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RESEARCH ARTICLE

LRRK2 Inhibition by BIIB122 in Healthy Participants and Patients with Parkinson's Disease

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ABSTRACT: Background: Leucine-rich repeat kinase 2 (*LRRK2*) inhibition is a promising therapeutic approach for the treatment of Parkinson's disease (PD).
Objective: The aim of this study was to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of the potent, selective, CNS-penetrant LRRK2 inhibitor BIIB122 (DNL151) in healthy participants and patients with PD.
Methods: Two randomized, double-blind, placebo-controlled studies were completed. The phase 1 study (DNLI-C-0001) evaluated single and multiple doses of BIIB122 for up to 28 days in healthy participants. The phase 1b study (DNLI-C-0003) evaluated BIIB122 for 28 days in patients with mild to moderate PD. The primary objectives were to investigate the safety, tolerability, and plasma pharmacokinetics of BIIB122. Pharmacodynamic outcomes included peripheral and central target inhibition and lysosomal pathway engagement biomarkers.
Results: A total of 186/184 healthy participants (146/145 BIIB122, 40/39 placebo) and 36/36 patients (26/26 BIIB122, 10/10 placebo) were randomized/treated in the phase 1 and phase 1b studies, respectively. In both studies, BIIB122 was generally well tolerated; no serious adverse events were reported, and the majority of treatment-emergent adverse events were mild. BIIB122 cerebrospinal fluid/unbound plasma concentration ratio was ~1 (range, 0.7–1.8). Dose-dependent median reductions from baseline were observed in whole-blood phosphorylated serine 935 LRRK2 (≤98%), peripheral blood mononuclear cell phosphorylated threonine 73 pRab10 (≤93%), cerebrospinal fluid total LRRK2 (≤50%), and urine bis (monoacylglycerol) phosphate (≤74%).
Conclusions: At generally safe and well-tolerated doses, BIIB122 achieved substantial peripheral LRRK2 kinase inhibition and modulation of lysosomal pathways downstream of LRRK2, with evidence of CNS distribution and target inhibition. These studies support continued investigation of LRRK2 inhibition with BIIB122 for the treatment of PD. © 2023 Denali Therapeutics Inc and The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: LRRK2 inhibitor; Parkinson's disease; clinical trials

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease,[1,2] the prevalence of which is expected to increase as the population ages.[3] Approved symptomatic therapies temporarily reduce motor symptoms; however, the development of medications that slow disease progression remains a major unmet need for patients living with PD.[4,5]

Genetic research has expanded our understanding of the cellular pathogenesis of PD, uncovering novel therapeutic targets.[6] Mutations in the leucine-rich repeat kinase 2 (*LRRK2*) gene are a common cause of autosomal dominant PD, accounting for ~4% of familial and 1% to 2% of sporadic PD cases.[7-9] Genetic evidence also suggests that the N551K R1398H LRRK2 haplotype is associated with reduced risk of developing PD[10,11] and may be associated with reduced LRRK2 kinase activity.[12,13] The majority of identified pathogenic variants in LRRK2 are located within its catalytic domains, including the most common pathogenic variant, G2019S.[14-17] These variants increase LRRK2 kinase activity, either through direct mechanisms within the kinase domain or through indirect mechanisms.[18-20] *LRRK2* mutations associated with increased kinase activity result in lysosomal dysfunction,[21-23] which can lead to impaired clearance and aggregation of toxic proteins, contributing to the pathology of PD.[24-26]

LRRK2 inhibitors correct lysosomal dysfunction and downstream neurodegeneration in *in vitro* and *in vivo* models of PD.[27-31] Lysosomal dysfunction is recognized as a central mechanism of PD pathogenesis; several mutations in genes, other than *LRRK2*, encoding lysosomal proteins and enzymes have been firmly linked to the risk of developing PD.[32-34] Increased LRRK2 kinase activity has also been observed in patients with other genetic forms of PD (eg, VPS35 D620N-linked PD) and nonhereditary idiopathic PD.[35,36] Common noncoding variants in LRRK2 are associated with increased risk of developing PD.[37] Thus, biochemical and genetic evidence support LRRK2 kinase inhibition as a promising therapeutic approach to achieve disease modification in a broad population of patients with PD beyond those carrying an LRRK2 mutation.

In initial clinical studies with a small-molecule LRRK2 inhibitor, DNL201, dose-dependent inhibition of LRRK2 kinase activity was observed in both healthy participants and patients with PD, measured by reduction in phosphorylated serine 935 (pS935) LRRK2 in whole-blood and phosphorylated threonine 73 (pT73) Rab10,[29] a direct substrate of LRRK2, in peripheral blood mononuclear cells (PBMCs).[20] A reduction in urine di-22:6-bis (monoacylglycerol) phosphate [BMP (22:6/22:6)] was also observed, providing evidence for modulation of lysosomal pathways downstream of LRRK2.[29,38-40] At doses that demonstrated robust LRRK2 kinase inhibition and lysosomal pathway engagement, DNL201 was generally safe and well tolerated when administered for up to 28 days. The pharmacokinetic (PK) profile for the oral formulation of DNL201 requires multiple daily doses. In this article, we report safety, tolerability, pharmacodynamics, and PK results from phase 1 healthy participant and phase 1b patient studies conducted with a second LRRK2 inhibitor, BIIB122 (also known as DNL151).

Subjects and Methods

Study Design

Phase 1 Study

DNLI-C-0001 (Clinicaltrials.gov: NCT04557800, EudraCT 2017-003730-82) was a randomized, double-blind, placebo-controlled single ascending dose (SAD) and multiple ascending dose (MAD) study in healthy participants (Supporting Information Fig. S1A). The primary objectives were to investigate the safety, tolerability, and plasma PK of single and multiple oral doses of BIIB122. Other objectives included characterization of cerebrospinal fluid (CSF) BIIB122 concentrations, whole-blood pS935 LRRK2 levels, PBMC pT73 Rab10 levels, urine BMP (22:6/22:6), and CSF total LRRK2 (tLRRK2).

The study was conducted at two clinical research units (CRUs) in the Netherlands between November 29, 2017, and February 21, 2021, and included Part A SAD (BIIB122 10–300 mg), Part B MAD (15–300 mg once daily [qd] for 10 days), Part C single-dose elderly (40 mg), Part D multiple-dose (225 mg qd for 28 days), and Part E MAD (150–400 mg twice daily [bid] for 14 days) cohorts (Supporting Information Fig. S1A). Eligible participants were randomized to BIIB122 or placebo (3:1) in Parts A and C (n = 8/cohort planned), Part D (n = 16 planned), and Parts B and E (n = 10/cohort planned) (4:1). Study design details are provided in the Supporting Information.

