Mechanistic early phase clinical pharmacology studies with disease-modifying drugs for neurodegenerative disorders

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CHAPTER 5

LRRK2 INHIBITION BY BIIB122 IN HEALTHY PARTICIPANTS AND PATIENTS WITH PARKINSON'S DISEASE

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Mov Disord. 2023 Mar;38(3):386-398. doi: 10.1002/mds.29297

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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 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 TEAEs were mild. BIIB122 CSF/unbound plasma concentration ratio was ~1 (range, 0.7-1.8). Dose-dependent median reductions from baseline were observed in whole-blood pS935 LRRK2 (≤98%), PBMC pT73 pRAB10 (≤93%), CSF tLRRK2 (≤50%), and urine BMP (≤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.

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 1-2% 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 (e.g., 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 ≤28 days. The pharmacokinetic profile for the oral formulation of DNL201 requires multiple daily doses. Here, we report safety, tolerability, pharmacodynamic, and pharmacokinetic (PK) results from phase 1 healthy participant and phase 1b patient studies conducted with a second LRRK2 inhibitor, BIIB122 (also known as DNL151).

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 (*Supplemental Figure S1A*). Primary objectives were to investigate the safety, tolerability, and plasma PK of single and multiple oral doses of BIIB122. Other objectives included characterization of 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 29 November 2017 and 21 February 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 (*Supplemental Figure S1A*). Eligible participants were randomized to BIIB122 or placebo (3:1) in PARTS A and C (N=8/cohort planned) and PART D (N=16 planned), and PARTS B and E (N=10/cohort planned) (4:1). Study design details are provided in the *Supplemental Material*.

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 (*Supplemental Figure S1B*). 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, UK, Belgium, and US from 03 July 03 2019 to 02 December 02 2020 (*Supplemental Figure S1B*). 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 *Supplemental Material*.

Inclusion/exclusion criteria

PHASE 1 STUDY Eligible participants were aged 18-50 years, inclusive, for PARTS A, B, D, and E and aged 60-75 years, inclusive, for PART C. Women of childbearing potential were excluded.

PHASE 1B STUDY Eligible participants were aged 30-75 years, inclusive, with mild to moderate PD with or without PD risk genes, and modified Hoehn & Yahr Stages 1-3. 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 1 patient with an LRRK2 mutation (R1441C) and 3 patients with β-glucocerebrosidase (GBA) 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 *Supplemental Material*.

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 (*Figure 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%]) (*Supplemental Table S1*). In PART C (elderly cohort), mean age (range) was 69.5 (67-74) years and 4 participants (50%) were male (*Supplemental Table 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 (*Figure 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 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 (SAEs) were reported, and the majority of TEAEs were mild in severity (*Supplemental Table S2* and *S3*). TEAEs leading to study drug discontinuation for BIIB122-treated participants included: 3 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 3 reported as unrelated to study drug (moderate influenza-like illness [N=1, 10 mg, single dose]; mild asymptomatic 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 (*Supplemental Table 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 (84%) participants (*Supplemental Table S3*). 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 (*Supplemental Table S3*). No clinically meaningful or dose-related changes were observed in vital signs, clinical laboratory values (including renal function parameters; *Supplemental Figure S2*), physical or neurological examinations, Columbia Suicide Rating Scale (C-SSRS), or PFTs (*Supplemental Figure S3*).

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 SAEs were reported, and the majority of TEAEs were mild or moderate in severity (*Supplemental Table S4*). TEAEs leading to study drug discontinuation were reported for 2 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 (1 each for 80 and 300 mg QD) had TEAEs of hypotension or orthostatic hypotension (both asymptomatic) that resolved while continuing study drug.

Overall, TEAEs were reported for 23 BIIB122-treated (89%) and 5 placebo-treated (50%) patients (*Supplemental Table S4*). 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; *Supplemental Figure S2*); physical or neurological examinations; C-SSRS; PFTs (*Supplemental Figure S3*); or MDS-UPDRS PART III, Non-Motor Symptoms Scale, or MOCA scores (*Supplemental Table S5*).

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 (*Supplemental Figure S4*, *Supplemental Table S6*). Following multiple-dose administration of BIIB122 15-300 mg QD for 10 or 28 days or BIIB122 150-400 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 (AR) 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 15-300 mg QD and 150-400 mg BID dose ranges (*Supplemental Table S6*).

