Building a Neuromuscular Franchise: Progress in ALS

June 5, 2019

Forward-looking statements

This presentation contains forward-looking statements, including statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, relating to our strategy and plans; clinical trials and data readouts and presentations; the potential benefits, safety, and efficacy of BIIB067 (tofersen), BIIB078, BIIB080, BIIB100, and BIIB110; the potential benefits, safety, and efficacy of SPINRAZA; the potential benefits of preclinical programs; the design, enrollment, and timing of the Phase 3 VALOR study of BIIB067 (tofersen), the Phase 1 study of BIIB078, the Phase 1 study of BIIB100, and the Phase 1a study of BIIB110; results from certain studies of BIIB067 (tofersen); the identification and treatment of amyotrophic lateral sclerosis; potential of our commercial business and pipeline programs; uncertainties associated with drug development and commercialization; our capital allocation and investment strategy; and anticipated benefits and potential of our investments, collaborations, and business development activities. Drug development and commercialization involve a high degree of risk, and only a small number of research and development programs result in commercialization of a product. Results in early stage clinical trials may not be indicative of full results or results from later stage or larger scale clinical trials and do not ensure regulatory approval. These forward-looking statements may be accompanied by such words as "aim," "anticipate," "believe," "could," "estimate," "expect," "forecast," "intend," "may," "plan," "potential," "possible," "vision," "will," "would," and other words and terms of similar meaning. You should not place undue reliance on these statements or the scientific data presented.

These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements, including we may not fully enroll our clinical trials or it may take longer than expected; the actual timing and final results of our clinical trials; the risk that unexpected concerns may arise from additional data or analysis, or regulatory authorities may require additional data or information or further studies, or may fail to approve, or refuse to approve, or may delay approval of our drug candidates, including BIIB067 (tofersen), BIIB078, BIIB080, BIIB100, and BIIB110; uncertainty of success and timing in the development and potential commercialization of our drug candidates, including BIIB067 (tofersen), BIIB078, BIIB080, BIIB100, and BIIB110, which may be impacted by, among other things, unexpected concerns that may arise from additional data or analysis, the occurrence of adverse safety events, failure to obtain regulatory approvals in certain jurisdictions, failure to protect and enforce data, intellectual property, and other proprietary rights and uncertainties relating to intellectual property claims and challenges; product liability claims; and third party collaboration risks. The foregoing sets forth many, but not all, of the factors that could cause actual results to differ from our expectations in any forward-looking statement. Investors should consider this cautionary statement, as well as the risk factors identified in our most recent annual or quarterly report and in other reports we have filed with the U.S. Securities and Exchange Commission.

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ALS R&D webcast call agenda

Introduction	**Matt Calistri** VP, Investor Relations
Overview	**Hani Houshyar, Ph.D.** Senior Director, Product Development and Commercialization Lead for Tofersen
Late Stage Programs	**Wildon Farwell, M.D.** Executive Medical Director, Clinical Development
Early Portfolio Review	**Chris Henderson, Ph.D.** VP, Head of Neuromuscular & Movement Disorders Research Unit
Conclusion	**Hani Houshyar, Ph.D.** Senior Director, Product Development and Commercialization Lead for Tofersen
Available for Q&A	**Michael Ehlers, M.D., Ph.D.** EVP, Research & Development

Overview

HANI HOUSHYAR, PH.D.

Senior Director,
Product Development and
Commercialization Lead for Tofersen

Significant opportunity in ALS

1 | ALS is a fatal disease with significant unmet medical need

2 | Applying learnings from prior clinical trials with the goal of increasing the probability of success for our pipeline in ALS

3 | Leveraging our success with SPINRAZA, including expertise in rare disease commercialization and intrathecal dosing, as we aim to build a neuromuscular disease franchise

4 | Positive proof-of-concept data for BIIB067 (tofersen) in SOD1 ALS may have positive implications for our ASO pipeline and other programs targeting ALS

5 | Advancing a broader portfolio for both familial and sporadic ALS, leading with genetically validated targets

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Amyotrophic Lateral Sclerosis (ALS)

DISEASE OVERVIEW

Rare, fatal, neurodegenerative disease characterized by motor neuron loss in the brain and spinal cord

Average survival after diagnosis of 3-5 years

Average age of symptom onset: 50 years

~ 15,000 newly diagnosed cases each year across the G7

PATHOPHYSIOLOGY

~90-95% sporadic, ~5-10% familial

Familial ALS caused by mutations in SOD1, C9orf72, others

Characterized by cytoplasmic inclusions in motor neurons

SYMPTOMS AND DISEASE PROGRESSION

Motor neuron degeneration leads to muscle weakness, atrophy, and stiffness leading to eventual paralysis and progressive decline in quality of life

Most common cause of death is respiratory failure

EPIDEMIOLOGY

G7 prevalence of ALS is ~55,000*

- Sporadic ALS: ~51,000*
- SOD1 ALS: ~1,400*
- C9orf72 ALS: ~3,100*
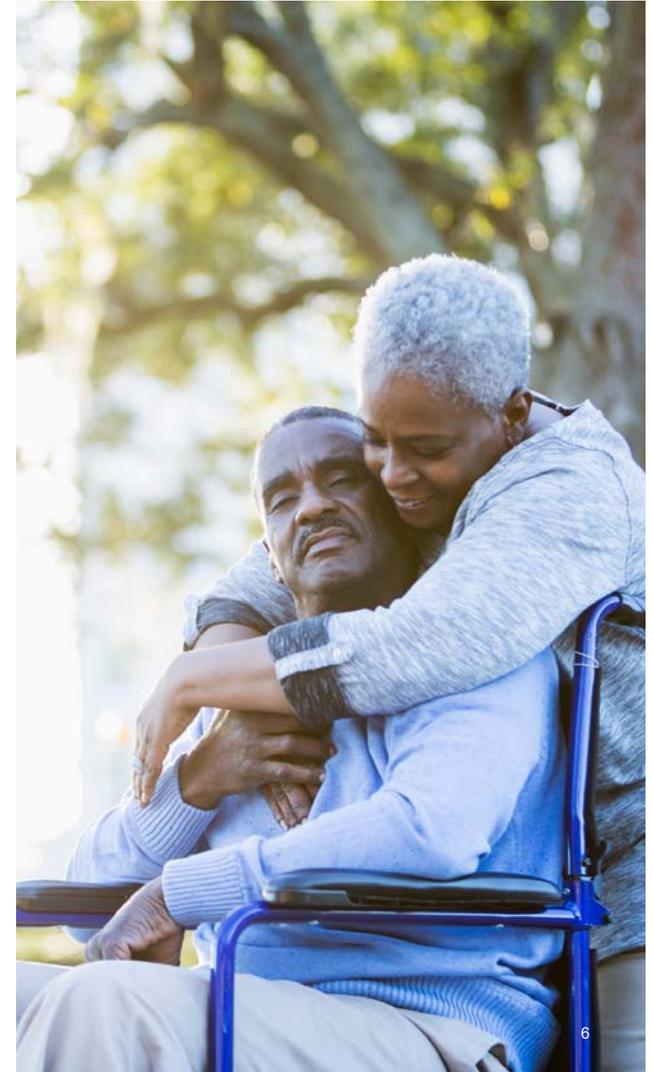
Biogen. *Biogen data on file. G7 countries include the U.S., Germany, the U.K., France, Italy, Spain, and Japan.

