Movement Disorders at Biogen

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DENALI

R&D Day
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Biogen

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; potential of, and expectations for, our commercial business and pipeline programs; capital allocation and investment strategy; clinical development programs, clinical trials, and data readouts and presentations; risks and uncertainties associated with drug development and commercialization; regulatory discussions, submissions, filings, and approvals and the timing thereof; the potential benefits, safety, and efficacy of our and our collaboration partners' products and investigational therapies; the anticipated benefits and potential of investments, collaborations, and business development activities; and our future financial and operating results. These forward-looking statements may be accompanied by such words as "aim," "anticipate," "believe," "could," "estimate," "expect," "forecast," "goal," "intend," "may," "plan," "potential," "possible," "prospect," "will," "would," and other words and terms of similar meaning. 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. You should not place undue reliance on these statements or the scientific data presented.

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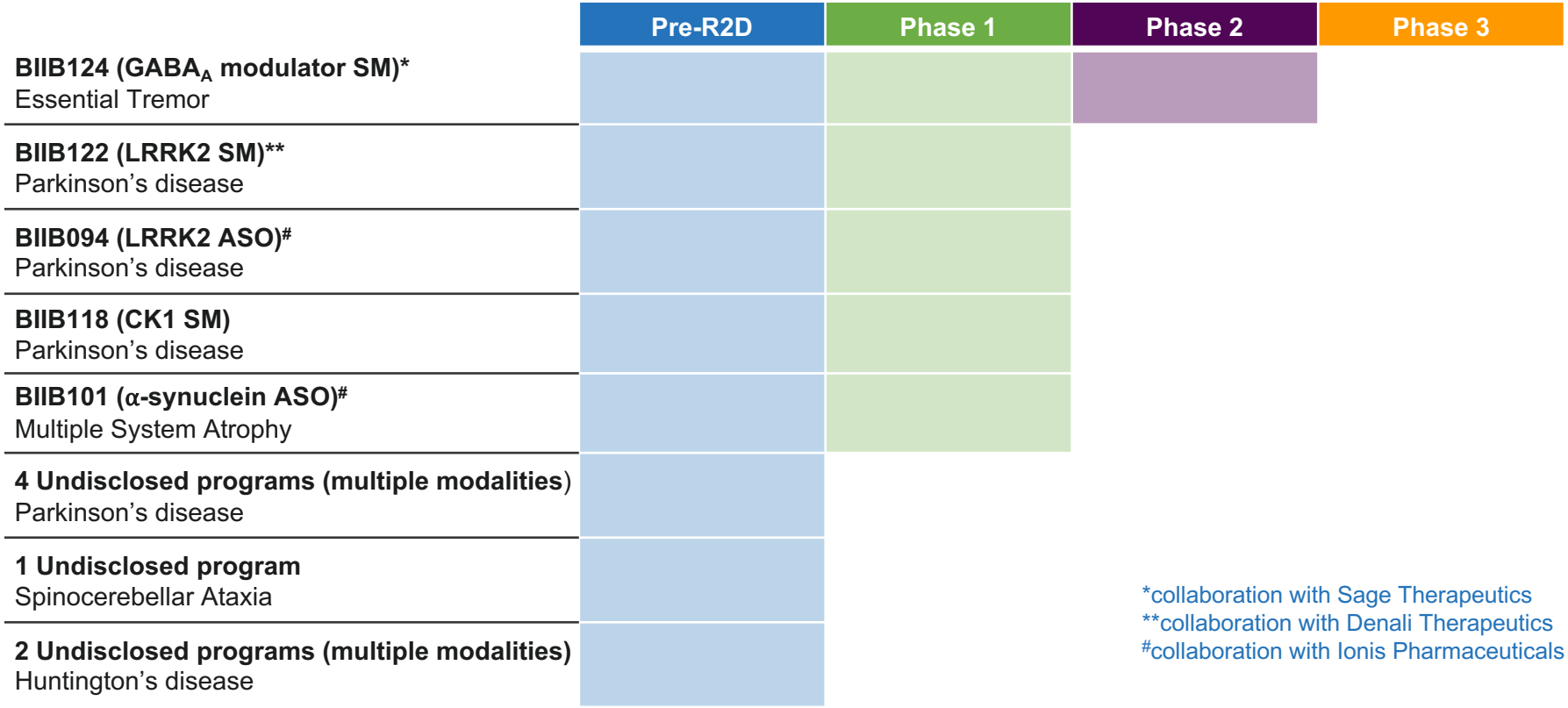
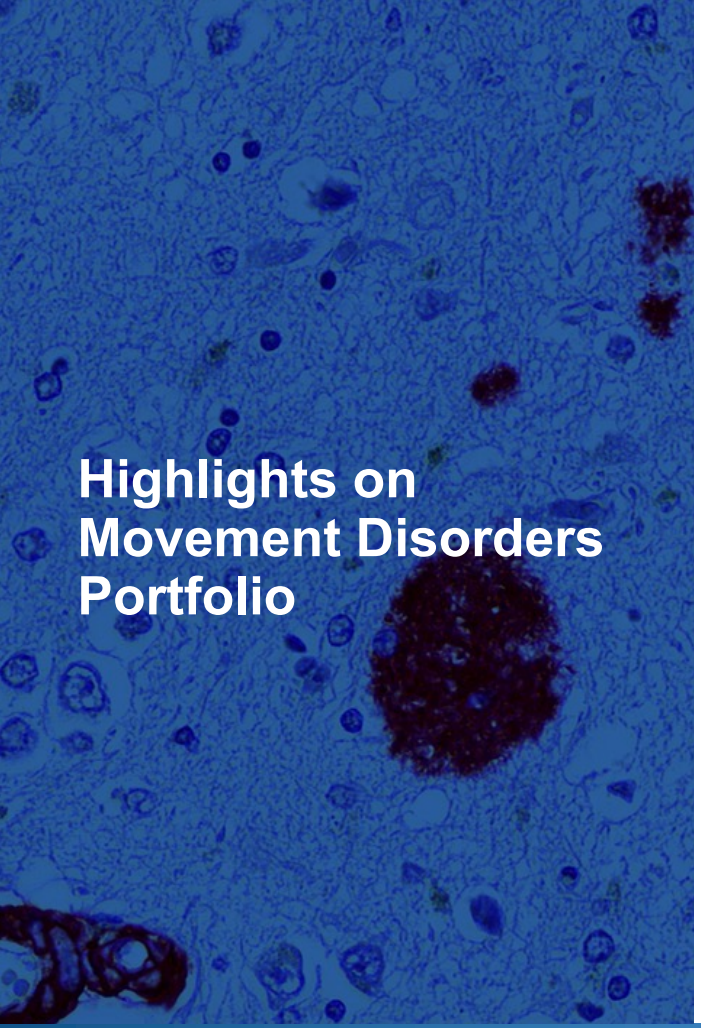
These statements are based on our current beliefs and expectations and speak only as of the date of this presentation. We do not undertake any obligation to publicly update any forward-looking statements.