Phase 1b Study

DNLI-C-0003 (Clinicaltrials.gov: NCT04056689, EudraCT 2019-001297-28) was a randomized, placebo-controlled, double-blind, parallel-arm study in patients with PD (Supporting Information Fig. S1B, Appendix S1). The primary objective was to evaluate the safety and tolerability of BIIB122 administered qd for 28 days. Other objectives were to characterize plasma BIIB122 PK and CSF concentrations, whole

blood pS935 LRRK2 levels, PBMC pT73 Rab10 levels, urine BMP (22:6/22:6), and CSF tLRRK2.

The study was conducted at seven CRUs in the Netherlands, United Kingdom, Belgium, and United States from July 3, 2019, to December 3, 2020 (Supporting Information Fig. S1B, Appendix S1). Patients were randomized to receive placebo or BIIB122 80 mg qd in Part 1 (n = 8 planned; 1:1), placebo or BIIB122 80 or 130 mg qd in Part 2 (n = 16 planned; 1:1:2), and placebo or BIIB122 300 mg qd in Part 3 (n = 10 planned; 1:4) for 28 days. Study design details are provided in the Supporting Information.

Inclusion/Exclusion Criteria

Phase 1 Study

Eligible participants were aged 18 to 50 years, inclusive, for Parts A, B, D, and E and aged 60 to 75 years, inclusive, for Part C. Women of childbearing potential were excluded.

Phase 1b Study

Eligible participants were aged 30 to 75 years, inclusive, with mild to moderate PD with or without PD risk genes and with modified Hoehn and Yahr stages 1 to 3. Women of childbearing potential were excluded. Patients with a Montreal Cognitive Assessment (MoCA) score <24 were excluded.

Study Outcomes

In both studies, safety and tolerability were assessed by adverse event (AE) monitoring, clinical laboratory tests, vital signs, ECGs, physical and neurological examinations, and neurological assessments. For the multiple-dose cohorts only, the Columbia-Suicide Severity Rating Scale (C-SSRS) and pulmonary function tests (PFTs) were performed. PK parameters, estimated from BIIB122 plasma and CSF concentrations, included area under the plasma concentration-time curve (AUC), maximum concentration (C_{max}), time to C_{max} (t_{max}), elimination half-life ($t_{1/2}$), trough plasma concentration (C_{trough}; multiple-dose cohorts only), and CSF/unbound plasma concentration ratio. Pharmacodynamic assessments included percent change from baseline in whole-blood pS935 LRRK2, PBMC pT73 Rab10, urine BMP (22:6/22:6) as a ratio to urine creatinine (ng BMP/mg creatinine), and CSF tLRRK2.

Statistical Analysis

Sample sizes were not based on power calculations but were considered sufficient to achieve the study objectives. In the phase 1 and phase 1b studies, data were summarized by treatment group (placebo group and each BIIB122 dose group, pooled as appropriate).

Data were summarized using descriptive statistics. Genotyping at baseline identified one patient with an *LRRK2* mutation (R1441C) and three patients with β-glucocerebrosidase variants; no genotype-specific analyses were conducted given the small number of carriers. The incidence of treatment-emergent AEs (TEAEs) (defined as AEs that occurred or worsened after initiation of study drug) was summarized.

Bioanalytical methods for quantification of BIIB122 and pharmacodynamic measures are provided in the Supporting Information.

Standard Protocol Approvals and Participant Consents

Study protocols, amendments, and informed consent forms were reviewed and approved by local institutional review boards/independent ethics committees. Written informed consent was obtained from each participant.

Results

Study Population

Phase 1 Study

Healthy participants (n = 186) were randomized to BIIB122 or placebo, and 96% (177/184) of treated participants completed study drug treatment (Fig. 1A).

Overall, mean age (range) of the healthy participants in Parts A, B, D, and E was 28.7 (18–50) years, and most were male (175 [99%]) (Supporting Information Table S1, Appendix S1). In Part C (elderly cohort), mean age (range) was 69.5 (67–74) years, and four participants (50%) were male (Supporting Information Table S1, Appendix S1).

Phase 1b Study

Patients with mild to moderate PD (n = 36) were randomized to BIIB122 or placebo, and 94% (34/36) of treated patients completed study drug treatment (Fig. 1B).

Overall, mean age (range) of patients was 61.9 (41–74) years, and 27 patients (75.0%) were male. In the BIIB122 300 mg qd group, the mean disease duration was longer, and mean baseline Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III score was higher (Table 1).

Safety

Phase 1 Study

BIIB122 was generally well tolerated at single doses of ≤300 mg and multiple doses of ≤400 mg bid in healthy participants. No serious AEs were reported, and the majority of TEAEs were mild in severity (Supporting Information Tables S2 and S3, Appendix S1).