PK variability was low to moderate; percent coefficient of variation (CV) ranged from 8.9% to 31% for $C_{max(ss)}$ and from 6.7% to 40% for AUC_{0-24} (*Supplemental Table S6*). 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 (*Figure 2A*). At higher doses, this ratio may be overestimated due to 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 (*Supplemental Figure S5*, *Supplemental Table S7*). Following multiple doses, mean $C_{max(ss)}$ and AUC_{0-tau} increased less than dose proportionally, and AR 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 (*Supplemental Table S7*). PK variability after QD dosing was low to moderate; CV ranged from 11% to 35% for $C_{max(ss)}$ and from 25% to 33% for AUC_{0-tau} (*Supplemental Table S7*). 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 (*Figure 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 (*Figure 3A*, *Supplemental Figure S6A*, *Supplemental Figure 7A*). Likewise, median PBMC pT73 RAB10, a direct substrate of LRRK2, was reduced from baseline at all BIIB122 doses (*Figure 3B*, *Supplemental Figure S6B*, *Supplemental Figure S7B*), 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 15-300 mg QD, and from 91% to 98% for 150-400 mg BID. Average reduction in PBMC pT73 RAB10 at steady state (median) ranged from 49% to 80% for 15-300 mg QD and from 79% to 93% for 150-400 mg BID.

Total LRRK2 was recently shown to be quantifiable in CSF.[42] We hypothesized that LRRK2 inhibition in the CNS would reduce total LRRK2 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% (*Figure 3C*, *Supplemental Figure S7C*), 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 (*Figure 3D*, *Supplemental Figure S6C*, *Supplemental Figure S7D*).

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 (*Figure 4A*, *Supplemental Figure S8A*, *Supplemental Figure S9A*). pS935 LRRK2 levels returned to approximately baseline values on DAY 42 (*Supplemental Figure S7A*). 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 (*Figure 4B*, *Supplemental Figure S8B*, *Supplemental Figure S9B*). While 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 (*Figure 4C*, *Supplemental Figure S9C*).

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 (*Figure 4D*, *Supplemental Figure S9D*). A larger BMP reduction with less variability was observed in the 300 mg QD group than in the lower BIIB122 doses and placebo.

DISCUSSION

In the clinical studies reported herein, 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 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 QD dosing. BIIB122 distributed equally to CSF and plasma, with a CSF/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 (*Supplemental Figure S10*), 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) vs 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 (*Figure 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]
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 due to reduced total LRRK2 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 ~20-50%, 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 of ≥ ~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% 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 (e.g., lightheadedness) suggests accommodation to hemodynamic fluctuations related to long-standing autonomic dysregulation in these patients.

Previously reported nonclinical toxicology studies evaluating multiple LRRK2 inhibitors demonstrated nonadverse, treatment-associated microscopic changes in lung (vacuolated type II pneumocytes) and kidney (pigmentation in renal tubular epithelial cells) that reversed following discontinuation of LRRK2 inhibition.[29,38,39] These nonadverse pulmonary and renal effects were attributed to on-target LRRK2 inhibition but 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 months 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 ≤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, 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.

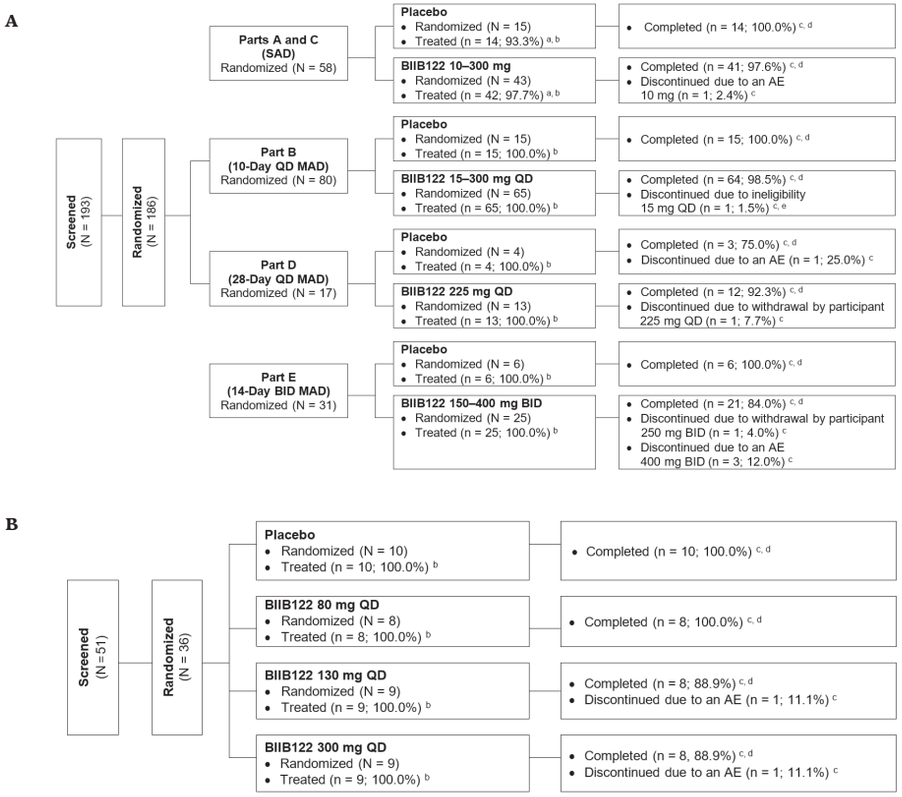
Our results support the selection of BIIB122 to advance to late-stage clinical studies in patients with PD given its favorable pharmacokinetic profile (compared to DNL201) supporting once daily dosing. Studies with two LRRK2 inhibitors (DNL201 and BIIB122) have confirmed substantial LRRK2 kinase inhibition 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.