Biogen has one of the leading movement disorders pipelines



*collaboration with Sage Therapeutics
**collaboration with Denali Therapeutics
#collaboration with Ionis Pharmaceuticals

ASO = antisense oligonucleotide; CK1 = casein kinase 1; GABA$_A$ = gamma-aminobutyric acid type A; LRRK2 = leucine rich repeat kinase 2; PAM = positive allosteric modulator; SM = small molecule



Highlights on Movement Disorders Portfolio

01 **Movement Disorders Pipeline and Strategy**

Multi-modality, multi-target approach

02 **Advances in Therapies for Parkinson's Disease**

BIIB122 (DNL 151) – LRRK2 Kinase Inhibitor
(in collaboration with Denali Therapeutics)

BIIB094 – LRRK2 ASO
(in collaboration with Ionis Pharmaceuticals)

BIIB118 – CK1 Inhibitor

03 **Novel Approach to Essential Tremor**

BIIB124 (SAGE-324) – $GABA_A$ PAM
(in collaboration with Sage Therapeutics)

Biogen's R&D strategy in movement disorders

Leverage scientific, clinical, and commercial synergies – and Biogen's multi-modality expertise – to address patient needs

Parkinson's disease:
Slow progression and address major untreated symptoms

- Despite dopamine replacement therapies, there is no disease-modifying therapy for Parkinson's disease
- Major clinical needs (e.g., cognitive deficits) remain untreated

Atypical Parkinsonism:
Target proteins that form aggregates in severe, rare Parkinsonisms

- Progressive supranuclear palsy (PSP) and Multiple system atrophy (MSA) are rapidly progressing, fatal conditions
- Tau and α-synuclein compounds have potential for PSP and MSA

Genetically defined movement disorders

- Mitigate risk by targeting genetic adjacencies

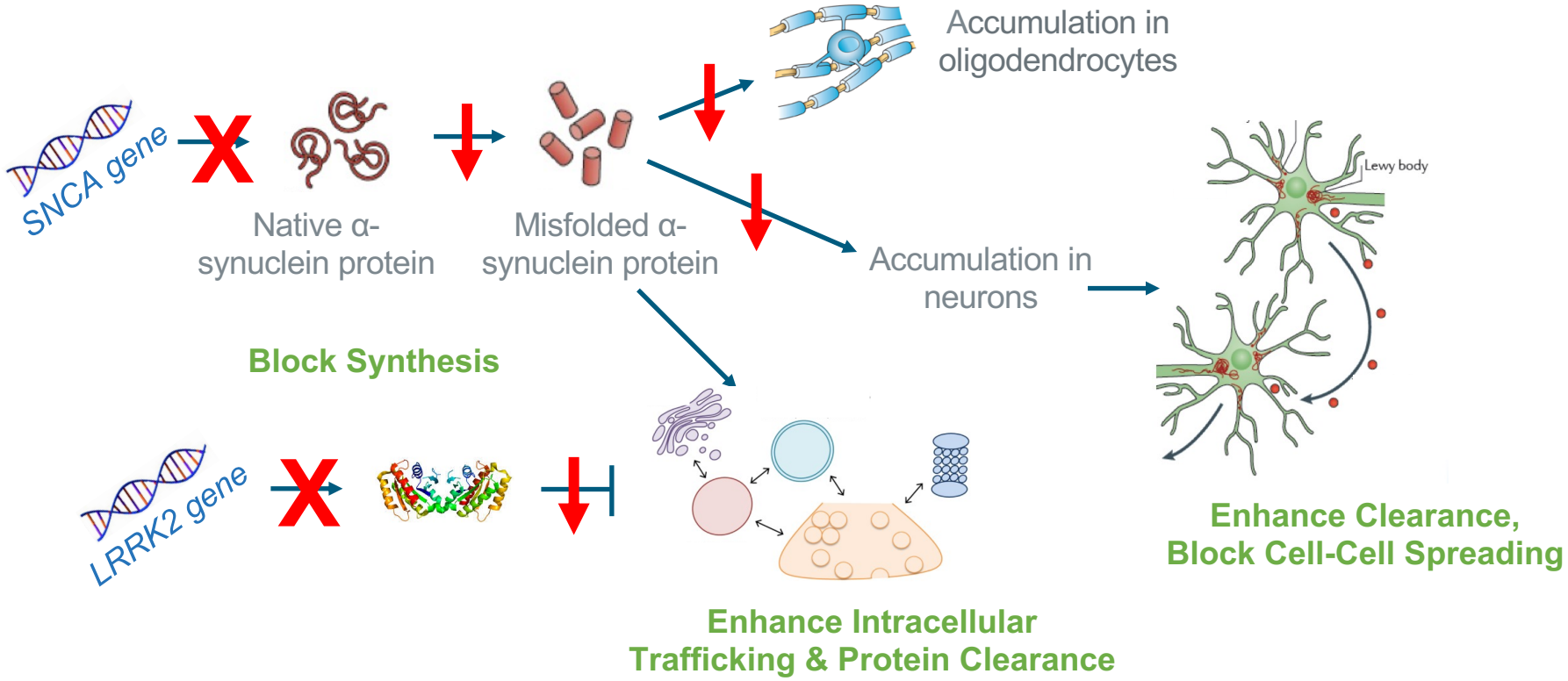
Disease modifying therapies are a critical unmet medical need in Parkinson's disease

- Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease[1,2]
- In 2020, approximately 10 million individuals with PD worldwide[3]
- Misfolded and aggregated forms of α-synuclein form intracellular proteinaceous inclusions called Lewy bodies and Lewy neurites, which, along with the loss of dopaminergic neurons in the substantia nigra, form the pathological characteristics of PD[4]
- Classic motor symptoms of PD include bradykinesia, rigidity, rest tremor, and postural instability[5,6]
- The average age of onset of motor manifestations is in the late 50s, with a broad range from age < 50 to > 80 years.[2]
- Treatment with dopamine replacement therapies (e.g., levodopa / dopamine agonists, MAO-B inhibitors) temporarily improves motor symptoms

1. Ascherio A, et al. *Lancet Neurol.* 2016
2. Poewe W, et al. *Nat Rev Dis Primers*. 2017
3. Parkinson Association of the Carolinas. https://www.parkinsonassociation.org/what-is-parkinsons-disease/. Accessed January 31, 2020
4. Bridi JC, et al *Front Neurosci.* 2018
5. Kalia LV et al *Lancet*. 2015
6. The Michael J. Fox Foundation for Parkinson's Research. https://www.michaeljfox.org/symptoms. Accessed November 15, 2019

MAO-B inhibitors = monoamine oxidase B inhibitors

Biogen's multi-prong approach to Parkinson's disease targeting α-synuclein and LRRK2



SCNA = alpha synuclein gene

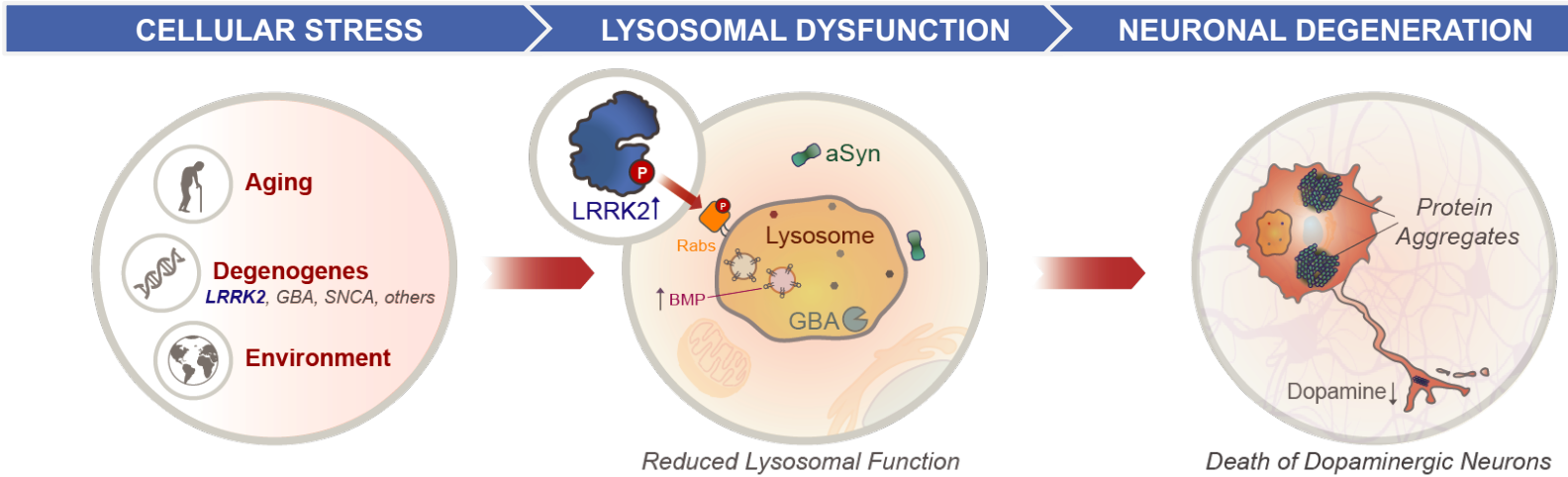
BIIB122 (DNL151)