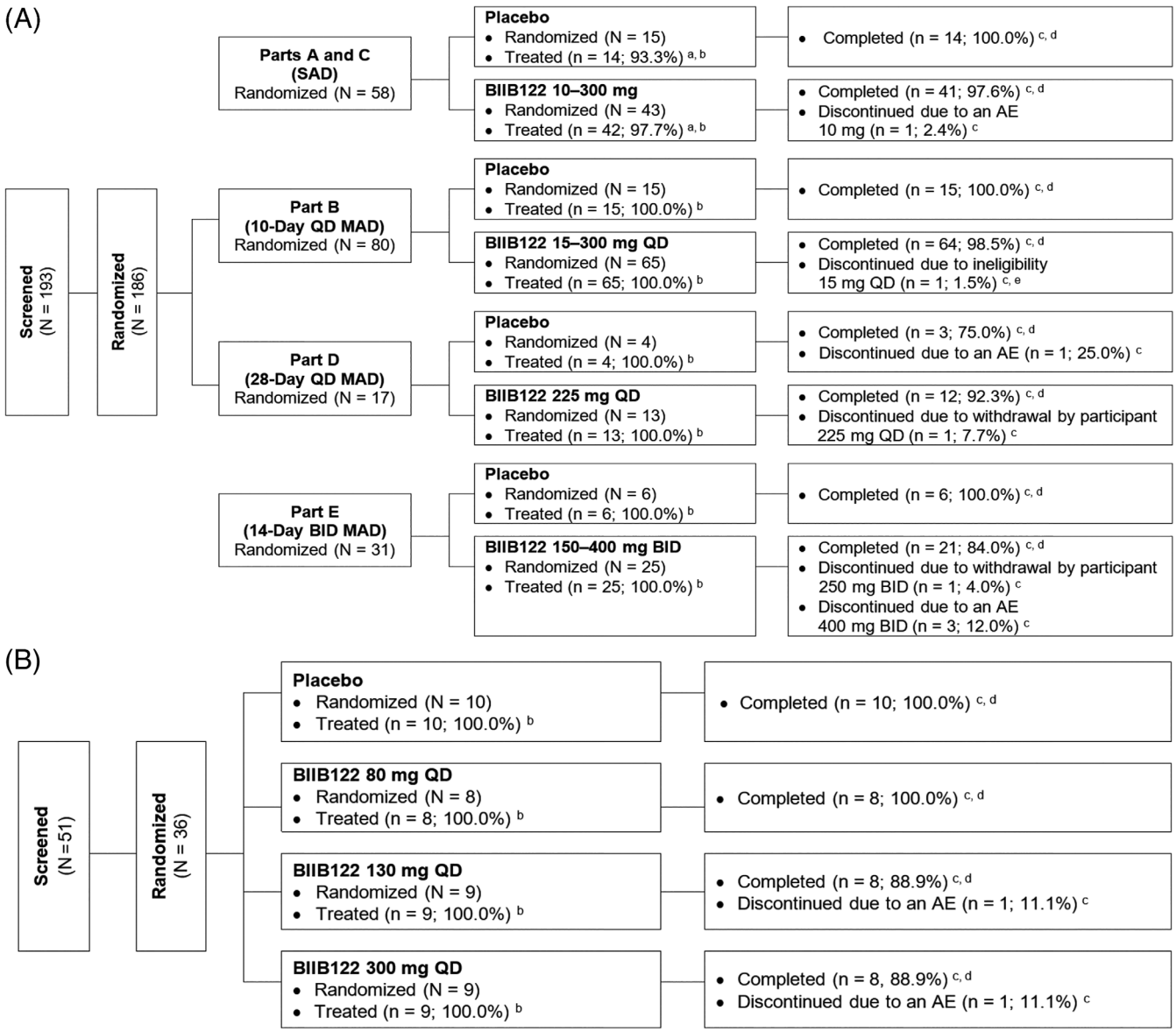

FIG. 1. CONSORT (consolidated standards of reporting trials) diagram. (**A**) Phase 1 study. (**B**) Phase 1b study. [a]Two participants in Part A were discontinued postrandomization but before study drug administration: one participant in the placebo group because of failure to obtain the baseline cerebrospinal fluid (CSF) sample and one participant in the BIIB122 10 mg group because of a vasovagal reaction after predose orthostatic testing. [b]The number of participants randomized was used as the denominator for calculation of percentages. [c]The number of participants who received each treatment was used as the denominator for calculation of percentages. [d]Completed treatment with study drug. [e]Participant was determined ineligible for the study (participant did not meet the inclusion criteria for pulmonary function test results [based on diffusing capacity of lungs for carbon monoxide (DLCO)]). AE, adverse event; BID, twice daily; MAD, multiple ascending dose; QD, once daily; SAD, single ascending dose.

TEAEs leading to study drug discontinuation for BIIB122-treated participants included three reported as related to study drug (moderate increased transaminases [n = 1, Part D, placebo]; moderate diarrhea, nausea, headache, and disturbance in attention [n = 1, 250 mg bid]; severe headache and malaise and mild myalgia [n = 1, 400 mg bid]) and three reported as unrelated to study drug (moderate influenza-like illness [n = 1, 10 mg, single dose]; mild asymptomatic coronavirus disease 2019 [COVID-19] based on COVID-19 test [n = 2, 400 mg bid]).

In the single-dose cohorts, TEAEs were reported for 30 BIIB122-treated (71%) and 9 placebo-treated (64%) participants (Supporting Information Table S2, Appendix S2). The most common TEAE in BIIB122-treated participants was headache (12 [29%] vs. 2 [14%] for placebo). In the multiple-dose cohorts, TEAEs were reported for 91 BIIB122-treated (88%) and 21 placebo-treated

TABLE 1 *Phase 1b study: demographics and other baseline characteristics*

Characteristics	Placebo (n = 10)	BIIB122 80 mg qd (n = 8)	BIIB122 130 mg qd (n = 9)	BIIB122 300 mg qd (n = 9)	Total (N = 36)
Age, y					
Mean (SD)	61.9 (7.6)	66.9 (3.3)	60.4 (6.1)	59.1 (10.9)	61.9 (7.8)
Median (min, max)	63.0 (48, 72)	67.5 (62, 70)	59.0 (51, 69)	65.0 (41, 74)	65.0 (41, 74)
Sex, n (%)					
Male	8 (80.0)	7 (87.5)	5 (55.6)	7 (77.8)	27 (75.0)
Female	2 (20.0)	1 (12.5)	4 (44.4)	2 (22.2)	9 (25.0)
Race, n (%)					
White	10 (100.0)	8 (100.0)	9 (100.0)	9 (100.0)	36 (100.0)
Ethnicity, n (%)					
Not Hispanic or Latino	10 (100.0)	8 (100.0)	9 (100.0)	9 (100.0)	36 (100.0)
BMI, kg/m^2					
Mean (SD)	25.40 (3.17)	28.50 (4.16)	26.36 (4.04)	25.81 (4.45)	26.43 (3.96)
Baseline Parkinson's disease medication concomitant use, n (%)	10 (100.0)	8 (100.0)	7 (77.8)	9 (100.0)	34 (94.4)
Dopamine replacement agents	9 (90.0)	7 (87.5)	6 (66.7)	9 (100.0)	31 (86.1)
Dopamine agonists agents	4 (40.0)	4 (50.0)	4 (44.4)	4 (44.4)	16 (44.4)
MAOB inhibitor agents	1 (10.0)	0 (0)	2 (22.2)	0 (0)	3 (8.3)
Other Parkinson's disease medications	2 (20.0)	1 (12.5)	0 (0)	2 (22.2)	5 (13.9)
Age at Parkinson's disease diagnosis, y					
Mean (SD)	57.4 (10.0)	62.8 (2.7)	57.1 (5.6)	53.4 (10.3)	57.5 (8.3)
Time since Parkinson's disease diagnosis, y					
Mean (SD)	4.50 (3.03)	4.13 (2.95)	3.33 (3.16)	5.67 (4.39)	4.42 (3.39)
Modified Hoehn and Yahr assessment, n (%)					
Stage 1	4 (40.0)	3 (37.5)	4 (44.4)	3 (33.3)	14 (38.9)
Stage 1.5	2 (20.0)	0 (0)	0 (0)	1 (11.1)	3 (8.3)
Stage 2	4 (40.0)	3 (37.5)	4 (44.4)	3 (33.3)	14 (38.9)
Stage 2.5	0 (0)	2 (25.0)	1 (11.1)	2 (22.2)	5 (13.9)
Baseline MDS-UPDRS Part III score (OFF state)					
Mean (SD)	29.8 (14.9)	29.9 (12.9)	26.1 (11.6)	35.8 (14.4)	30.4 (13.5)
Baseline NMSS total score					
Mean (SD)	18.0 (8.5)	36.5 (19.8)	24.3 (17.6)	38.4 (24.9)	28.8 (19.6)
Baseline MoCA total score					
Mean (SD)	27.6 (1.6)	27.5 (1.5)	27.1 (1.5)	27.1 (1.8)	27.3 (1.6)