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Critical unmet need for effective treatment options for ALS

Tremendous emotional and physical burden on patients, families, and caregivers

Substantial financial burden on both families and healthcare system

Currently approved treatments provide only a modest effect on motor function and survival

- o Riluzole and edaravone are the only approved treatments for ALS in the U.S.

THERE IS AN URGENT NEED FOR EFFECTIVE, DISEASE-MODIFYING THERAPIES FOR ALS

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Learnings from previous failures reshaped our approach to ALS

DEXPRAMIPEXOLE:
A case study in ALS drug development

Despite lack of clear mechanistic rationale, dexpramipexole demonstrated encouraging early clinical results

Phase 3 EMPOWER study failed to demonstrate differentiation from placebo on prespecified efficacy endpoints

Learnings from rich dataset in over 800 patients reshaped Biogen's approach to clinical development in ALS

KEY LEARNINGS
from previous ALS trials

Evaluate genetically validated targets in defined patient populations

Pursue the most appropriate modality for each target

Implement biomarkers of target engagement and disease activity in early-stage studies

Employ sensitive clinical endpoints

Drug exposure → **Target engagement biomarker** → **Surrogate marker of efficacy** → **Clinical efficacy**

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EVALUATE GENETICALLY VALIDATED TARGETS IN DEFINED PATIENT POPULATIONS

Mutations in SOD1: the first identified genetic cause of ALS

Expansions in C9orf72: the most common genetic cause of ALS

Aim to apply learnings from these genetic targets in order to tackle **sporadic ALS** and pursue complementary approaches for **muscle strengthening**

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PURSUE THE MOST APPROPRIATE MODALITY FOR EACH TARGET

Antisense oligonucleotides (ASOs): powerful tool to modulate genetically validated targets in the CNS

- ASOs enable **selective, dose-dependent, and reversible** targeting of genetically defined drivers of disease
    - SOD1, C9orf72

- Based on SPINRAZA experience, we believe ASOs represent **most advanced genetically based approach for targeting neurological diseases**

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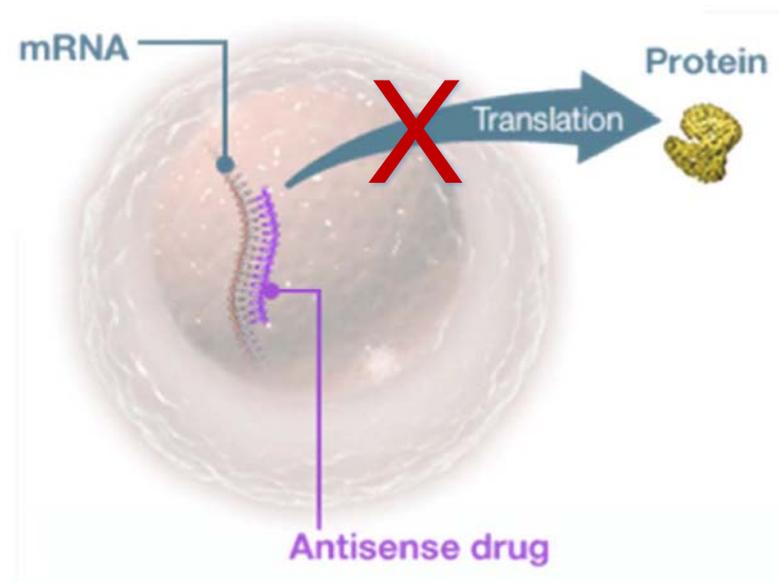
IMPLEMENT BIOMARKERS
of target engagement and disease activity in early-stage studies

Target engagement biomarkers

- CSF SOD1 protein levels

Disease activity biomarkers

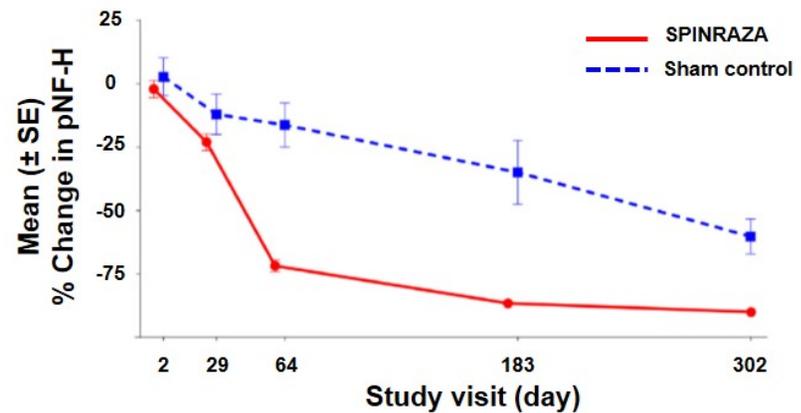- Elevated neurofilament level as a potentially promising biomarker of axonal degeneration

Biogen. *Adapted from Lu et al., Neurology, 2015; #Adapted from Darras et al., Ann Clin Transl Neurol, 2019

Baseline neurofilament level is associated with survival in ALS*

Log-rank (Mantel-Cox) test:
Chi square: 34.83
$p < 0.0001$

Percent survival

- Lowest third
- Middle third
- Highest third

Tertile cutoff levels: Cohort-specific

Time to event from baseline (months)
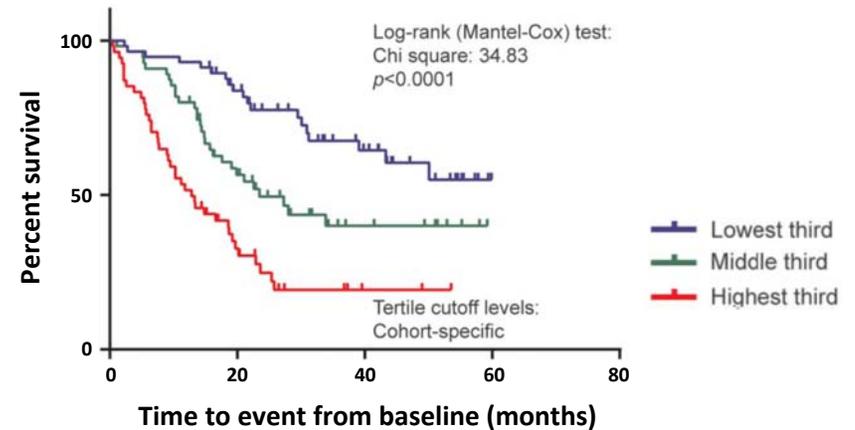
Neurofilament level is decreased following SPINRAZA treatment in SMA#