A selective, small molecule central nervous system-penetrant LRRK2 kinase inhibitor under investigation for the treatment of Parkinson's disease

In collaboration with Denali Therapeutics – Carole Ho, MD, Chief Medical Officer & Head of Development

The statements included in this presentation are Denali's and do not necessarily reflect those of Biogen or any other party.

Role of LRKK2 in the pathophysiology of Parkinson's disease



Lysosomal dysfunction plays a central role in the pathology of Parkinson's disease[1,2]

LRRK2 activity is increased in Parkinson's disease and negatively regulates lysosomal function[2,3]

LRRK2 inhibition rescues lysosomal function and normalizes protein processing[4-7]

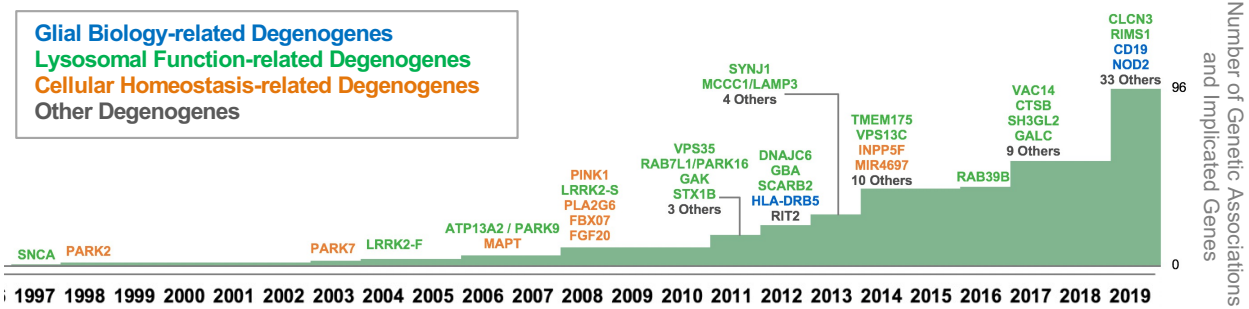
1. Wallings, et al Trends Neurosci 42, 899-912 (2019)
2. Dehay B, et al. Mov Disord. 2013;28:725-732.
3. DiMaio, et al Sci Transl Med 2018:10(451).
4. Khan NL, et al. Brain. 2005;128:2786-2796.
5. Jaleel M, et al. Biochem J. 2007;405:307-317.
6. West AB, et al. Human Mol Gen. 2007;16;223-232.
7. Sheng Z, et al. Sci Transl Med. 2012;4:164ra161.

aSyn = alpha synuclein; GBA = glucocerebrosidase gene

Rationale for LRRK2 as a therapeutic target

Genetic studies highlight multiple lysosomal function related genes in Parkinson's disease

Lysosomal dysfunction is central to the pathogenesis of Parkinson's disease



Human LRRK2 LoF variants do not have functional consequences

Human LRRK2 LoF variants support safety of targeting LRRK2

LoF = loss-of-function

LRRK2 Inhibition may be therapeutically beneficial in LRRK2 mutation carriers and idiopathic Parkinson's disease

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

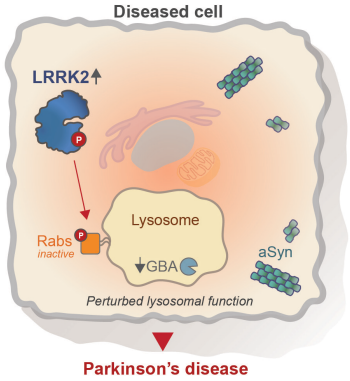
PARKINSON'S DISEASE

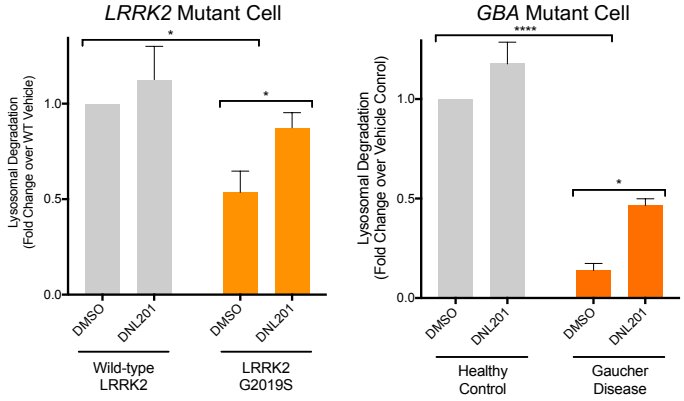
LRRK2 activation in idiopathic Parkinson's disease

Roberto Di Maio[1,2,3], Eric K. Hoffman[1,2], Emily M. Rocha[1,2], Matthew T. Keeney[1,2], Laurie H. Sanders[1,2,4], Briana R. De Miranda[1,2], Alevtina Zharikov[1,2], Amber Van Laar[1,2], Antonia F. Stepan[5], Thomas A. Lanz[5], Julia K. Kofler[6], Edward A. Burton[1,2,7], Dario R. Alessi[8], Teresa G. Hastings[1,2], J. Timothy Greenamyre[1,2,7]*

LRRK2 activation is established in familial Parkinson's with kinase activating mutations; LRRK2 activation may also drive idiopathic disease

LRRK2 inhibitors may have therapeutic potential to treat LRRK2 and other drivers of lysosomal dysfunction





BIIB122/DNL151 Phase 1 and Phase 1b Study Design

Phase 1 study (DNLI-C-0001)

Single-ascending dose (SAD) and 10-day, 14-day, and 28-day multiple-ascending dose (MAD) parts in healthy volunteers (HVs)

PART A, C	PART B, D	PART E
Single Dose Part A: young HV (n = 40) Part C: elderly HV (n = 8)	Multiple Doses QD Dosing Part B: 10-day (n = 63) Part D: 28 day (n = 17)	Multiple Doses BID Dosing Part E: 14-day (n – 31)
Doses: **10-300 mg**	**Doses:** **15-300 mg QD**	**Doses:** **150-400mg BID**
N=56 total (7 cohorts) (6:2, active: PBO)	N=97 total (9 cohorts) Part B:(8:2, active: PBO) Part D: (12:4, active: PBO)	N=31 total (3 cohorts) (8:2, active: PBO)

