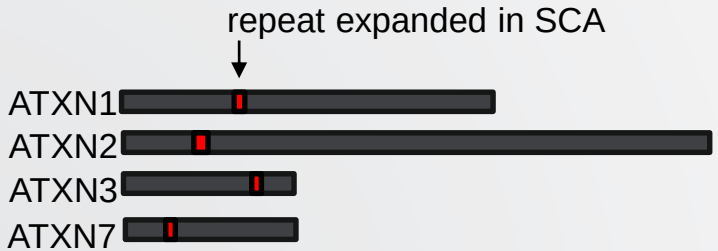
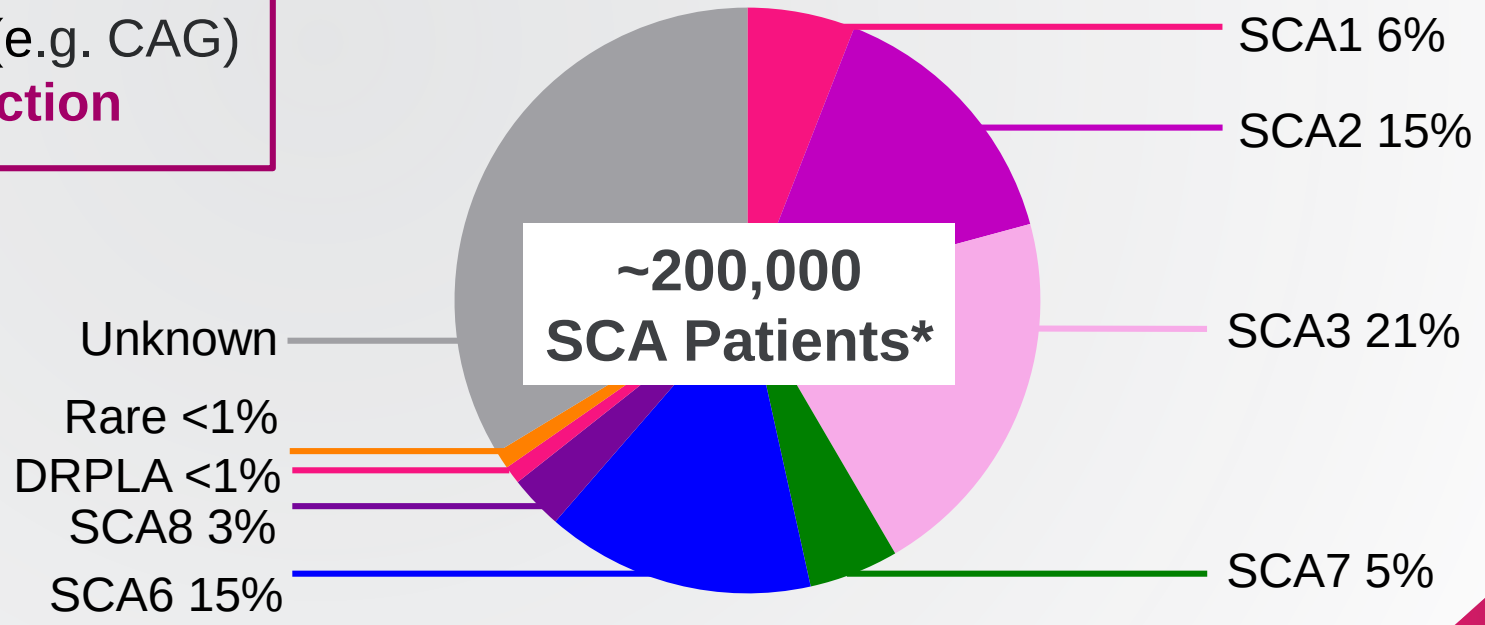
Spinocerebellar Ataxias are a Growing Class of More Than 30 Diseases Affecting ~200,000* SCA Patients

- Progressive neurodegenerative diseases with **predominant cerebellar dysfunction**, but often accompanied by broader CNS involvement
- Most prevalent diseases in the class are **dominantly inherited expansion** (e.g. CAG) mutations, with a **toxic gain of function**





*Worldwide distribution of SCA subtypes [Schöls et al 1997, Moseley et al 1998, Saleem et al 2000, Storey et al 2000, Tang et al 2000, Maruyama et al 2002, Silveira et al 2002, van de Warrenburg et al 2002, Dryer et al 2003, Brusco et al 2004, Schöls et al 2004, Shimizu et al 2004, Zortea et al 2004, Jiang et al 2005, Jiang et al 2013]. Figure published courtesy of L Schöls, P Bauer, T Schmidt, T Schulte, O Reiss of University of Tübingen and Ruhr-University Bochum, Germany. Gene Reviews. Hereditary Ataxia Overview.