Mean (± SE) % Change in pNF-H

- SPINRAZA
- Sham control

Study visit (day)

EMPLOY SENSITIVE CLINICAL ENDPOINTS

If shown in prospective studies to be clinically meaningful, these novel endpoints have **potential to reduce size and duration of clinical studies required for approval**
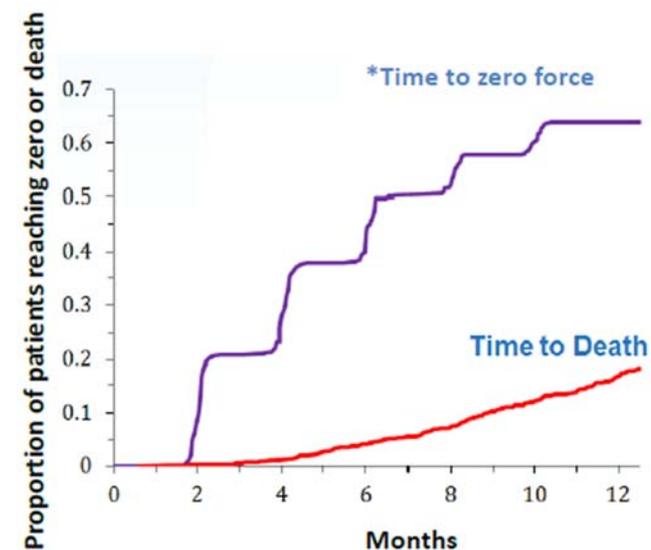
Handheld dynamometry*

Handheld dynamometry data from the Phase 3 EMPOWER study[#]

*Time to zero force

Time to Death

*Douma et al., Sports Sci Med Rehabil, 2014;
#Liu et al, AAN, 2017

Potential to build on the success of SPINRAZA

BUILDING DEPTH IN NEUROMUSCULAR DISORDERS

Applying direct synergies in our scientific and clinical development capabilities

Global commercial footprint and expertise, including the intricacies of rare disease commercialization

World-class ASO and intrathecal dosing expertise in collaboration with Ionis Pharmaceuticals

LEVERAGING GLOBAL COMMERCIAL FOOTPRINT IN SMA
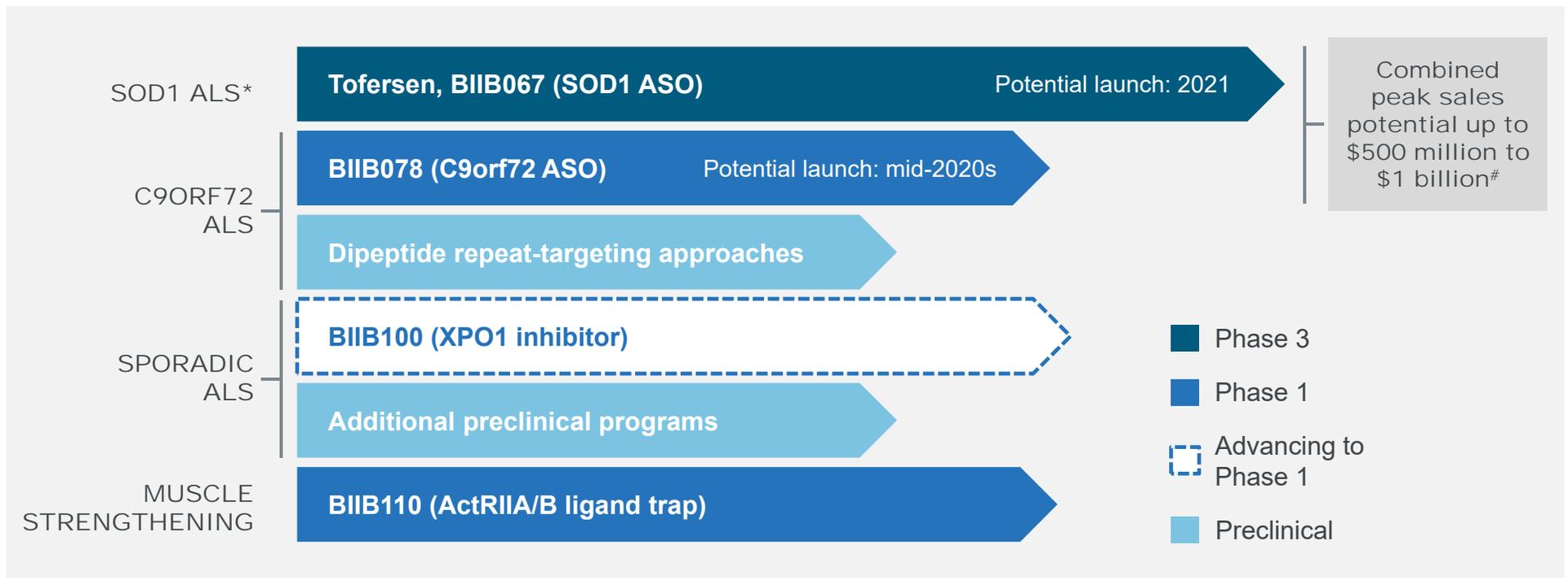
Plan to leverage overlapping neuromuscular field force to maximize efficiency

~ 40-50% overlap between ALS centers and SMA centers in the U.S. and E.U.*

Potential to enhance community engagement with neuromuscular associations and advocacy groups

Current ALS pipeline targets distinct patient segments

Segment	Program	
SOD1 ALS*	**Tofersen, BIIB067 (SOD1 ASO)**	Potential launch: 2021
C9ORF72 ALS	**BIIB078 (C9orf72 ASO)**	Potential launch: mid-2020s
	Dipeptide repeat-targeting approaches	
SPORADIC ALS	**BIIB100 (XPO1 inhibitor)**	
	Additional preclinical programs	
MUSCLE STRENGTHENING	**BIIB110 (ActRIIA/B ligand trap)**	

Combined peak sales potential up to $500 million to $1 billion#

Legend:
- Phase 3
- Phase 1
- Advancing to Phase 1
- Preclinical

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Late Stage Programs

WILDON FARWELL, M.D.