Primary Endpoints	• Adverse events (AEs) and serious adverse events (SAEs), clinically significant changes in laboratory tests, ECGs, pulmonary function, physical and neurological examinations • Plasma PK
Secondary Endpoints	• Cerebrospinal fluid (CSF) PK • Pharmacodynamic measure of pS935 in whole blood (change from Baseline to steady state)

Phase 1b trial (DNLI-C-0003)

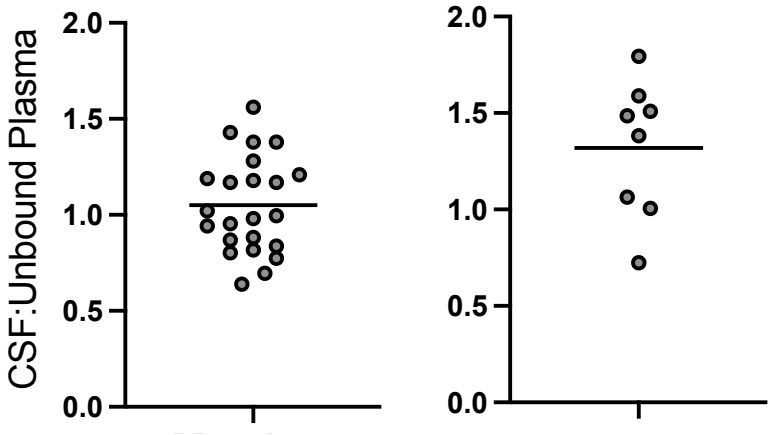
Parallel-group design of BIIB122/DNL151 in patients with PD

PART 1	PART 2	PART 3
Doses: **80 mg or PBO QD**	**Doses:** **130 mg, 80 mg or PBO QD**	**Doses:** **300 mg or PBO QD**
N=8 (1:1, 80 mg: PBO)	N=17 total (2:1:1, 130 mg: 80 mg :PBO)	N=11 total (4:1, 300 mg: PBO)

Primary Endpoints	• AEs and SAEs, clinically significant changes in laboratory tests, ECGs, pulmonary function, physical and neurological examinations
Secondary Endpoints	• Cerebrospinal fluid (CSF) PK • Pharmacodynamic measure of pS935 in whole blood (change from Baseline to steady state)

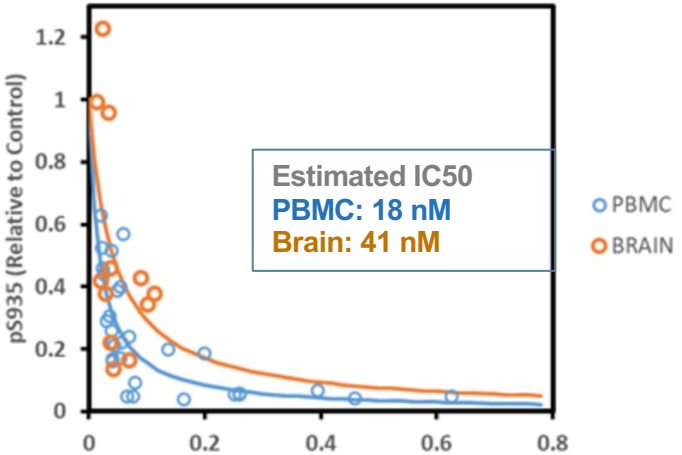
BIIB122/DNL151 is brain penetrant in humans and non-human primate (NHP) and inhibits brain LRRK2 kinase activity

CSF:PLASMA PK RATIO (STEADY STATE)



Parkinson's Patients (Day 28) NHP (Day 11)

KINASE INHIBITION IN BRAIN & PBMC RELATIVE TO UNBOUND DNL151 CONCENTRATION (NHP)



Unbound DNL151 plasma concentration (μM)

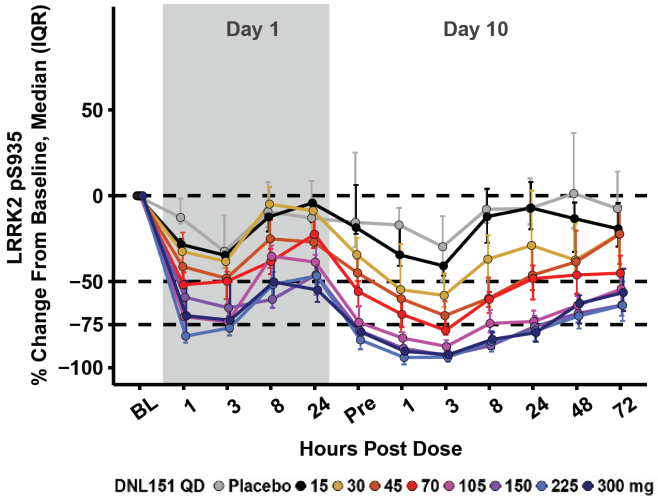
- BIIB122/DNL151 demonstrates CSF penetration with steady-state mean CSF to unbound plasma ratio of ~ 1.0 in healthy volunteers and Parkinson's patients
- Kinase inhibition in cynomolgus in peripheral blood mononuclear cells is well correlated with brain

CSF = cerebrospinal fluid; PBMC = peripheral blood mononuclear cells; pS935 = phosphorylation of Serine 935 of LRRK2; PK= pharmacokinetics

Phase 1 healthy volunteer data supports target engagement

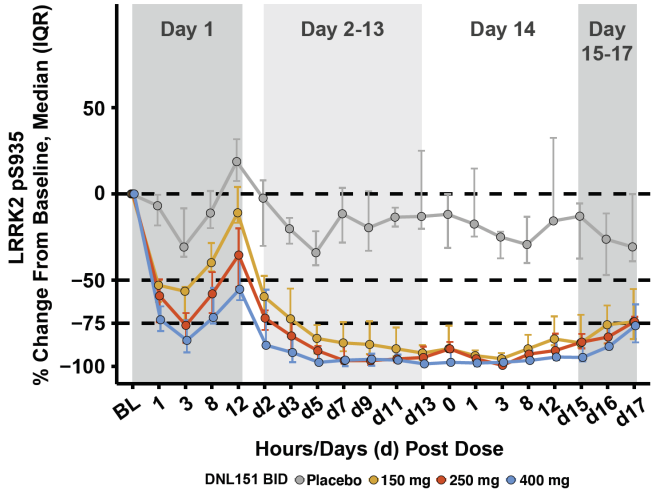
Target Engagement

QD Cohorts



Target Engagement

BID Cohorts



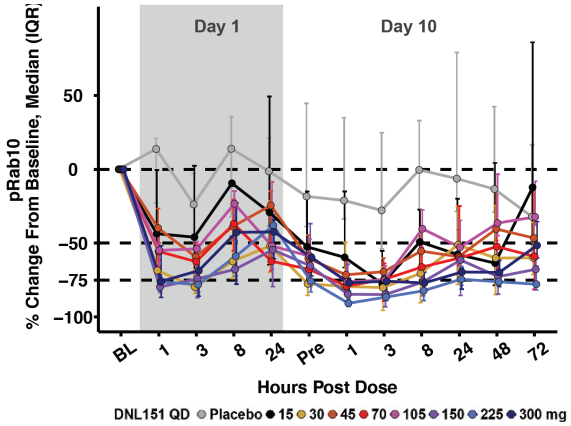
BIIB122/DNL151 achieved LRRK2 target engagement across broad dose ranges and was generally well tolerated in healthy volunteers