Our Medicines Target the Primary Mechanism of Disease Pathogenesis in Dominantly Inherited SCAs

ATXN2 SCA2 therapy

Nature. 2017 Apr 20;544(7650):362-366. doi: 10.1038/nature22044. Epub 2017 Apr 12.

Antisense Oligonucleotide Therapy for Spinocerebellar Ataxia Type 2

Daniel R Scoles [1], Pratap Meera [2], Matthew D Schneider [1], Sharan Paul [1], Warunee Dansithong [1], Karla P Figueroa [1], Gene Hung [3], Frank Rigo [3], C Frank Bennett [3], Thomas S Otis [2], Stefan M Pulst [1]

ATXN3 SCA3 therapy

Ann Neurol. 2018 Jul;84(1):64-77. doi: 10.1002/ana.25264. Epub 2018 Aug 6.

Oligonucleotide Therapy Mitigates Disease in Spinocerebellar Ataxia Type 3 Mice

Hayley S McLoughlin [1], Lauren R Moore [1], Ravi Chopra [1], Robert Komlo [1], Megan McKenzie [1], Kate G Blumenstein [1], Hien Zhao [2], Holly B Kordasiewicz [2], Vikram G Shakkottai [1], Henry L Paulson [1]

ATXN1 SCA1 therapy

JCI Insight. 2018 Nov 2;3(21):e123193. doi: 10.1172/jci.insight.123193.

Antisense Oligonucleotide-Mediated ataxin-1 Reduction Prolongs Survival in SCA1 Mice and Reveals Disease-Associated Transcriptome Profiles

Jillian Friedrich [1 2], Holly B Kordasiewicz [3], Brennon O'Callaghan [1 2], Hillary P Handler [1 4], Carmen Wagener [1 2], Lisa Duvick [1 2], Eric E Swayze [3], Orion Rainwater [1 2], Bente Hofstra [1 2], Michael Benneyworth [5], Tessa Nichols-Meade [5], Praseuth Yang [1 2], Zhao Chen [1 2], Judit Perez Ortiz [1 4], H Brent Clark [2], Gülin Öz [6], Sarah Larson [6], Huda Y Zoghbi [7], Christine Henzler [8], Harry T Orr [1 2]

ATXN7 SCA7 therapy

Sci Transl Med. 2018 Oct 31;10(465):eaap8677. doi: 10.1126/scitranslmed.aap8677.

Antisense Oligonucleotides Targeting Mutant Ataxin-7 Restore Visual Function in a Mouse Model of Spinocerebellar Ataxia Type 7

Chenchen Niu [1], Thazah P Prakash [2], Aneeza Kim [2], John L Quach [3], Laryssa A Huryn [4], Yuechen Yang [5], Edith Lopez [5], Ali Jazayeri [2], Gene Hung [2], Bryce L Sopher [6], Brian P Brooks [4], Eric E Swayze [2], C Frank Bennett [2], Albert R La Spada [7 5 8 9 10]

IONIS™

Advancing the Ionis-owned Neurological Disease Pipeline

Holly Kordasiewicz

IONIS

Ionis' Neurological Disease Pipeline

MEDICINES	INDICATION	PARTNER	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3
Tominersen (IONIS-HTT$_{Rx}$)	Huntington's disease	Roche				
Tofersen (IONIS-SOD1$_{Rx}$)	ALS	Biogen				
TTR-L$_{Rx}$	TTR Amyloidosis	Ionis				
IONIS-MAPT$_{Rx}$	Alzheimer's disease	Biogen				
IONIS-C9$_{Rx}$	ALS	Biogen				
ION859	Parkinson's disease	Biogen				
IONIS-DNM2-2.5$_{Rx}$	Centronuclear myopathy	Dynacure				
ION464	Multiple System Atrophy	Biogen				
ION541	ALS	Biogen				
ION363	ALS	Ionis				
ION581	Angelman syndrome	Biogen				
ION260	Undisclosed	Biogen				
ION716	Prion diseases	Ionis				
ION373	Alexander disease	Ionis				
ION283	Lafora disease	Ionis				
Numerous development candidates						