Executive Medical Director,
Clinical Development

# Targeting genetically defined SOD1 ALS to increase POS

Mutations in SOD1 were the **first identified genetic cause of ALS**

SOD1 gene encodes a ubiquitously expressed enzyme called **superoxide dismutase 1**

Mutated SOD1 is prone to misfold and can interfere in multiple cellular processes

SOD1 ALS cases are characterized by cytoplasmic **inclusions of aggregated SOD1 protein selectively in motor neurons**

Data indicate that **toxicity of mutant SOD1 is derived from a gain-of-function mechanism**
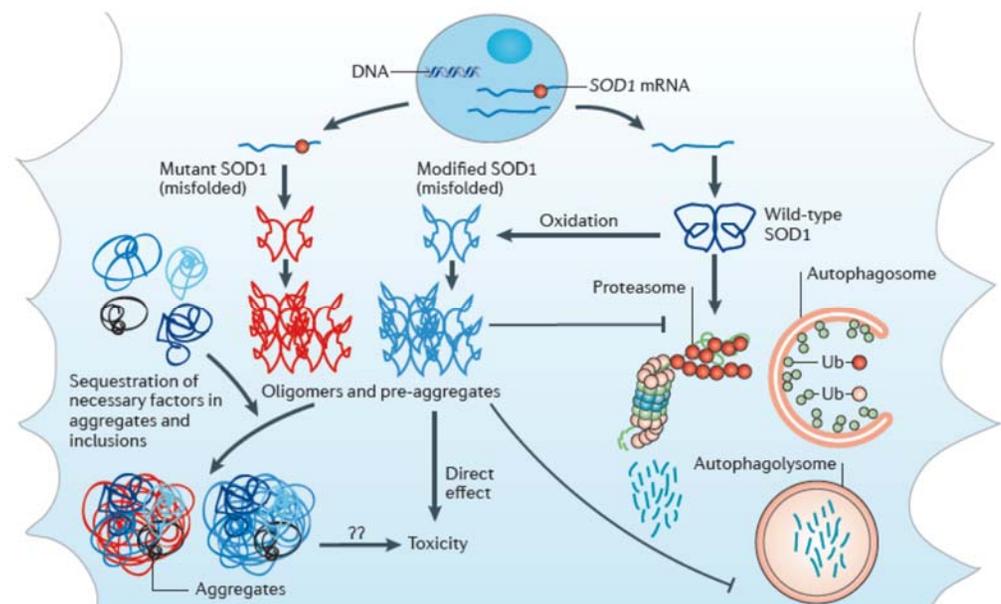
Robberecht and Philips, 2013

ASOs can induce RNase H-mediated degradation of target RNA Transcripts

Collaboration with Ionis Pharmaceuticals provides distinct ASO chemistries to enable **MULTIPLE MECHANISMS OF ACTION**
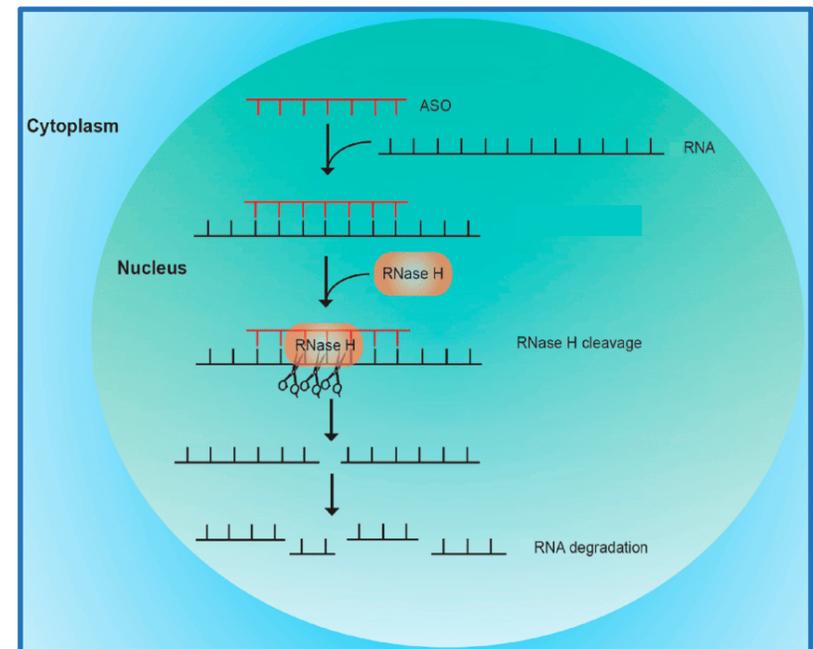
Modulate splicing of pre-mRNA transcripts

- **SPINRAZA** (SMN2)

Induce **RNase H-mediated degradation** of target RNA transcripts

- **Tofersen** (SOD1 in ALS)
- **BIIB078** (C9orf72 in ALS)
- **BIIB080** (tau in Alzheimer's disease and other tauopathies)

RNase H-mediated RNA degradation (tofersen, BIIB078, BIIB080)

Tofersen phase 1/2 multiple ascending dose study

OBJECTIVE:
To evaluate the safety, tolerability, PK, PD, and exploratory efficacy of tofersen in people with SOD1 ALS

POPULATION

> 18 years old

Documented SOD1 mutation

Weakness attributed to ALS

FVC ≥ 50% of predicted value[b]

MAD STUDY[a]

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*

ALSFRS-R scores, SVC, HHD megascore, CSF pNFH

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50 participants total, randomized 3:1 tofersen:placebo in each cohort

3 loading doses on Days 1, 15, and 29; maintenance doses on Days 57 and 85

Approximately 31 weeks including: up to 7-week screening period, 12-week dosing period, and 12-week follow-up period

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Interim safety, PK, and PD results of tofersen phase 1/2 study

Tofersen was generally well tolerated at doses up to and including 100 mg

Most AEs were mild or moderate in severity, and included headache, procedural pain, and post-lumbar puncture syndrome