BID = twice daily; BL = baseline; IQR = interquartile range; QD = once daily

Phase 1 healthy volunteer data supports effects on pathway biology and lysosomal function

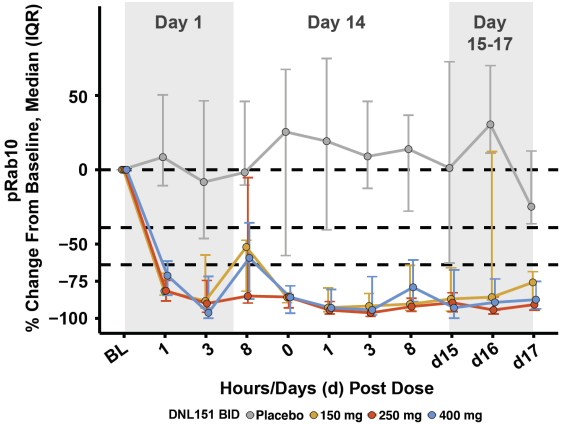
Pathway Engagement

Reduction of pRAB10 (PBMCs) QD



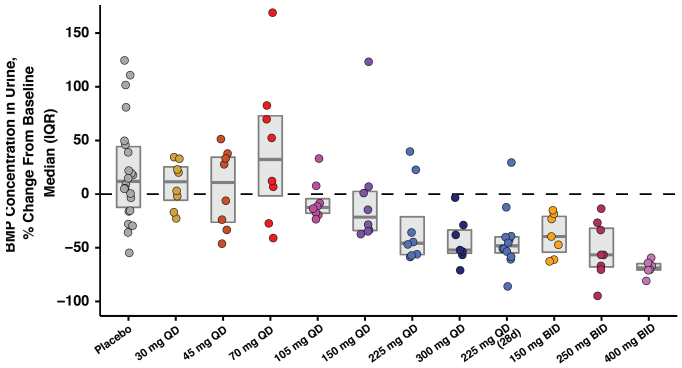
Pathway Engagement

Reduction of pRAB10 (PBMCs) BID



Lysosomal Function

Reduction of BMP (Urine)



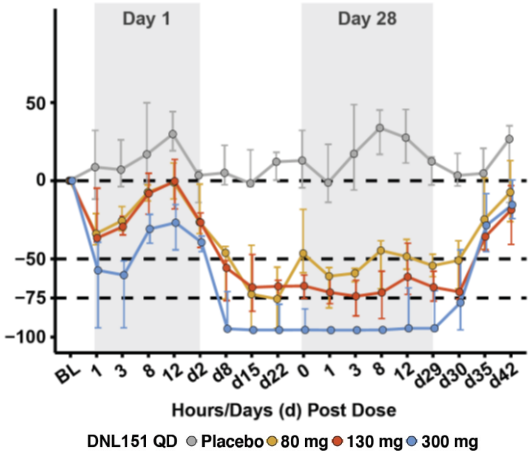
BIIB122/DNL151 achieved downstream biological pathway engagement at doses above 70 mg QD and modulated lysosomal function at doses of 225 mg QD and higher

BMP = bis(monoacylglycerol); pRAB10 = phosphorylation of RAB10

Phase 1b Parkinson's disease patient data supports dose selection and advancement to late-stage studies

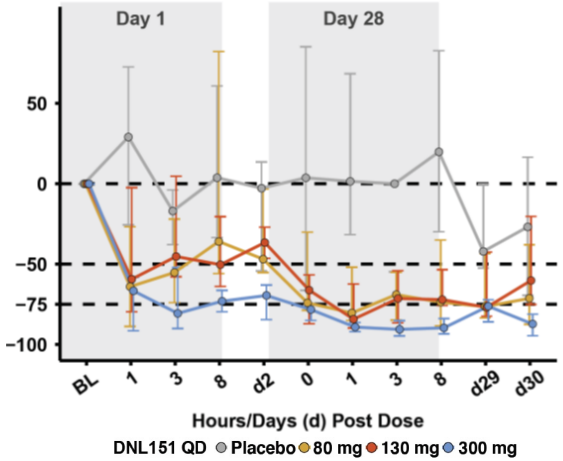
Target Engagement

Reduction of pS935 LRRK2 (Whole blood)



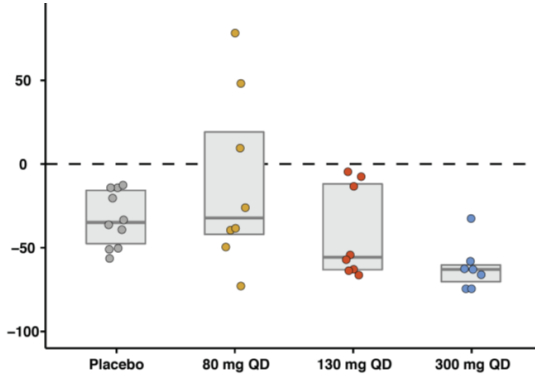
Pathway Engagement

Reduction of pRAB10 (PBMCs)



Lysosomal Function

Reduction of BMP (Urine)



BIIB122/DNL151 achieved LRRK2 target engagement and downstream biological pathway engagement, and was generally well tolerated in healthy volunteers and patients with Parkinson's disease

BIIB122 advancing to late-stage development

ENGAGING PATIENT NETWORKS

Parkinson's Foundation

PD GENEration

MAPPING THE FUTURE OF PARKINSON'S DISEASE

Perelman School of Medicine
University of Pennsylvania

The MIND Initiative

The Molecular Integration in Neurological Diagnosis

FOX INSIGHT

YOUR EXPERIENCE FUELING RESEARCH

PDBP

NIH National Institute of Neurological Disorders and Stroke

ENGAGE PARKINSON'S

CENTOGENE

THE RARE DISEASE COMPANY

Rostock International Parkinson's Disease Study (ROPAD)

Luebeck International Parkinson's Disease Project (LIPAD)

Parkinson's Families Projects

Families in research for Parkinson's

Novel potential treatment of Parkinson's disease

- Mutations in LRRK2 are one of the most common genetic risk factors in Parkinson's and inhibiting LRRK2 has broad potential in Parkinson's Disease
- BIIB122/DNL151 is an investigational, selective, central nervous system–penetrant LRRK2 kinase inhibitor
- Data generated by the Phase 1 (healthy volunteer) and Phase 1b (patient) studies support goal to improve lysosomal function and slow progression of disease
- Plan to advance BIIB122/DNL151 into late-stage development

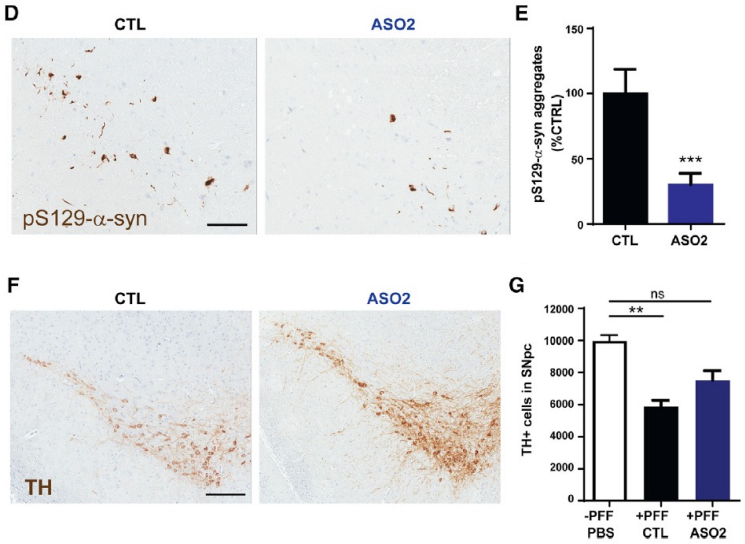
BIIB094

A selective, ASO targeting mRNA of LRRK2 under investigation for the treatment Parkinson's disease