Note: BIIB122 was administered as a powder-in-capsule (PiC) formulation at the 80- and 130-mg doses and as a tablet formulation at the 300-mg dose. The pooled placebo group includes patients who received placebo in either PiC or tablet form.
Abbreviations: qd, once daily; SD, standard deviation; min, minimum; max, maximum; BMI, body mass index; MAOB, monoamine oxidase B; MDS-UPDRS Part III, Movement Disorders Society Unified Parkinson's Disease Rating Scale Part III; NMSS, Non-Motor Symptoms Scale; MoCA, Montreal Cognitive Assessment.

(84%) participants (Supporting Information Table S3, Appendix S1). The most common TEAE in BIIB122-treated participants was headache (53 [51%] vs. 9 [36%] for placebo), the incidence and severity of which was dose dependent. TEAEs of myalgia with no associated increase in creatine phosphokinase were reported at the highest

BIIB122 doses (Supporting Information Table S3, Appendix S1). No clinically meaningful or dose-related changes were observed in vital signs, clinical laboratory values (including renal function parameters; Supporting Information Fig. S2, Appendix S1), physical or neurological examinations, C-SSRS, or PFTs (Supporting Information Fig. S3, Appendix S1).

Phase 1b Study

BIIB122 was generally well tolerated at doses of 80, 130, or 300 mg qd for ≤28 days in patients with PD. No serious AEs were reported, and the majority of TEAEs were mild or moderate in severity (Supporting Information Table S4, Appendix S1). TEAEs leading to study drug discontinuation were reported for two BIIB122-treated patients: severe hypotension (asymptomatic), reported as not related to study drug (n = 1, 130 mg qd), and mild hypotension (asymptomatic), reported as related to study drug (n = 1, 300 mg qd); both had preexisting hypotension or orthostatic hypotension. These events resolved without intervention after study drug discontinuation. Two additional patients (one each for 80 and 300 mg qd) had TEAEs of hypotension or orthostatic hypotension (both asymptomatic) that resolved while continuing the study drug.

Overall, TEAEs were reported for 23 BIIB122-treated (89%) and 5 placebo-treated (50%) patients (Supporting Information Table S4, Appendix S1). The most common TEAE in BIIB122-treated patients was headache (11 [42%] vs. 2 [20%] for placebo). No clinically meaningful or dose-related changes were observed in clinical laboratory values (including renal function parameters; Supporting Information Fig. S2, Appendix S1), physical or neurological examinations, C-SSRS, PFTs (Supporting Information Fig. S3, Appendix S1), or MDS-UPDRS Part III, Non-Motor Symptoms Scale, or MoCA scores (Supporting Information Table S5, Appendix S1).

Pharmacokinetics

Phase 1 Study

In healthy participants, BIIB122 oral absorption was rapid after single and multiple doses, with median t_{max} ranging from 1.0 to 1.5 hours (Supporting Information Fig. S4, Supporting Information Table S6, Appendix S1). After multiple-dose administration of BIIB122 15 to 300 mg qd for 10 or 28 days or BIIB122 150 to 400 mg bid for 14 days in healthy participants, mean C_{max} at steady state [$C_{max(ss)}$] and AUC from time 0 through tau ($AUC_{0–tau}$) increased less than dose proportionally. At steady state, mean accumulation ratio based on C_{max} or $AUC_{0–tau}$ decreased with increasing dose. After the last dose of BIIB122, mean $t_{1/2}$ ranged from 47 to 93 hours across the 15 to 300 mg qd and 150 to 400 mg bid dose ranges (Supporting Information Table S6, Appendix S1).

PK variability was low to moderate; percent coefficient of variation ranged from 8.9% to 31% for $C_{max(ss)}$ and from 6.7% to 40% for $AUC_{0–24}$ (Supporting Information Table S6, Appendix S1). Steady state appeared to be reached after 6 days of dosing, based on C_{trough} over time.

The mean BIIB122 CSF/unbound plasma concentration ratio (calculated using a fixed unbound fraction in plasma from *ex vivo* measurements) ranged from 0.7 to 1.8 across the 30 to 300 mg qd and 150 to 400 mg bid dose ranges (Fig. 2A). At higher doses, this ratio may be overestimated because of modest increases in BIIB122 unbound fraction at higher total plasma concentrations. Nonetheless, mean ratios were at or above unity (1.0) for most doses, indicating extensive BIIB122 CNS distribution in healthy participants.

Phase 1b Study

After single and multiple doses of BIIB122 80, 130, and 300 mg qd for 28 days, BIIB122 oral absorption was rapid, with median t_{max} ranging from 1.1 to 1.6 hours (Supporting Information Fig. S5, Supporting Information Table S7, Appendix S1). After multiple doses, mean $C_{max(ss)}$ and $AUC_{0–tau}$ increased less than dose proportionally, and accumulation ratio based on C_{max} or $AUC_{0–tau}$ decreased as BIIB122 dose increased from 80 to 300 mg qd. After the last dose (day 28), mean $t_{1/2}$ ranged from 70 to 122 hours across the 80 to 300 mg dose range (Supporting Information Table S7, Appendix S1).

PK variability after qd dosing was low to moderate; percent coefficient of variation ranged from 11% to 35% for $C_{max(ss)}$ and from 25% to 33% for $AUC_{0–tau}$ (Supporting Information Table S7, Appendix S1). Steady-state plasma concentrations appeared to be reached after 7 days, based on C_{trough} over time.

The mean BIIB122 CSF/unbound plasma concentration ratio ranged from 0.95 to 1.2 across the 80 to 300 mg qd dose range (Fig. 2B), indicating extensive CNS distribution of BIIB122 in patients with PD.