Table 1 Phase 1B study: demographics and other baseline characteristics.

Characteristic	Placebo (N = 10)	BIIB122			Total (N = 36)
		80 mg QD (N = 8)	130 mg QD (N = 9)	300 mg QD (N = 9)	
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	2 (22.2)	0	3 (8.3)
Other Parkinson's disease medications	2 (20.0)	1 (12.5)	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 & 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	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	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)

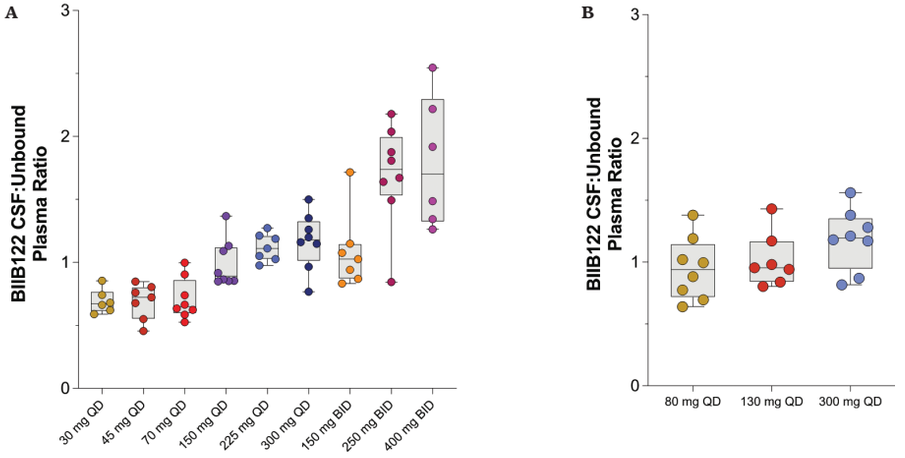
BMI = body mass index / MAOB = monoamine oxidase B / MAX = maximum / MDS-UPDRS PART III = Movement Disorders Society Unified Parkinson's Disease Rating Scale Part III / MIN = minimum / MOCA = Montreal Cognitive Assessment / NMSS = Non-Motor Symptoms Scale / PIC = powder-in-capsule / QD = once daily. / BIIB122 was administered as a 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.

Figure 1 CONSORT (consolidated standards of reporting trials) diagram. A. Phase 1 study. B. Phase 1B study.