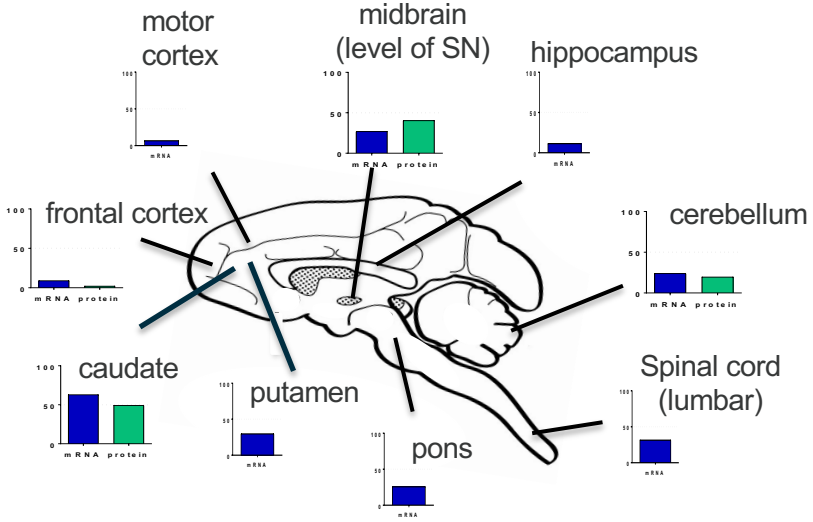
> In collaboration with Ionis Pharmaceuticals

LRRK2 ASO reduces α-syn pathology in mouse model and reduces LRRK2 mRNA and protein in NHP after IT delivery

ASO Reduces mRNA/Protein by ~50% and Attenuates a-Syn Pathology & Neuronal Loss in Mouse PFF Model



ASO Reduces LRRK2 mRNA & protein in multiple brain regions in NHP



Tracy Cole, Patrick Trapa, Melissa Berman, Omar Mabrouk – Ionis / Biogen

IT = intrathecal; mRNA = messenger RNA; NHP = non-human primate; PFF = preformed fibril; SN= substantia nigra

BIIB094 clinical development

Ongoing phase 1 SAD/MAD study

A study to evaluate the safety, tolerability, and pharmacokinetics of BIIB094 in adults with Parkinson's disease

Key Endpoints	• Primary: Incidence of adverse events and serious adverse events
	• Secondary: CSF and serum concentrations of LRRK2 ASO (Cmax, AUC, Tmax , $T_{1/2}$)
	• Exploratory:
	  ◦ Clinical scales including MDS-UPDRS
	  ◦ CSF levels of LRRK2 Protein

Population (planned n=82)	• PD diagnosed within the last 7 years • Treatment naïve or stable symptomatic therapy
Design	• SAD: 6 ascending dose cohorts (randomized to BIIB094 or placebo) – single intrathecal (IT) dose • MAD: 5 ascending dose cohorts (randomized to BIIB094 or placebo) – single monthly IT dose for 4 consecutive months

AUC = area under the curve; Cmax = maximum concentration;; MAD = multiple ascending dose; MDS-UPDRS = Movement Disorders Society sponsored revision of the Unified Parkinson's Disease Rating Scale; SAD = single ascending dose; Tmax = time at Cmax;T1/2 = half life

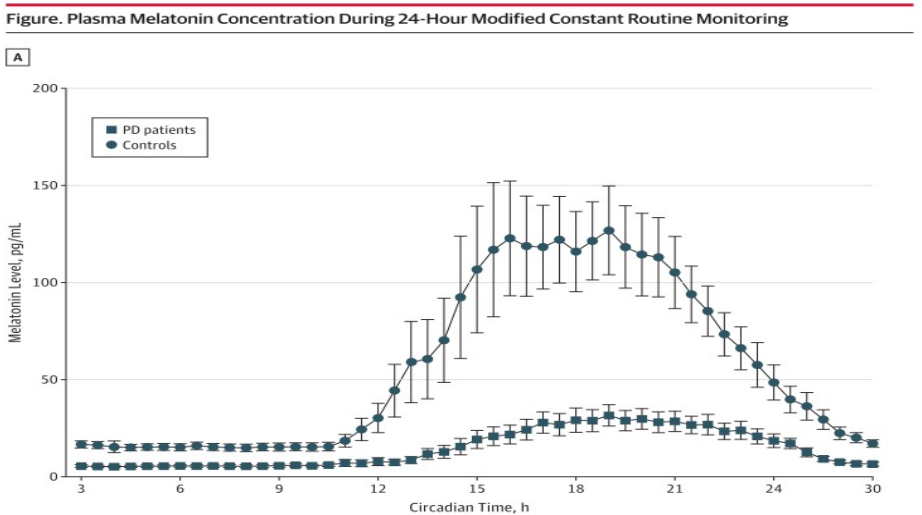
BIIB118

A selective, small-molecule, central nervous system-penetrant, dual inhibitor of CK1δ and CK1ε under investigation for the treatment of Circadian rhythm disruptions in Parkinson's disease

BIIB118 could compensate for decreased circadian amplitude and improve sleep and other non-motor symptoms