Pharmacodynamics

Phase 1 Study

After multiple-dose administration of BIIB122 in healthy participants, median whole-blood pS935 LRRK2 was reduced from baseline in a dose-dependent manner (Fig. 3A, Supporting Information Fig. S6A, S7A, Appendix S1). Likewise, median PBMC pT73 Rab10, a direct substrate of LRRK2, was reduced from baseline at all BIIB122 doses (Fig. 3B, Supporting Information Fig. S6B, S7B, Appendix S1), indicating inhibition of the biochemical pathways downstream of LRRK2. Average reduction in whole-blood pS935 LRRK2 at steady state (median) ranged from 15% to 87% for 15 to 300 mg qd and from 91% to 98% for

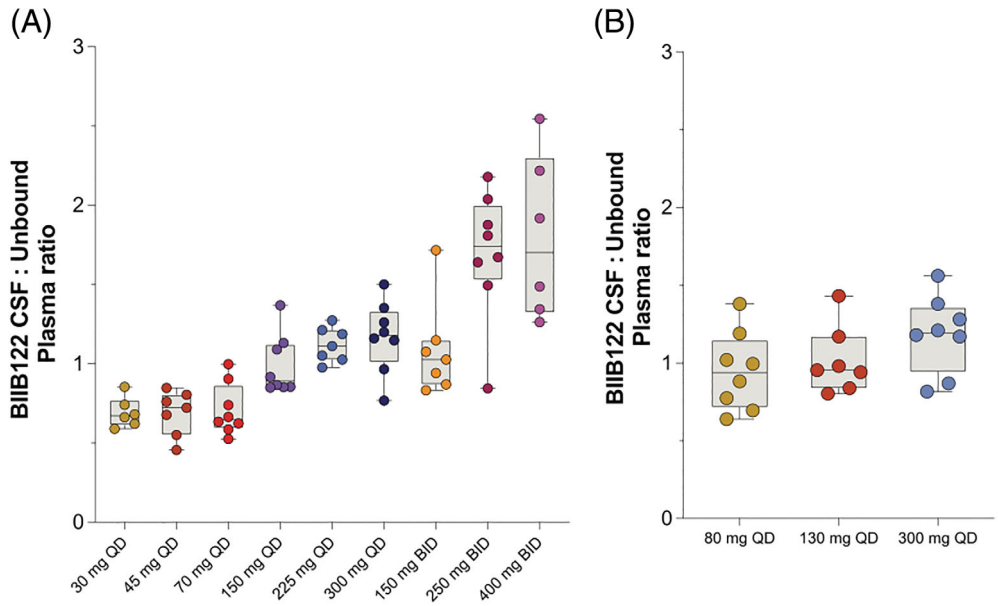

FIG. 2. BIIB122 cerebrospinal fluid (CSF)-to-unbound plasma concentration ratios after multiple doses in healthy participants in the phase 1 study and patients with Parkinson's disease in the phase 1b study. (**A**) Part B (15–300 mg qd for 10 days; n = 44) and Part E (150–400 mg bid for 14 days; n = 21) in the phase 1 study in healthy participants. (**B**) Parts 1 through 3 (80–300 mg qd for 28 days; n = 23) in the phase 1b study in patients with PD. CSF samples were not collected in healthy participants in Part D. Unbound plasma concentrations were calculated from total plasma concentrations by applying an unbound fraction of 0.024, which was determined from *ex vivo* measurements (using ultracentrifugation) of clinical samples from healthy participants who received BIIB122 30 mg qd (cohort B2) and 225 mg qd (cohort B7) in the phase 1 study. Data are described using box plots, with the error bars representing the minimum to maximum data points. BID, twice daily; PD, Parkinson's disease; QD, once daily.

150 to 400 mg bid. Average reduction in PBMC pT73 Rab10 at steady state (median) ranged from 49% to 80% for 15 to 300 mg qd and from 79% to 93% for 150 to 400 mg bid.

tLRRK2 was recently shown to be quantifiable in CSF.[42] We hypothesized that LRRK2 inhibition in the CNS would reduce tLRRK2 in CSF, either by reducing LRRK2 levels in brain or by reducing LRRK2 secretion into CSF via exosomes.[38,39,43-45] BIIB122 dose-dependently reduced median CSF tLRRK2 levels from baseline at doses ≥150 mg qd and ≥150 mg bid by ~20% to 50% (Fig. 3C, Supporting Information Fig. S7C, Appendix S1), demonstrating sustained CNS kinase inhibition at these doses.

Urine BMP (22:6/22:6), a lysosomal lipid that is a mechanistic marker of modulation of the pathways downstream of LRRK2,[29,39-41] was reduced from baseline at BIIB122 doses ≥225 mg qd (median change, −45% to −52% for BIIB122 vs. −3% to +9% for placebo) and ≥150 mg bid (median change, −19 to −74% for BIIB122 vs. +31% for placebo) at the maximal reduction time point of 8–12 hours postdose, on day 10 or 28 (for qd regimen) or day 14 (for bid regimen), providing peripheral evidence of an effect on LRRK2-dependent lysosome function at these doses (Fig. 3D, Supporting Information Fig. S6C, S7D, Appendix S1).

Phase 1b Study

In patients with PD, average whole-blood pS935 LRRK2 reduction at steady state (median) was 49%, 70%, and 90% in the BIIB122 80, 130, and 300 mg qd groups, respectively (Fig. 4A, Supporting Information Fig. S8A, S9A, Appendix S1). pS935 LRRK2 levels returned to approximately baseline values on day 42 (Supporting Information Fig. S7A, Appendix S1). Reduction of pT73 Rab10 was demonstrated in all dose groups, with average PBMC pT73 Rab10 reduction at steady state (median) of 70%, 72%, and 83% in the 80, 130, and 300 mg qd groups, respectively (Fig. 4B, Supporting Information Fig. S8B, S9B, Appendix S1). Although the 80 and 130 mg qd dose groups did not show a reduction from baseline of tLRRK2 that was greater than the placebo group, a median reduction of 34% from baseline in CSF tLRRK2 on day 28 was observed in the 300 mg qd group, confirming sustained CNS kinase inhibition at that dose (Fig. 4C, Supporting Information Fig. S9C, Appendix S1).

Median decreases from baseline to day 28 in urine BMP (22:6/22:6) levels were 32%, 56%, and 63% in the 80, 130, and 300 mg qd dose groups, respectively, compared with 35% in the placebo group (Fig. 4D, Supporting Information Fig. S9D, Appendix S1). A larger BMP reduction with less variability was observed