CSF exposure of tofersen and SOD1 target engagement were greatest in the 100 mg treatment arm
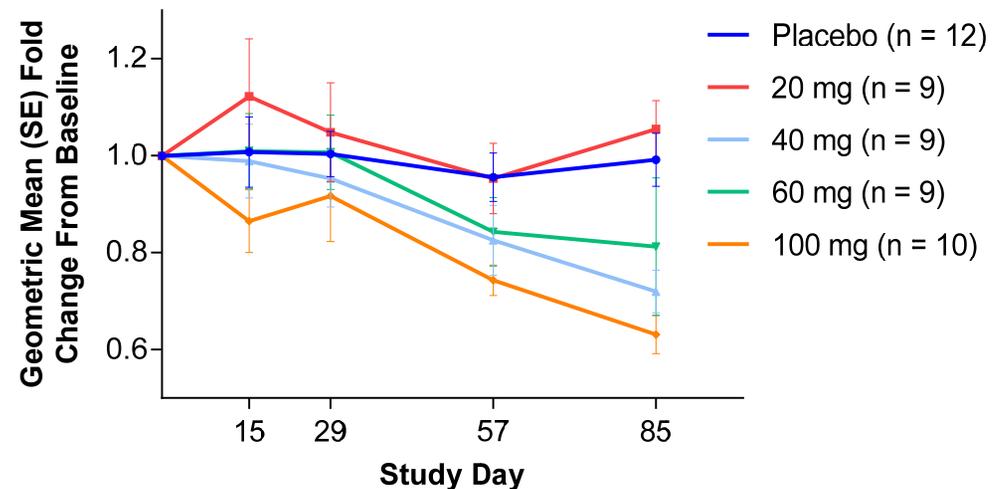
- Maximal reduction of CSF SOD1 level at Day 85 observed in participants treated with tofersen 100 mg (average 37% reduction) vs. no reduction in placebo group, p=0.002

Treatment with tofersen was associated with a trend toward lowering pNFH levels in the CSF

CSF SOD1 Concentration

Placebo (n = 12)
20 mg (n = 9)
40 mg (n = 9)
60 mg (n = 9)
100 mg (n = 10)

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

Interim exploratory efficacy results: tofersen 100 mg demonstrated a slowing of decline across clinical measures
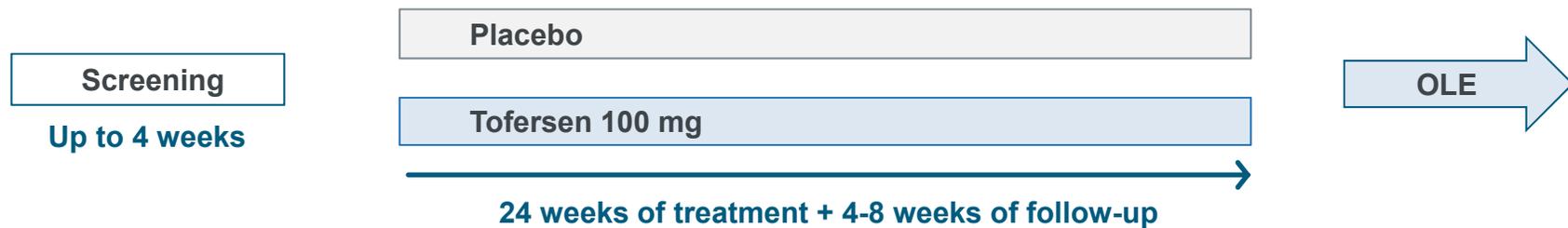
Clinical Function: ALSFRS-R

Respiratory Function: SVC (% predicted)

Muscle Strength: HHD Megascore
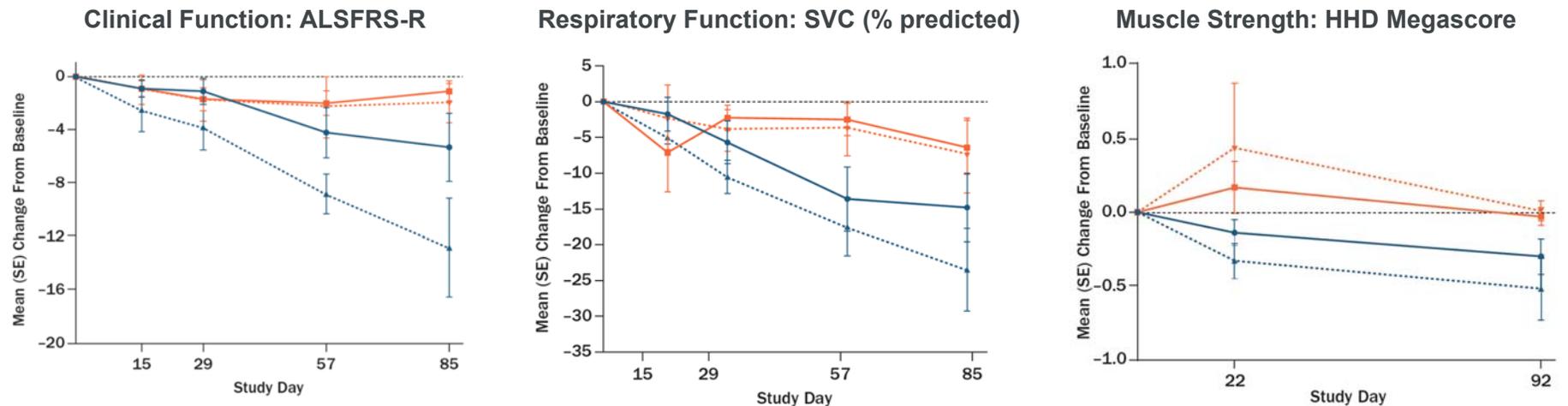
	OVERALL POPULATION		FAST PROGRESSORS	
	Placebo (n=12)	100 mg (n=10)	Placebo (n=4)	100 mg (n=4)
Change from BL to Day 85 in ALSFRS-R	-5.3	-1.1	-12.8	-2.0
Change from BL to Day 85 in SVC (% predicted)	-14.8	-6.4	-23.5	-7.5
Change from BL to Day 92 in HHD Megascore	-0.30 (n=11)	-0.03	-0.52	0.01

— Overall tofersen 100 mg

--- Fast-progressing tofersen 100 mg

— Overall placebo

--- Fast-progressing placebo

Miller et al., AAN, 2019

Phase 3 VALOR study of tofersen in SOD1 ALS

Screening
Up to 4 weeks

Placebo

OLE

Tofersen 100 mg

24 weeks of treatment + 4-8 weeks of follow-up

POPULATION (N = ~ 60):
- Broad population of ALS patients with confirmed SOD1 mutation
- Geographic location: U.S., E.U., Canada, Japan, Australia

PRIMARY ENDPOINT
Analysis based on ALSFRS-R score

IN ACTIVE DISCUSSIONS WITH REGULATORS
as we collaborate to further define the scope of the clinical data package required to support the registration of tofersen

Biogen.   OLE = open label extension

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Leveraging learnings from SPINRAZA and SMA

MAGNITUDE OF TREATMENT EFFECT MAY DEPEND UPON THE CLINICAL STAGE AT WHICH TREATMENT IS INITIATED

Early, or even pre-symptomatic, treatment may be associated with greater efficacy