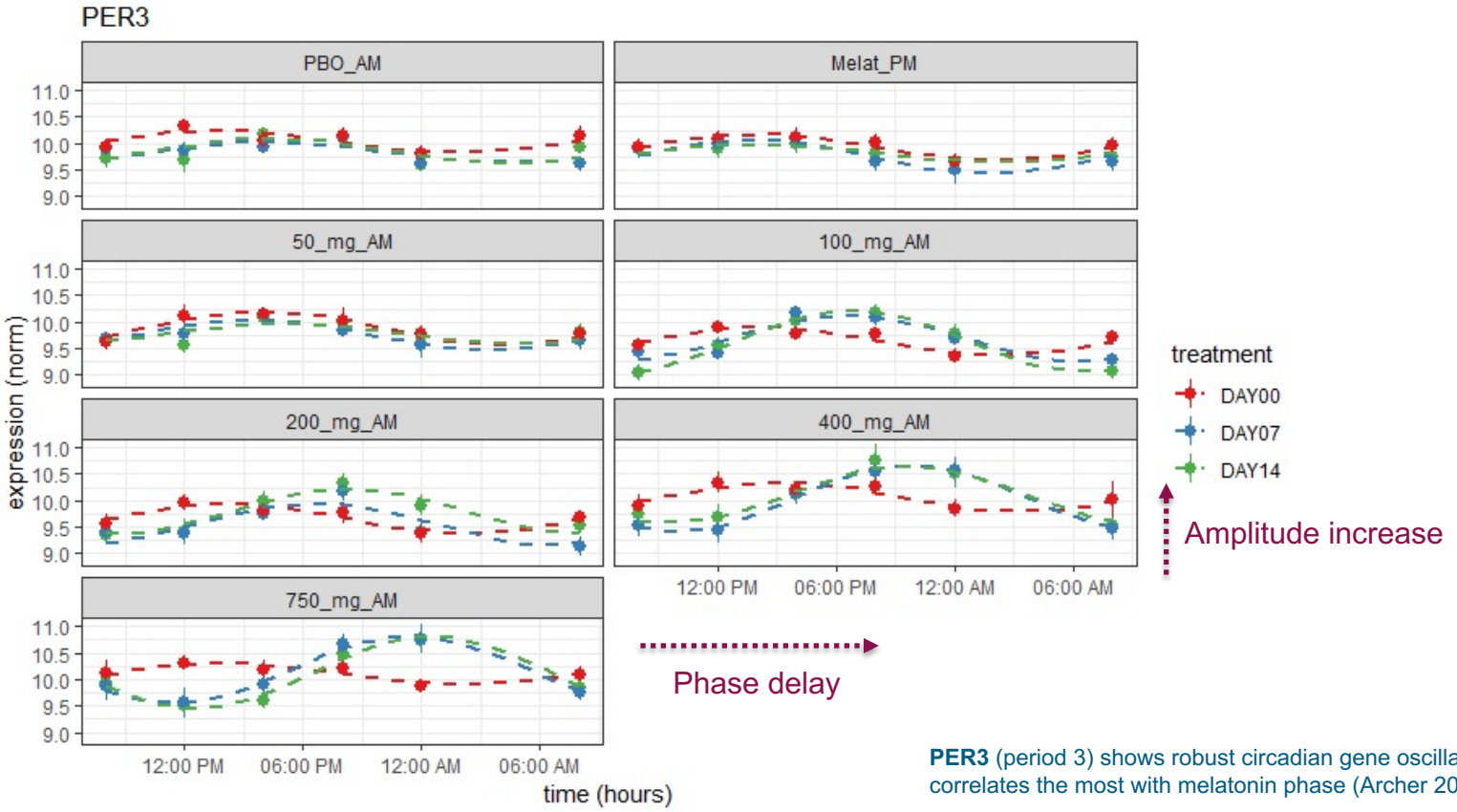
- Sleep-wake disturbances are common non-motor symptoms of Parkinson's disease
  - Sleep maintenance, insomnia, and sleep fragmentation are the most prevalent with 37-58% of Parkinson's patients reporting insomnia[1,2]
- Sleep disturbances are associated with fatigue, depressive symptoms, worse cognition, and overall decreased quality of life[3-6]
- Dampening of multiple physiological circadian rhythms, particularly a significant decrease in 24-hour melatonin secretion, have been observed in Parkinson's disease vs age-matched controls[7]
- BIIB118 is a circadian agent proposed to minimize circadian rhythm disruptions

Blunted physiological (i.e., melatonin) and molecular (i.e., circadian genes, not shown) circadian rhythms in PD[7]



1. Chaudhuri KR et al. Mov Disord. 2010
2. Ou R et al. J Neurol Sci. 2016
3. Chung S et al. J Clin Sleep Med. 2013
4. Duncan GW et al. Mov Disord. 2014
5. Gros P et al. Clin Geriatr Med. 2020
6. Neikrug AB et al. J Clin Sleep Med. 2013
7. Videnovic A et al. Neurol. 2014

Dose-related effect on circadian phase shift and amplitude in healthy volunteers



PER3 (period 3) shows robust circadian gene oscillations and correlates the most with melatonin phase (Archer 2008)

BIIB124 (SAGE-324)

Oral neuroactive steroid $GABA_A$ PAM under investigation for the treatment of Essential Tremor

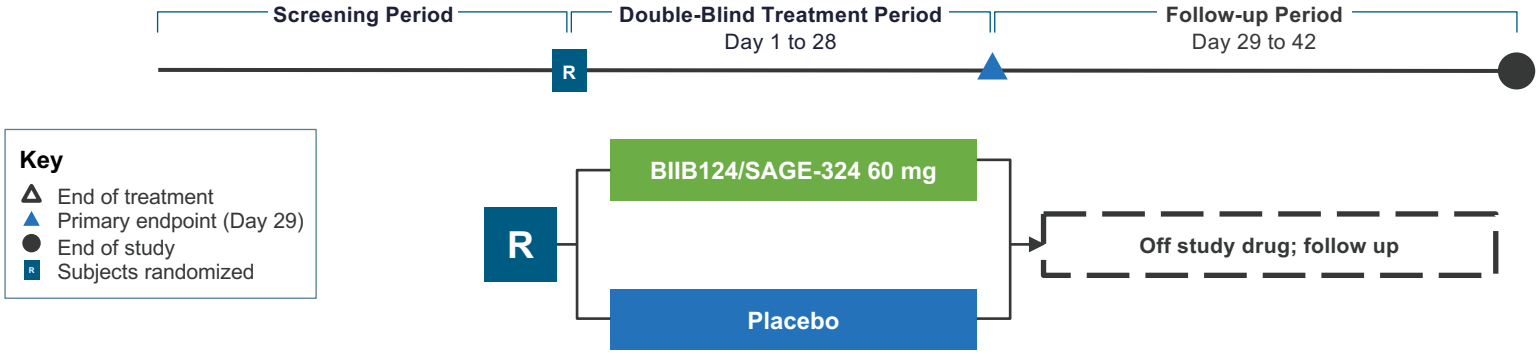
> In collaboration with Sage Therapeutics

Unmet medical need in essential tremor calls for novel treatments

- Essential tremor (ET) is one of the most prevalent movement disorder; affecting an estimated 6.4 million adults in the US[1]
- Activities of daily living are adversely impacted by ET,[2,3] contributing negatively to psychosocial well-being,[3,4] general anxiety,[3] and overall quality of life[3,5]
- High unmet need: 50% of treated patients do not respond or have sub-optimal response to standard of care treatment for ET[5]
- Deficits in inhibitory signaling may play a role in the pathophysiology of ET. $GABA_A$ PAMs have the potential to enhance inhibitory activity of the GABAergic system, the major inhibitory neurotransmitter system in the brain
- BIIB124/SAGE-324 is an investigational oral neuroactive steroid $GABA_A$ PAM with good oral bioavailability and long half-life providing flexibility in dosing
- A single dose of BIIB124/SAGE-324 reduced tremor nearly 50% in a Phase 1 open label study with ET patients

1. Crawford SO et al. Poster Presented at: 3rd Pan American Parkinson's and Movement Disorders Congress; 2020
2. Koller WC et al. Ann Neurol. 1994
3. Louis ED et al. Park Relat Disord. 2015
4. Traub RE et al. Park Relat Disord. 2010
5. Louis ED. Front Neurol. 2012

BIIB124/SAGE-324 Ph2a study (KINETIC) evaluated efficacy, safety and tolerability in essential tremor

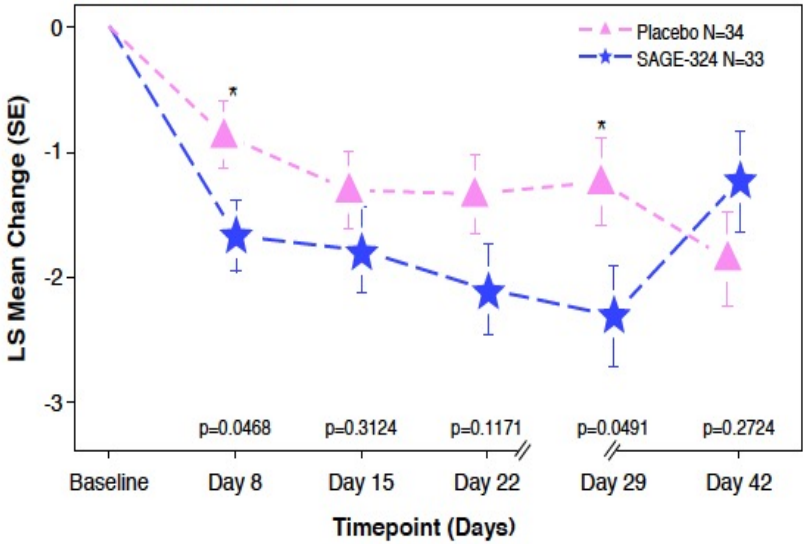


- 1:1 randomization to 60mg or placebo orally in the morning for 28 days (n=69)
- **Inclusion criteria:** 18-80 years with ET diagnosis: isolated action tremor bilateral upper limb at least 3 years duration, with or without tremors in other locations and absence of other neurological signs, and willing to discontinue ET medications
- **Primary endpoint (Efficacy):** Change from baseline compared to placebo in the The ET Rating Assessment Scale (TETRAS)[1] Performance Subscale Item 4 upper limb tremor score on Day 29