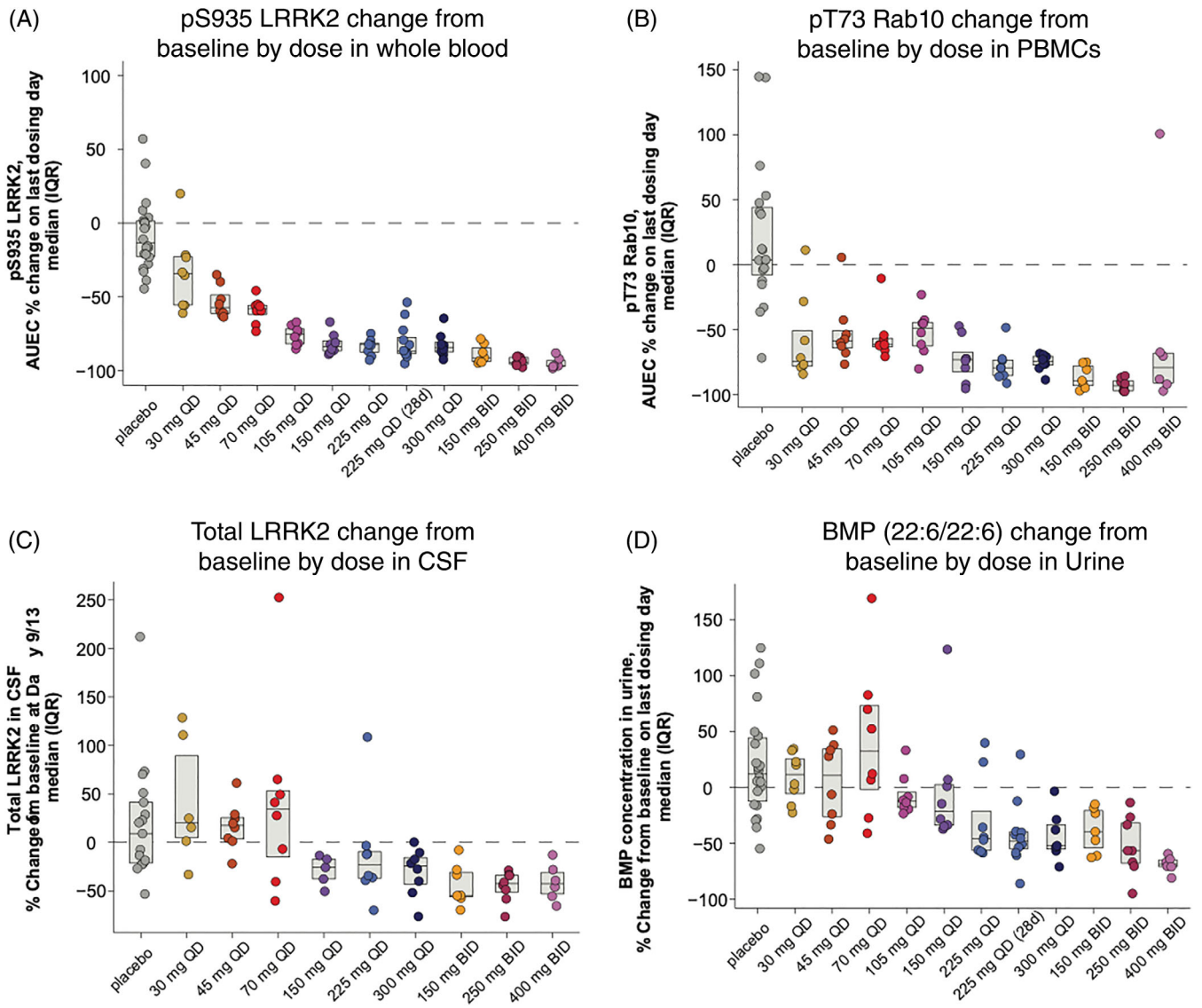

FIG. 3. Phase 1 study: Dose-dependent target and pathway engagement in healthy participants in multiple-dose cohorts. Pharmacodynamics of LRRK2 inhibition in healthy participants from the phase 1 multiple-dose cohorts (Parts B, D, and E). (**A**) pS935 LRRK2 reduction from baseline in whole blood. (**B**) pT73 Rab10 reduction from baseline in PBMCs. Inhibition of LRRK2 over the dosing interval at steady state, as measured by average reduction in whole-blood pS935 LRRK2 and PBMC pT73 Rab10, was calculated as the median percent change from baseline time-adjusted AUEC on the last dosing day. Whole-blood and PBMC samples were collected at the following time points: day −1; day 1 predose; and on the last dosing day at predose and 1, 3, 8, and 12 hours (for bid only) or 24 hours (for qd only) postdose. Baseline was calculated as the average of day −1 and day 1 predose values. (**C**) Total LRRK2 reduction from baseline in CSF. CSF samples were collected at the following time points: day −1 and day 9, 4 hours postdose for Part B and day −1 and day 13, 4 hours postdose for Part E. (**D**) Urine BMP reduction from baseline in response to LRRK2 inhibition. Urine samples were collected on day −1, day 1 predose (Part E only), and 8–12 hours postdose on the last day of dosing. Urine BMP concentrations were reported as a ratio to urine creatinine concentrations (ng BMP/mg creatinine). For Part E, baseline was calculated as the average of day −1 and day 1 predose values. AUEC, area under the effect curve from time 0 to 24 hours (or 12 hours for Part E); BID, twice daily; BMP, bis(monoacylglycerol)phosphate; BMP (22:6/22:6), di-docosahexaenoyl bis(monoacylglycerol)phosphate; CSF, cerebrospinal fluid; IQR, interquartile range; LRRK2, leucine-rich repeat kinase 2; PBMC, peripheral blood mononuclear cell; pS935, phosphorylated serine 935; pT73, phosphorylated threonine 73; QD, once daily.

in the 300 mg qd group than in the lower BIIB122 doses and placebo.

Discussion

In the clinical studies reported in this article, the small-molecule LRRK2 inhibitor BIIB122 was generally safe and well tolerated across a broad dose range in both healthy participants and patients with PD. Biomarker results demonstrated dose-dependent peripheral LRRK2 kinase inhibition based on reduction in whole-blood pS935 LRRK2 and PBMC pT73 Rab10, modulation of the lysosomal pathway downstream of LRRK2 based on reduction in urine BMP, and central LRRK2 kinase inhibition based on reduction in CSF tLRRK2. Thus, in these early-phase