Exploring ways to increase use of genetic testing in ALS and to potentially study earlier patient populations as we aim to define the most optimal time to initiate treatment

NEUROFILAMENT MAY BE A VALUABLE BIOMARKER OF EARLY EFFICACY AND DISEASE PROGRESSION

Potential utility in both clinical trial execution and potentially in early patient identification

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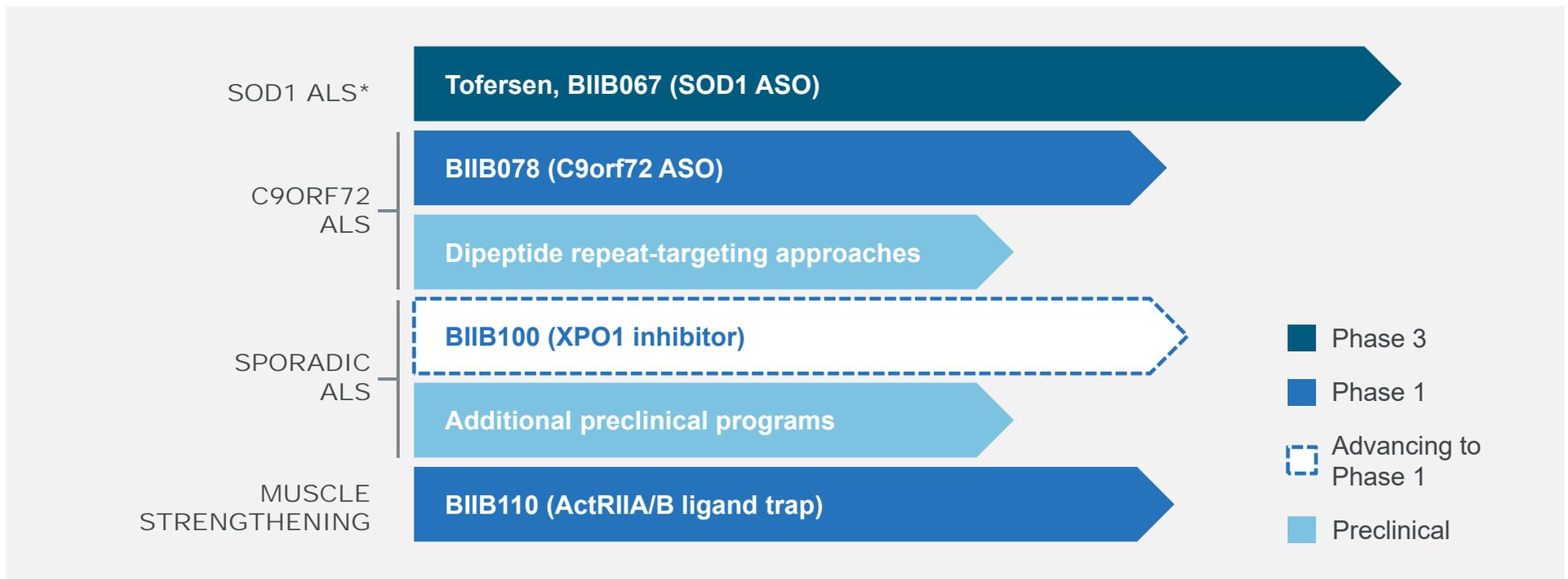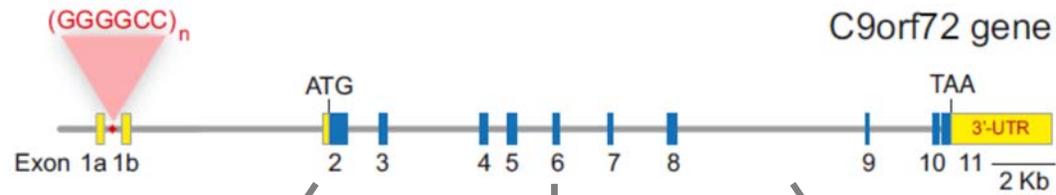# Current ALS pipeline targets distinct patient segments

Our vision is to build a deep ALS pipeline across multiple modalities, including ASOs, biologics, small molecules, and gene therapy
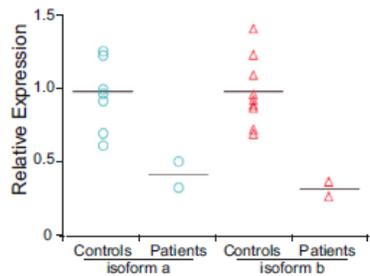
Segment	Program
SOD1 ALS*	Tofersen, BIIB067 (SOD1 ASO) — Phase 3
C9ORF72 ALS	BIIB078 (C9orf72 ASO) — Phase 1
	Dipeptide repeat-targeting approaches — Preclinical
SPORADIC ALS	BIIB100 (XPO1 inhibitor) — Advancing to Phase 1
	Additional preclinical programs — Preclinical
MUSCLE STRENGTHENING	BIIB110 (ActRIIA/B ligand trap) — Phase 1

Legend:
- Phase 3
- Phase 1
- Advancing to Phase 1
- Preclinical

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Hexanucleotide repeat expansions in C9orf72 cause ALS
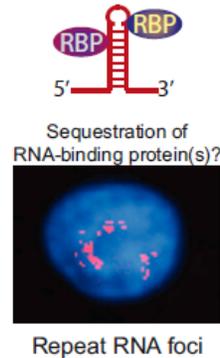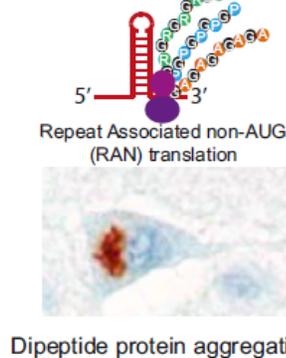
Targeted by C9orf72 ASO