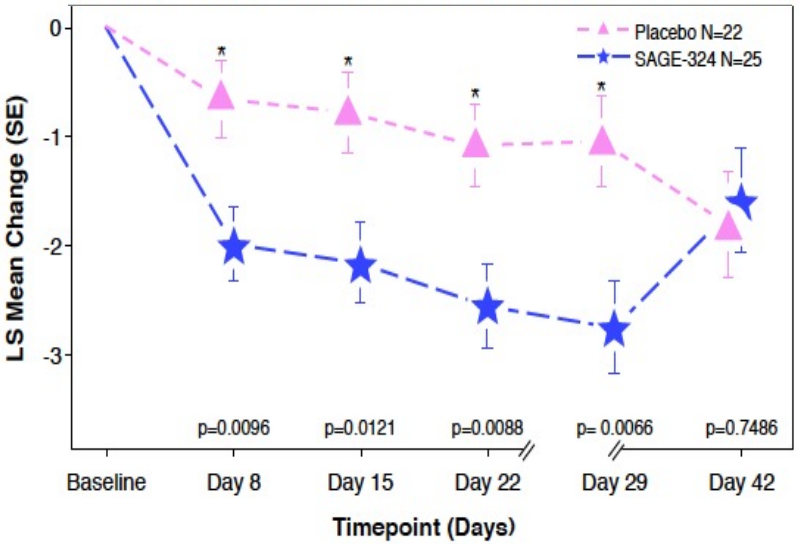
1. Elble R et al. J Neurol Neuromedicine. 2016

KINETIC study met its primary endpoint

BIIB124/SAGE-324 showed a statistically significant reduction from baseline in Upper Limb Tremor Score at Day 29 (Full Analysis Set)



Greater and statistically significant reductions in those with severe upper limb tremor at baseline (TETRAS Upper Limb Score ≥ 12) during treatment period (Subgroup Analysis)



KINETIC study safety and tolerability results inform design of Phase 2b dose ranging study

Kinetic study: Key safety and tolerability findings

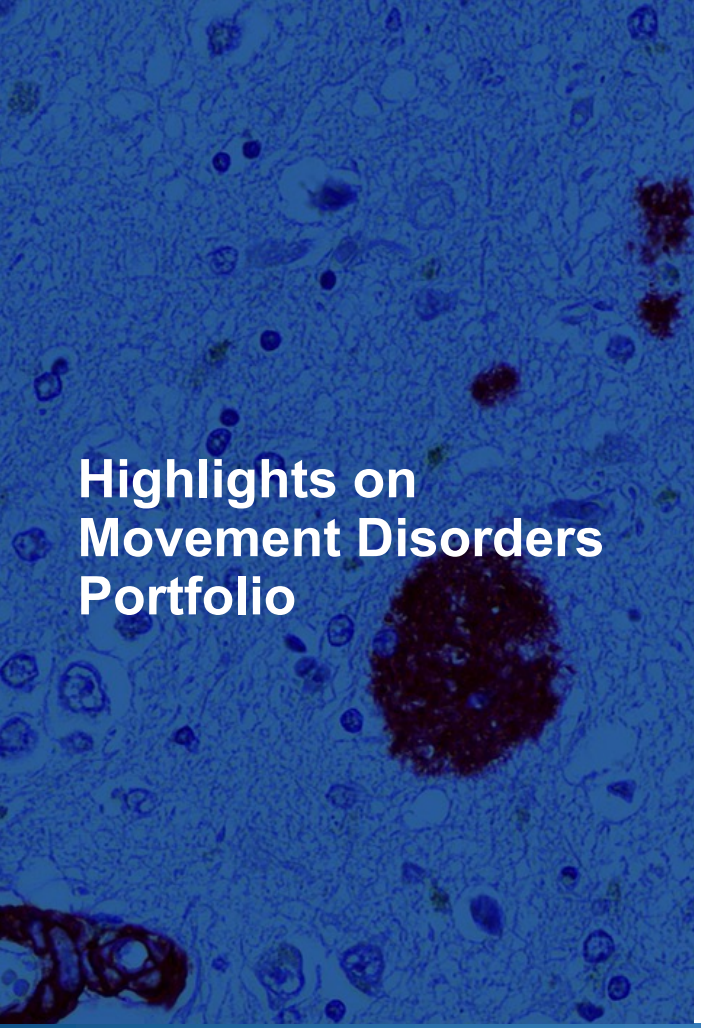
- The trial evaluated treatment of BIIB124/SAGE-324 at the **higher end of the predicted dose range**
- Daily dose could be down-titrated to 45 mg or 30 mg if 60 mg was not well tolerated
  - Down-titration of dose occurred in 62% of patients who received BIIB124/SAGE-324
  - Discontinuations due to treatment emergent adverse events occurred in 27% of patients BIIB124/SAGE-324
- Adverse events were generally consistent with the safety profile observed to date[1]
- Most common treatment emergent adverse events that occurred in >10% of patients in the BIIB124/SAGE-324 treatment group and at a rate at least twice as high as that of patients in the placebo group were somnolence (68%), dizziness (38%), balance disorder (15%), diplopia (12%), dysarthria (12%), gait disturbance (12%)

Phase 2b Study Considerations

The efficacy and safety profile observed to date support further development of BIIB124/SAGE-324 as a potential therapeutic option for patients with ET

- Ph2b dose ranging study is designed to identify a dose with the best benefit-risk profile by evaluating a wide exposure range.
- Strategies to improve tolerability include nighttime dosing and inclusion of doses lower than 60 mg

1. Paskavitz J et al. Presented at: International Congress of Parkinson's Disease and Movement Disorders 2019.



Highlights on Movement Disorders Portfolio

01 Movement Disorders Strategy and Pipeline

Growing multi-modality, multi-target approach in Movement disorders with a focus on Parkinson's disease

02 Advances on LRRK2 Targeting Therapies for Parkinson's Disease

BIIB122 (DNL 151) – LRRK2 Kinase Inhibitor

- Phase 1 and 1b studies support goal to improve lysosomal function and slow progression of disease.
- Program advancing into late-stage development in idiopathic PD and LRRK2 mutation carriers

BIIB094 – LRRK2 ASO

- Ongoing SAD/MAD study to evaluate the safety, tolerability, and pharmacokinetics in PD patients

BIIB118 – CK1 Inhibitor

- Program advancing for treatment of Circadian rhythm disruptions in PD

03 Novel Approach to Essential Tremor

BIIB124 (SAGE-324) – $GABA_A$ PAM

- Ph2 study met primary endpoint (efficacy)
- Program advancing to Ph2b dose ranging study