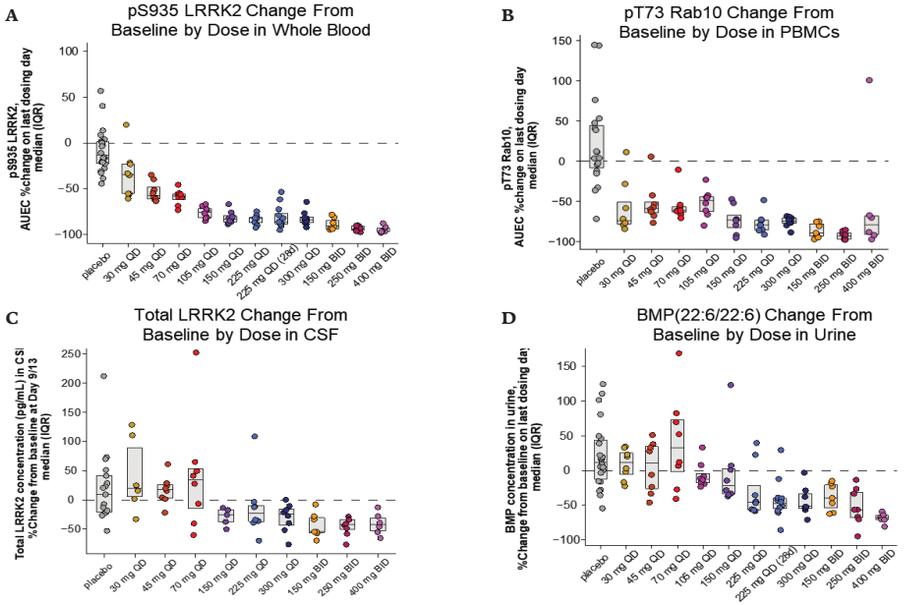
a) Two participants in PART A were discontinued post-randomization but before study drug administration: 1 participant in the placebo group due to failure to obtain the baseline CSF sample, and 1 participant in the BIIB122 10 mg group due to a vasovagal reaction following predose orthostatic testing. / 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 DLCO]). / AE = adverse event / BID = twice daily / MAD = multiple ascending dose / QD = once daily / SAD = single ascending dose.

Figure 2 BIIB122 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. BIIB122 CSF-to-unbound plasma concentration ratios. 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 on file). Data are described using boxplots, with the error bars representing the minimum to maximum data points.



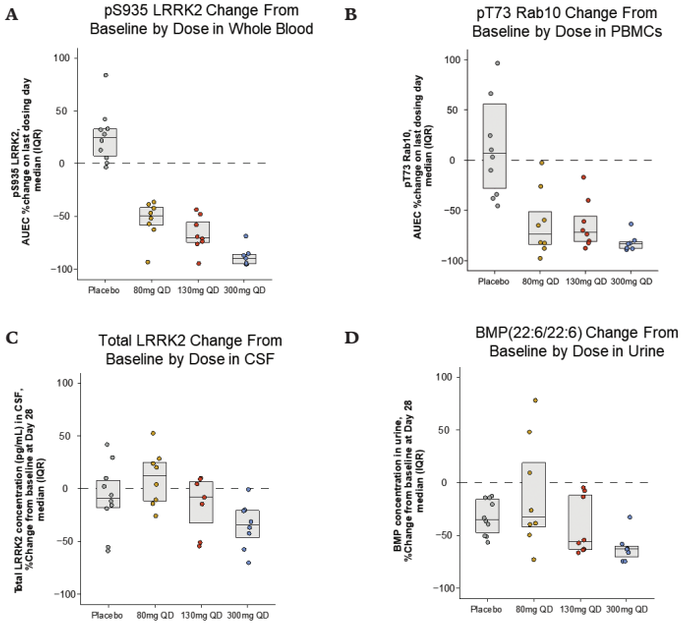
BID = twice daily / PD = Parkinson's disease / QD = once daily.

Figure 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 zero 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 / 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.

Figure 4 Phase 1B study: dose-dependent target and pathway engagement in patients with Parkinson's disease 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 zero to 24 hours (or 12 hours for PART E).



BMP = bis(monoacylglycerol)phosphate / BMP(22:6/22:6) = di-docosahexaenoyl bis(monoacylglycerol)phosphate 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.

Supplemental methods

STUDY CONDUCT In each part of the phase 1 study, participants were admitted to the CRU on DAY −2 and remained confined for the duration of dosing. Study drug (powder-in-capsule [PIC]) was administered in the morning in PARTS A, B, C, and D, or in the morning and evening (i.e., every 12 hours) in PART E. Participants were discharged 1 day after the last dose and returned for an outpatient follow-up visit ~1 (all parts) and 2 (PART D only) weeks after the last dose.

In each part, of the phase 1B study eligible patients were admitted to the CRU on DAY −2 for ≤5 days. Weekly outpatient visits were conducted for 3 weeks and patients were readmitted to the CRU on DAY 27 for ≤4 days for the final dose on DAY 28 and safety, PK, and pharmacodynamic assessments. Two additional outpatient safety follow-up visits were completed ~1 and ~2 weeks after the last dose.

RANDOMIZATION AND BLINDING In both clinical studies, participants were randomly assigned to treatment based on randomization lists generated using a permuted blocks randomization scheme. For the phase 1 study, for each study part and individual cohort, allocation to treatment was according to a predetermined random order. The randomization list was generated by unblinded contract research organization statisticians using a computer program. For the phase 1B study, randomization was performed using an interactive response technology (IRT) system, and the randomization list included study part–specific block sizes.