Target C9orf72 dipeptide repeats

Ling et al., 2013
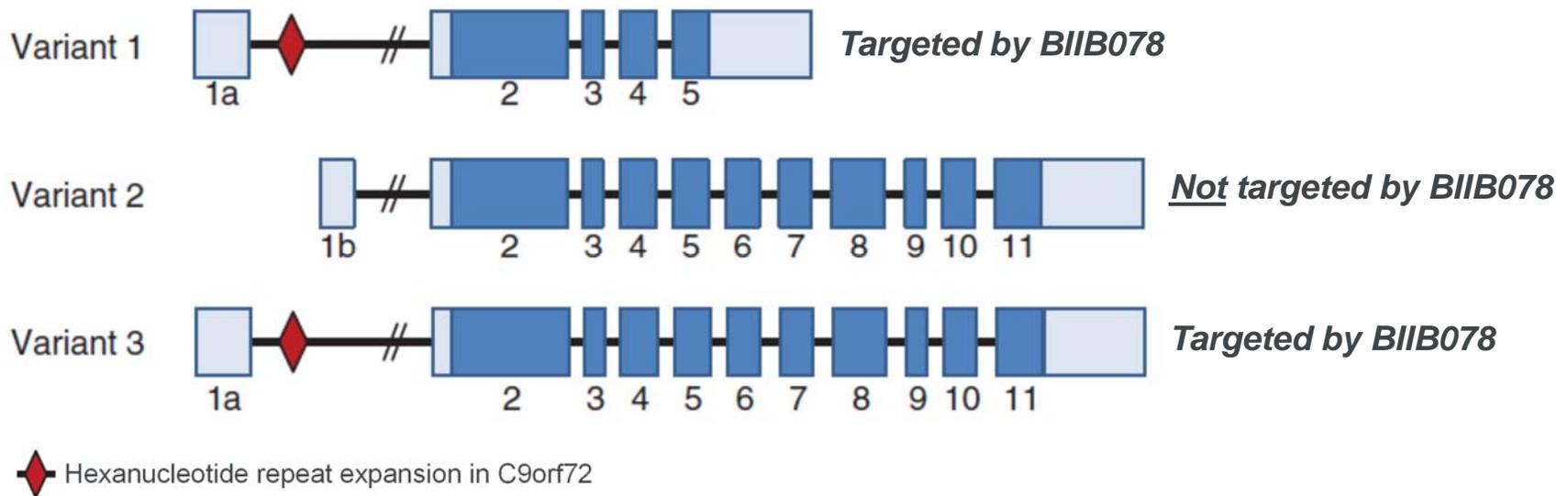
BIIB078 selectively targets expansion-containing C9orf72 transcripts to reduce risk of on-target toxicity
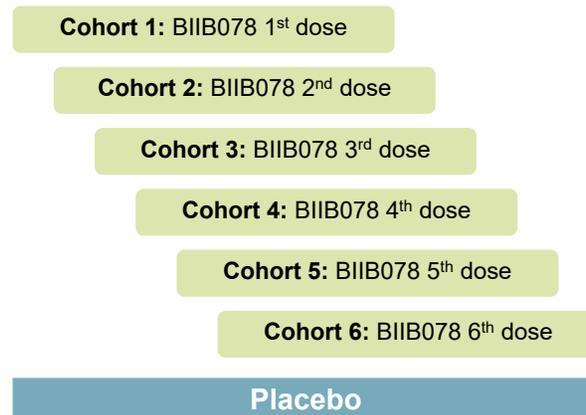
Advancing Phase 1 study of BIIB078 in C9orf72 ALS

POPULATION

> 18 years old

ALS patients with confirmed expansion in C9orf72

Slow vital capacity ≥ 50% of predicted value

Concomitant use of riluzole/edaravone allowed

MAD STUDY

Cohort 1: BIIB078 1st dose

Cohort 2: BIIB078 2nd dose

Cohort 3: BIIB078 3rd dose

Cohort 4: BIIB078 4th dose

Cohort 5: BIIB078 5th dose

Cohort 6: BIIB078 6th dose

Placebo

ENDPOINTS

Primary	**Secondary**
Safety and tolerability	PK measures of BIIB078

Exploratory endpoints include

ALSFRS-R scores, SVC, HHD megascore, CSF C9orf72-RAN dipeptide protein, CSF pNFH

80 participants total	First patient dosed September 2018	Intrathecal injection (BIIB078 or placebo): 3 loading doses followed by 2 maintenance doses	Patients followed for approximately 8 months	Data expected in 2021

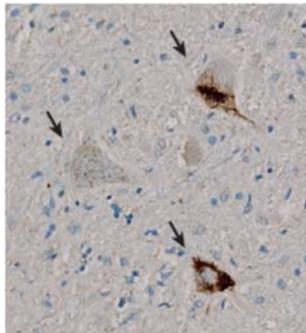Biogen.

RAN = repeat-associated non-ATG

Targeting nucleocytoplasmic export in ALS with BIIB100

NUCLEOCYTOPLASMIC TRANSPORT DYSFUNCTION IN ALS

Accumulation of **cytoplasmic inclusions** in motor neurons is a pathological hallmark of ALS
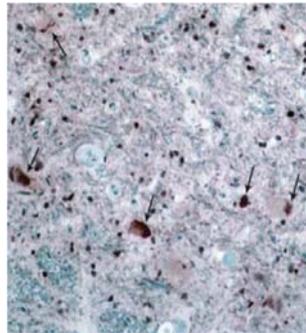
- Hypothesized to be caused by deficits in nucleocytoplasmic transport

TDP-43 inclusions   **FUS inclusions**

Taylor et al., 2016   *Deng et al., 2010*

BIIB100: SELECTIVE INHIBITOR OF EXPORTIN 1 (XPO1)

Exportin 1 (Xpo1): Nuclear transport factor that mediates the nuclear export of many proteins containing nuclear export signals

Hypothesis: Xpo1 inhibition may reduce nuclear protein export and prevent the formation of neuronal cytoplasmic inclusions
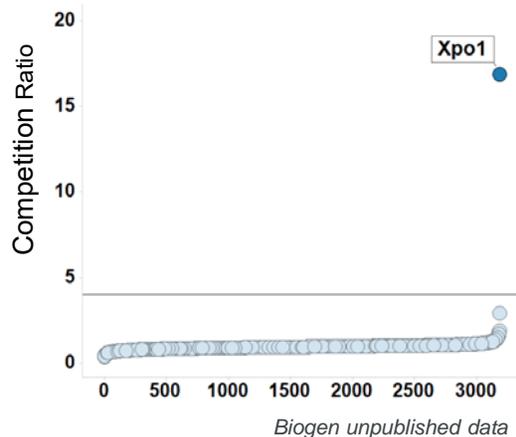
BIIB100

TDP-43 = TAR DNA-binding protein 43; FUS = fused in sarcoma
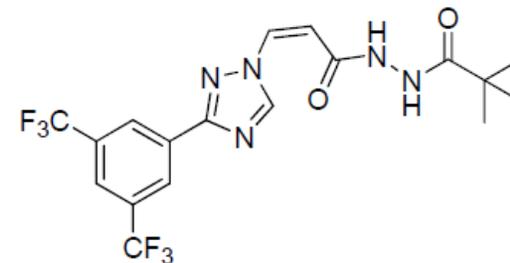
BIIB100 is a selective compound with evidence of preclinical efficacy in multiple ALS models