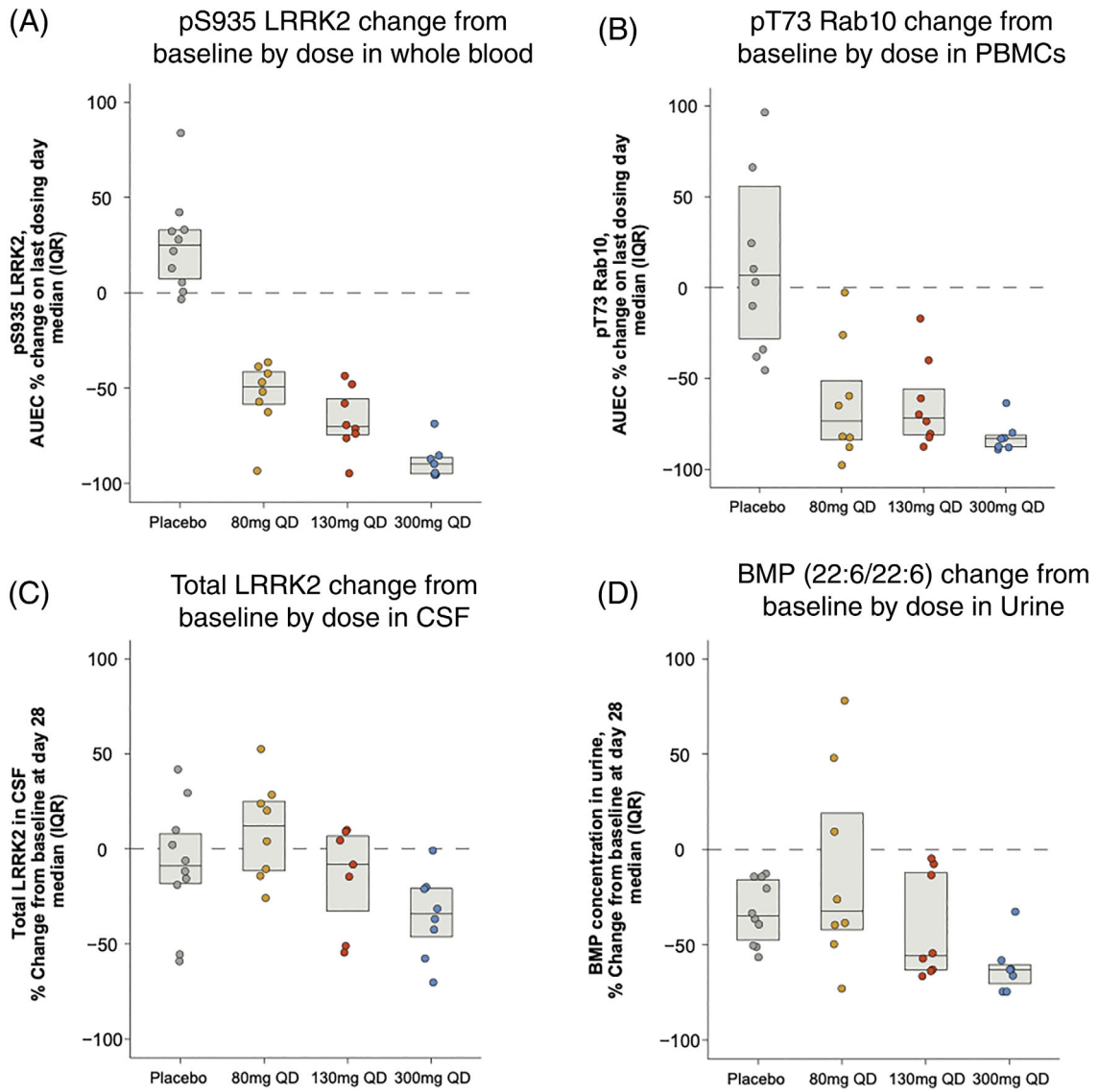

FIG. 4. Phase 1b study: dose-dependent target and pathway engagement in patients with PD in multiple-dose cohorts. Pharmacodynamics of LRRK2 inhibition in patients with PD in the phase 1b study. (**A**) pS935 LRRK2 reduction from baseline in whole blood. (**B**) pT73 Rab10 reduction from baseline in PBMCs. One placebo outlier for pT73 Rab10 with >100% increase is not shown. Inhibition of LRRK2 over the dosing interval at steady state, as measured by average reduction in whole-blood pS935 LRRK2 and PBMC pT73 Rab10, was calculated as the median percent change from baseline time-adjusted AUEC on the last dosing day. Whole-blood and PBMC samples were collected at the following time points: day −1, day 1 predose, and on the last dosing day at predose and 1, 3, 8, and 24 hours postdose. Baseline was calculated as the average of day −1 and day 1 predose values. (**C**) Total LRRK2 reduction from baseline in CSF in response to LRRK2 inhibition. CSF was collected at day −1 and day 28 3 hours postdose. (**D**) Urine BMP reduction from baseline in response to LRRK2 inhibition. Urine samples were collected on day −1 and 1–6 hours postdose on the last day of dosing. Urine BMP concentrations were reported as a ratio to urine creatinine concentrations (ng BMP/mg creatinine). AUEC, area under the effect curve from time 0 to 24 hours (or 12 hours for Part E); BMP, bis(monoacylglycerol)phosphate; BMP(22:6/22:6), di-docosahexaenoyl bis(monoacylglycerol) phosphate; CSF, cerebrospinal fluid; IQR, interquartile range; LRRK2, leucine-rich repeat kinase 2; PBMC, peripheral blood mononuclear cell; PD, Parkinson's disease; pS935, phosphorylated serine 935; pT73, phosphorylated threonine 73; qd, once daily.

studies, LRRK2 kinase inhibition levels sufficient to modulate lysosomal pathways downstream of LRRK2 were safely achieved with daily oral dosing of BIIB122.

In healthy participants and patients with PD, BIIB122 was rapidly absorbed, with a $t_{1/2}$ that supports once daily dosing. BIIB122 distributed equally to CSF and plasma, with a CSF to unbound plasma concentration ratio of ∼1, reflecting extensive CNS distribution of BIIB122. Importantly, no meaningful difference in BIIB122 PK was observed between patients with PD and healthy participants (Supporting Information Fig. S10, Appendix S1), supporting the relevance of safety and pharmacodynamic data from healthy participants to patients with PD.

In both studies, substantial, dose-dependent, peripheral LRRK2 kinase inhibition was observed, as

measured by whole-blood pS935 LRRK2 and PBMC pT73 Rab10, with ≤98% reduction in pS935 LRRK2 observed on the last day of dosing. Because protein phosphorylation is frequently measured relative to the corresponding total protein amount as a normalization factor, in a subset of cohorts we measured total Rab10 in PBMC lysates as a potential normalization factor for pRab10 reduction. There was no meaningful difference in the normalized (pT73 Rab10 as a ratio to total Rab10) versus unnormalized (pT73 Rab10) pharmacodynamic response variability, direction, or magnitude of effect (data not shown). Given that we did not collect total Rab10 data for every cohort in our studies, we therefore proceeded with pharmacodynamic quantitation in PBMCs using pT73 Rab10 reduction. Similar levels of LRRK2 kinase inhibition were observed in both study populations at corresponding dose levels, indicating that pharmacodynamic data from these early-phase studies can be used to predict dose–response relationships in future patient studies. We previously demonstrated that peripheral inhibition of LRRK2 kinase activity, as measured by pS935 LRRK2, corresponds closely with that in the brain in animals treated with DNL201, another brain-penetrant LRRK2 inhibitor.[29] Together with the DNL201 data, the high CSF penetrance of BIIB122 (Fig. 4) supports projections of strong LRRK2 kinase inhibition in the CNS, of similar magnitude to that in the periphery.