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Numerous development candidates						

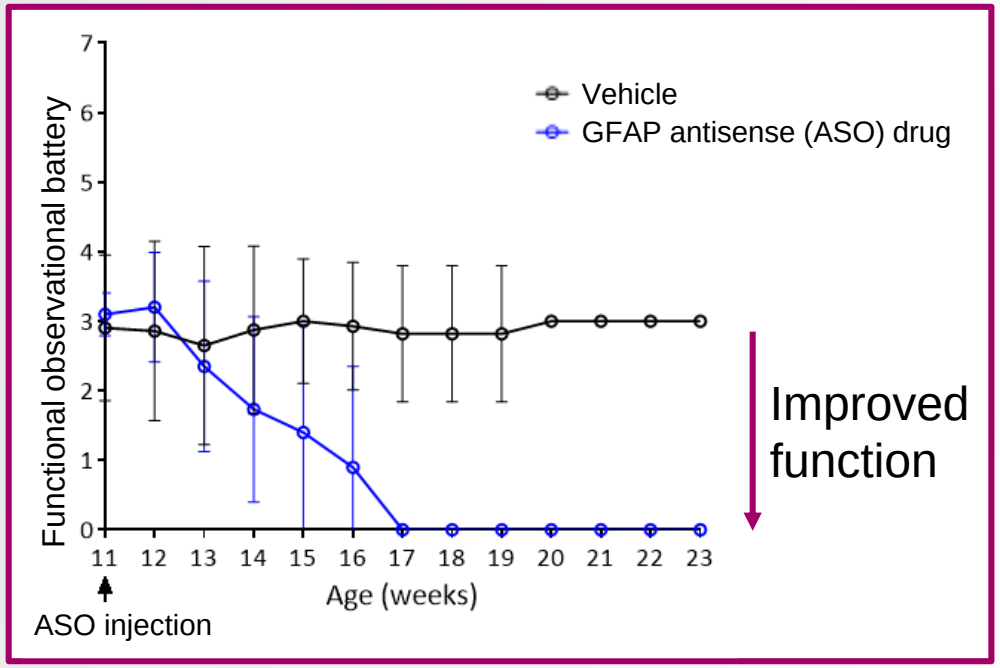
ION373

For patients with Alexander disease

- Ultra rare disease that is severe, rapidly progressing and often fatal
- Patients often experience seizures, loss of body movements, development delays
- No cure for Alexander disease

ION373 Targets GFAP for the Treatment of Alexander Disease

- **Alexander** disease (AxD) is an often **fatal** primary disorder of astrocytes, caused by autosomal dominant gain-of-function mutations in GFAP, an astrocytic intermediate filament[1]
- Mutations in **GFAP** cause spontaneous **overexpression** of GFAP that **accumulates** in intra-astrocytic **inclusions** called **Rosenthal** fibers, the pathological hallmark of the disease[2]
- GFAP **antisense** treatment in rodent models **reverses spontaneous** GFAP **overexpression**, **Rosenthal** fibers, astro- and micro-gliosis, and **restores** body **weight** and limb **strength**[3]



IONIS™

1. Brenner et al., *Nat Genet*, 2001; 2. Rosenthal, *Beitr Pathol Anat*, 1898; Messing et al., *J Neurosci*, 2012; 3.Hagemann et al., *Ann Neurol*. 2018