BIIB100 IS HIGHLY SELECTIVE FOR XPO1	SLOWS FUNCTIONAL DECLINE IN SOD1 TRANSGENIC MICE	EXTENDS SURVIVAL IN AN AAV-TDP43 RODENT MODEL

Competitive binding (10 µM)

Biogen unpublished data

>3,000 identified reactive cysteines correspond to nearly 2,000 proteins

Only Cys528 of Xpo1 was differentially enriched

Compound Muscle Action Potential

- SOD1; Vehicle (n=13)
- SOD1; BIIB100 (0.5mpk) (n=11)
- SOD1; BIIB100 (1.0mpk) (n=10)
- SOD1; BIIB100 (2.0mpk) (n=13)

Daily dosing; Biogen unpublished data

* $p < 0.05$ two-way ANOVA

- - - Vehicle
—— BIIB100

Biweekly dosing; Karyopharm unpublished data

Myostatin signaling is a genetically validated target for muscle strengthening

MYOSTATIN LOSS-OF-FUNCTION MUTATIONS ARE ASSOCIATED WITH MUSCLE HYPERTROPHY

Schuelke et al., 2004   *McPherron et al., 1997*

BIIB110 MECHANISM OF ACTION
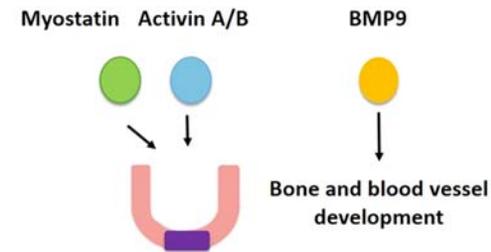
BIIB110: Extracellular ActRII domain
with BMP9-sparing hinge

BIIB110 acts as a ligand trap to bind and inhibit signaling of both myostatin and activin, while sparing BMP9

Sparing of BMP9 is hypothesized to reduce off-target toxicity previously observed with other myostatin inhibitors

Currently in a Phase 1a study in healthy volunteers

Initial development in SMA, and aim to **expand to additional neuromuscular disorders**, including ALS

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Enriching the target portfolio for sporadic ALS

We see further opportunity to address the needs of patients with sporadic ALS

- No single gene responsible; need to deeply understand the biology

Field has advanced over the past 5 years
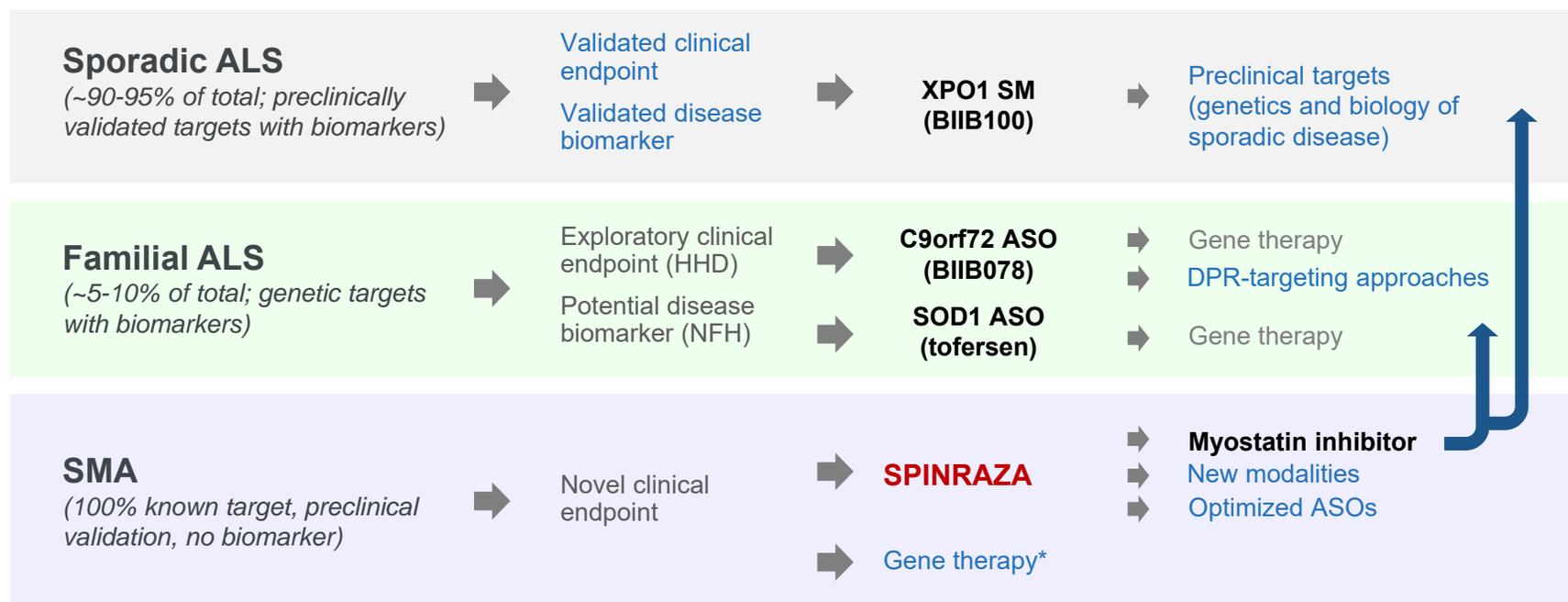
- Evidence for targets related to TDP-43, Ataxin-2, FUS, stress pathways, axonal regeneration, and nucleocytoplasmic transport

Established a high-throughput *in vivo* target validation core to identify agents active in multiple preclinical models

Aim to have at least 5 ALS programs in the clinic, across both familial and sporadic disease, within the next 3 years

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Building a neuromuscular disorders franchise

Legend: Approved In Clinic Preclinical Exploratory

Sporadic ALS
(~90-95% of total; preclinically validated targets with biomarkers)
➡ Validated clinical endpoint
Validated disease biomarker
➡ **XPO1 SM (BIIB100)**
➡ Preclinical targets (genetics and biology of sporadic disease)

Familial ALS
(~5-10% of total; genetic targets with biomarkers)
➡ Exploratory clinical endpoint (HHD)
Potential disease biomarker (NFH)
➡ **C9orf72 ASO (BIIB078)**
➡ **SOD1 ASO (tofersen)**
➡ Gene therapy
➡ DPR-targeting approaches
➡ Gene therapy

SMA
(100% known target, preclinical validation, no biomarker)
➡ Novel clinical endpoint
➡ **SPINRAZA**
➡ Gene therapy*
➡ **Myostatin inhibitor**
➡ New modalities
➡ Optimized ASOs

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Conclusion

HANI HOUSHYAR, PH.D.

Senior Director,
Product Development and
Commercialization Lead for Tofersen