A quantitative method to measure CSF tLRRK2 levels has been recently published.[42] We hypothesized that LRRK2 kinase inhibition in the brain would reduce tLRRK2 levels in the CNS via two possible mechanisms: (1) LRRK2 kinase inhibition has been reported to reduce LRRK2 protein levels in some cellular models and in brain and other tissues in animals studies, although this effect is not universally observed across all species and tissues studied;[27,38,39,43,46] and (2) LRRK2 inhibition has also been reported to reduce LRRK2 secretion into biofluids via exosomes.[44,45] We hypothesized that LRRK2 inhibition in the CNS would be reflected by a reduction in CSF tLRRK2 either because of reduced tLRRK2 levels in the brain or reduced LRRK2 secretion into CSF in exosomes, enabling confirmation of a CNS pharmacodynamic response in humans. At steady state, BIIB122 reduced CSF tLRRK2 levels from baseline at doses ≥150 mg qd by ~20% to 50%, demonstrating sustained CNS LRRK2 kinase inhibition at these doses. Lower-dose groups did not show a median reduction in tLRRK2, likely reflecting a need for sustained high levels of inhibition in the brain to achieve an observable reduction in CSF. This observation highlights the need for further study of the relationship between LRRK2 inhibition in the brain and CSF tLRRK2 reduction. Likewise, additional biomarker assays of lysosomal modulation in CSF are needed to provide evidence of modulation of PD pathological processes.

BMP is a phospholipid found exclusively on the intraluminal vesicles of late endosomes and lysosomes.[40] Individuals with lysosomal dysfunction, including those with the G2019S LRRK2 mutation, have increased levels of urine BMP.[41,47] LRRK2 kinase inhibition has been shown to reduce and therefore correct urine BMP in both animal models and patients with elevated BMP levels.[29,38,39] In healthy participants and patients with PD, urine BMP (22:6/22:6) was reduced at doses ≥225 mg qd. Consistent with our previous findings with DNL201,[29] reductions in urine BMP were achieved at pS935 LRRK2 inhibition levels ~≥80%. BIIB122 treatment achieved peripheral LRRK2 kinase inhibition levels sufficient to modulate peripheral BMP, an effect that is likely translated to the CNS, given the high brain penetrance of the drug.[29] BIIB122 exposures demonstrating modulation of the lysosomal pathway downstream of LRRK2 are anticipated to have the highest potential for demonstrating clinical efficacy.

BIIB122 was generally well tolerated in both healthy participants and patients with PD. TEAEs of hypotension and/or orthostatic hypotension were reported for ~15% of BIIB122-treated patients, whereas no such events were reported in BIIB122-treated healthy participants, despite higher BIIB122 doses administered. Hypotension and orthostatic hypotension have been reported in ~40–60% of patients with PD, and the incidence increases with longer PD duration, disease severity, and levodopa usage.[48,49] The etiology of the hypotension and orthostatic hypotension reported in our patient study remains unclear. The lack of associated symptoms (eg, light-headedness) suggests accommodation to hemodynamic fluctuations related to long-standing autonomic dysregulation in these patients.

Previously reported nonclinical toxicology studies evaluating multiple LRRK2 inhibitors demonstrated non-adverse, treatment-associated microscopic changes in lung (vacuolated type II pneumocytes) and kidney (pigmentation in renal tubular epithelial cells) that reversed after discontinuation of LRRK2 inhibition.[29,38,39] These non-adverse pulmonary and renal effects were attributed to on-target LRRK2 inhibition but were not associated with cellular injury or inflammation and did not result in pulmonary or renal functional changes in chronic toxicology studies (exposures ≤39 weeks).[29,38,39,50,51] Preclinical toxicology studies of 6- and 9-month treatment duration with BIIB1222 in rats and monkeys, respectively, were also completed to support chronic dosing in humans. In early-phase clinical studies conducted with two LRRK2 inhibitors, DNL201[29] and BIIB122, no pulmonary or renal functional changes were observed for up to 28 days across

all doses studied, providing reassurance that BIIB122 can be safely administered at doses with substantial LRRK2 kinase inhibition.

The main limitations of the early-phase studies include small sample sizes, a short duration of dosing, and a gender imbalance, with a majority of participants being male. Long-term safety of LRRK2 inhibition in patients with PD remains to be evaluated. Support for safety of chronic LRRK2 inhibition may be derived from studies of LRRK2 loss-of-function genetic variant carriers, which demonstrate no effect on life expectancy or increase in renal or pulmonary disease.[52,53] Future clinical studies with larger patient populations studied over months to years will inform long-term safety and efficacy of LRRK2 inhibition in patients with PD.

Our results support the selection of BIIB122 to advance to late-stage clinical studies in patients with PD given its favorable PK profile (compared with DNL201) supporting once daily dosing. Studies with two LRRK2 inhibitors (DNL201 and BIIB122) have confirmed substantial LRRK2 kinase inhibition and lysosomal pathway modulation at exposures with acceptable safety and tolerability, providing support for LRRK2 inhibition as a potential therapeutic approach to modify PD progression. ■

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Author Contributions

D.J., P.C., C.H., and M.D.T. were responsible for the development of the clinical study design, execution of the phase 1 and phase 1b studies, and interpretation and analysis of the reported results. S.H-R. was responsible for study designs and biomarker sample analysis and interpretation of results. M.S.G., J.J.C., D.G., and K.F. were responsible for biomarker sample analysis and interpretation of results. O.S.M. was responsible for developing tLRRK2 biomarker assay, biomarker sample analysis, and interpretation of results. R.M. participated in study designs and was responsible for statistical design and analysis of the reported data. V.M.D. and M.T.B. were responsible for analysis and interpretation of pharmacokinetics data. J.D.V. was responsible for the discovery and development of the compound BIIB122 (DNL151) and interpretation and analysis of the reported results. A.C-H. was responsible for the execution of the phase 1 and phase 1b studies and interpretation and analysis of the reported results. M.F.J.M.V. and G.J.G. were investigators who co-led the phase 1b clinical study, investigators for the phase 1 study, and participated in interpretation and analysis of the reported results. J.v.d.W.d.R. was the lead investigator for the phase 1 clinical study and participated in interpretation and analysis of the reported results. J.A.A.C.H. was an investigator for the phase 1 and phase 1b clinical studies and in interpretation and analysis of the reported results. D.D., A.G.H., and K.S.-L. participated in study designs and interpretation and analysis of results. D.J., S.H.-R., M.F.J.M.V., M.D.T., and V.M.D. drafted the manuscript, and all authors reviewed the manuscript.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.