ION716

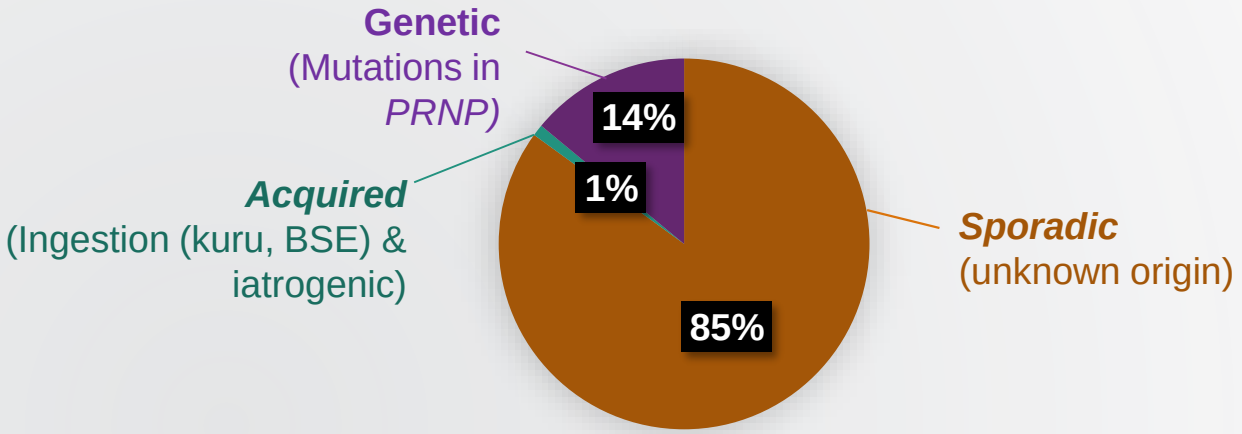
For patients with Prion diseases

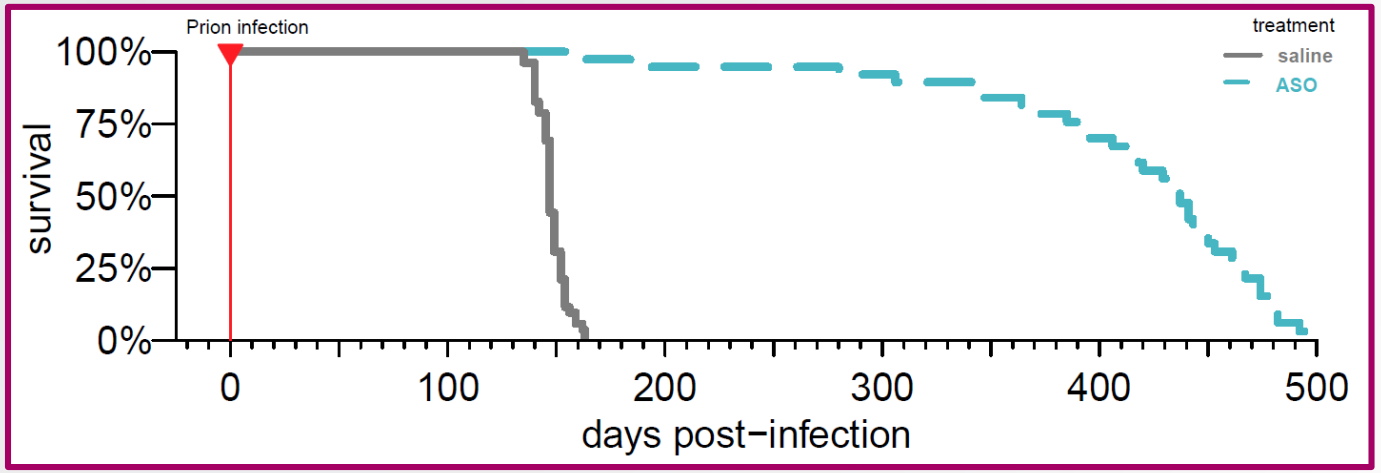
- Rare, rapidly progressing and fatal neurological diseases
- Symptoms include difficulty walking, speaking and rapidly developing dementia
- Death occurs within months to years following symptom onset
- No cure or effective treatment

IONIS™

Suppression of PRNP for the Treatment of Prion Diseases (ION716)

- **Prion** diseases are **fatal neurodegenerative** diseases caused by **misfolding** of the cellular **prion** protein (PrP^{C}) into misfolded, proteinaceous scrapie PrP^{Sc}
- **ION716** targets the PRNP RNA, and is predicted to **treat all forms** of prion disease[1]
- **ASO-mediated suppression** of **PRNP** can dramatically **delay disease** in rodent models of prion disease





1. Raymond et al., JCII 2019

ION283

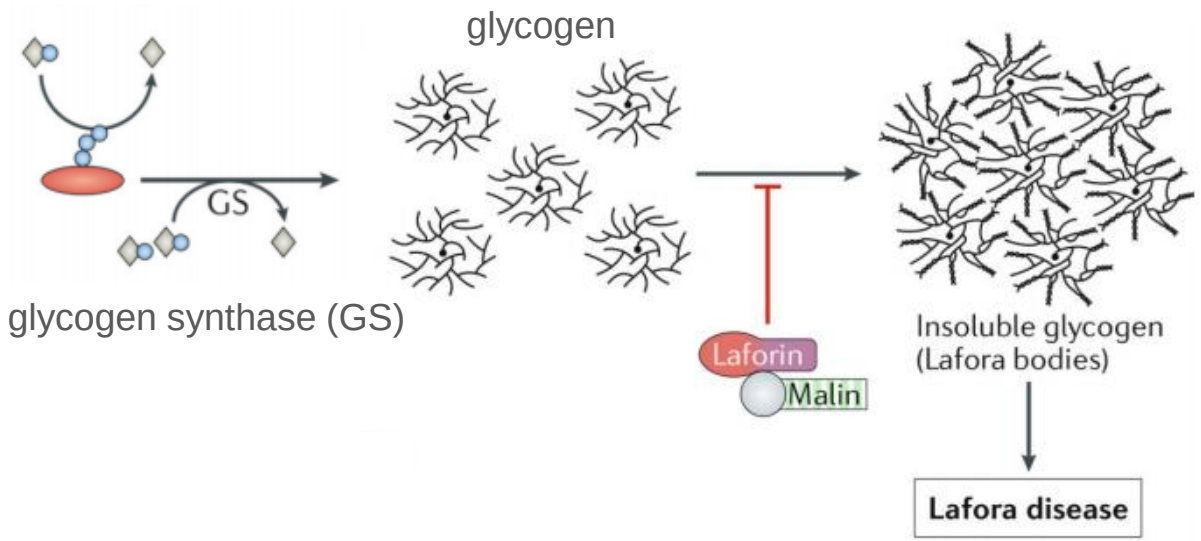
For patients with Lafora disease

- Ultra rare, fatal genetic disorder resulting in severe epilepsy and dementia
- Onset typically in childhood
- No available treatments

IONIS™

ION283 Targets Glycogen Synthase (GYS1) for the Treatment of Lafora Disease

- **Lafora** disease (LD) is a rare and **fatal** autosomal recessive **genetic** disorder which results in **severe** and progressive **epilepsy** and **dementia**
  - No cure or treatment available
  - Typical onset in childhood
- Caused by **loss of function** mutations in EPM2A (Laforin) and EPM2B (Malin), genes involved in glycogen processing, resulting in glycogen accumulation and **polyglucosan aggregates** (Lafora bodies)
- **Targeting glycogen** synthase, results in a decrease in glycogen and **prevention** of **Lafora** bodies



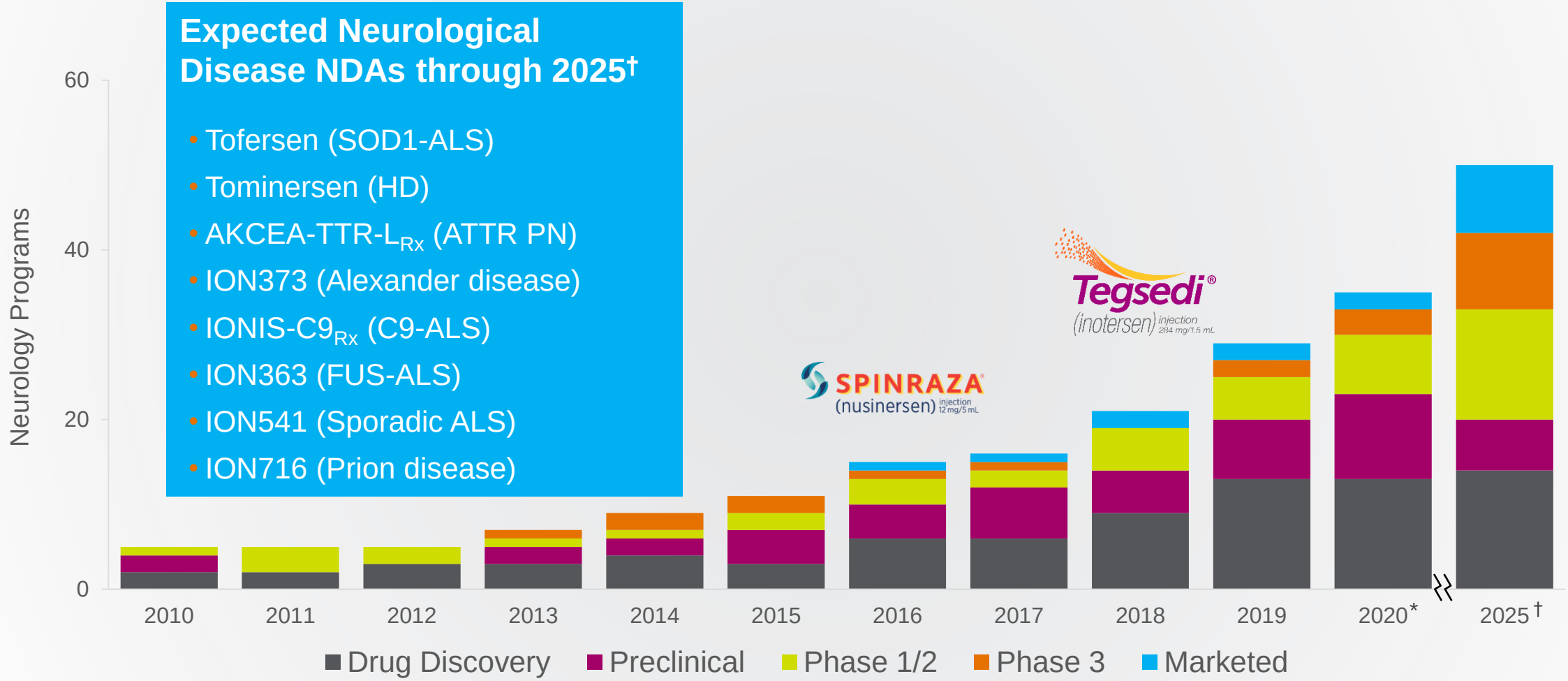
Adapted from Nitsche et al. *Nat Rev Neurol* 2018

Ionis: The Leader in Targeting Neurological Diseases

Brett Monia

IONIS

Projected Ionis Neurological Disease Pipeline



*Projected by year-end 2020. †Projected by year-end 2025

Next Wave of Potential Commercial Products

Anticipated NDA filings for Neurological medicines through 2025

2021		2025 and beyond	
		ION363 ***FUS-ALS***	
		AKCEA-APOCIII-L_{Rx} ***Severe hypertriglyceridemia***	**ION541** ***Sporadic ALS***
		ION373 ***Alexander disease***	**IONIS-TMPRSS6-L_{Rx}** ***β-thalassemia***
		IONIS-GHR-L_{Rx} ***Acromegaly***	**IONIS-HBV_{Rx}** ***Hepatitis B virus infection***
	AKCEA-APOCIII-L_{Rx} ***FCS***	**IONIS-$C9_{Rx}$** ***C9-ALS***	**Vupanorsen** (AKCEA-ANGPTL3-L_{Rx}) ***CV/metabolic disease***
	Tominersen (IONIS-HTT_{Rx}) ***Huntington's disease***	**IONIS-PKK-L_{Rx}** ***Hereditary angioedema***	**ION716** ***Prion diseases***
Tofersen (IONIS-$SOD1_{Rx}$) ***SOD1-ALS***	**AKCEA-TTR-L_{Rx}** ***hATTR polyneuropathy***	**AKCEA-TTR-L_{Rx}** ***ATTR cardiomyopathy***	**AKCEA-APO(a)-L_{Rx}** (TQJ230) ***Cardiovascular disease***

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Cardiometabolic Webcast

Ionis to host an investor webcast focused on our Cardiometabolic franchise in 2H20

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Q&A Session

IONIS

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A commitment
to **science,**
to **medicine**
and to **patients**