Both clinical studies were performed in a double-blind fashion, with the following controls used to maintain the double-blind status:

- For both the phase 1 and phase 1B studies, placebo capsules were identical in appearance, quantity, and packaging to the BIIB122 capsules. For the phase 1B study, placebo tablets were identical in appearance, quantity, and packaging to the BIIB122 tablets.
- The study participants, investigator's study site staff (except for the site pharmacist), medical monitors, and all other individuals involved with the study conduct remained blinded to treatment assignments until study closure.
- An unblinded pharmacist was assigned at the site and prepared the study drug for dispensing at the site. The unblinded pharmacist was also responsible for counting the returned capsules/tablets for drug accountability.

PHARMACOKINETIC SAMPLE ANALYSIS Plasma and CSF concentrations of BIIB122 were measured using liquid chromatography–tandem mass spectrometry (LC-MS/MS). Briefly, aliquots of 10 µL of calibration standards (STDS), quality-control (QC) samples, blank matrix, and study samples were transferred to a clean 96-well plate. A total of 125 µL of water:ammonium hydroxide (100:1) was added to each well. A total of 25 µL of acetonitrile:water (40:60) was added to wells containing blanks, and 25 µL of internal standard solution [750 nM of BIIB122-D6 in acetonitrile:water (40:60)] was added to all other wells. After 800 µL of methyl tert-butyl ether (MTBE) was added to each well, the samples were mixed using a Hamilton Microlab STAR automation system. After centrifugation, 100 µL of the upper organic layer was transferred to a clean 96-well plate, evaporated to dryness under purified nitrogen gas flow and reconstituted in 250 µL of acetonitrile:water:formic acid (40:60:0.2) before the samples were analyzed using LC-MS/MS. The LC-MS/MS analyses were performed on a Waters Acquity UPLC® system (Waters CO., Milford, MA) coupled with a Sciex API 4000™ mass spectrometer (AB SCIEX, Redwood City, CA). High-performance liquid chromatography (HPLC) was established on a Kinetex® XB-C18 column (2.6 mm, 50 × 2.1 mm) (Phenomenex, Torrance, CA) and the column was kept at 40°C during the run. The two mobile phases used were water:formic acid (100:0.2) and acetonitrile:formic acid (100:0.2). The multiple-reaction monitoring transition monitored for BIIB122 and BIIB122-D6 were 422.2 to 353.3 and 428.2 to 359.3, respectively. The declustering potential (DP) was at 50 V and collision energy (CE) was at 22 V. The bioanalysis method was fully validated and met the acceptance criteria for intra- and inter-run precision and accuracy defined in the 2018 Food and Drug Administration (FDA) Bioanalytical Method Validation Guidance, with a lower limit of quantification (LLOQ) of 0.015 mM.

PHARMACODYNAMIC BIOFLUID SAMPLE COLLECTION Whole blood was collected in a tripotassium ethylenediaminetetraacetic acid (K3EDTA) blood collection tube, and the tube was inverted gently to mix the anticoagulant well with the blood. Whole-blood samples were aliquoted within 60 minutes of collection and stored at −70°C until shipment.

Human peripheral blood mononuclear cells (PBMCs) were isolated from whole blood collected in Vacutainer CPT™ sodium heparin tubes (BD 362780) following the manufacturer's protocol. PBMCs were resuspended in lysis buffer (1× cell lysis buffer with PHOSSTOP™ phosphatase inhibitor, complete

protease inhibitor, and Benzonase®) and incubated for 20 minutes. PBMC lysate was then centrifuged at 12000 × g for 20 minutes at 4°C. Supernatant was aliquoted and stored at −70°C until shipment.
CSF was collected by lumbar puncture. The first 0.5 mL of CSF was discarded, then samples were collected for pharmacokinetic and pharmacodynamic analyses. CSF samples were aliquoted and stored at −70°C until shipment.

Urine was collected either as a pooled sample or a spot sample in which participants were asked to collect a sterile, midstream urine specimen. Pooled samples were stored at 4°C until the end of the collection period. Urine samples were then centrifuged at 2500 × g at 4°C, aliquoted, and stored at −70°C until shipment.

PHARMACODYNAMIC SAMPLE ANALYSIS Whole blood was lysed by adding equal parts of lysis buffer and incubated on ice for 20 minutes. Samples were then centrifuged at 2600 × g for 20 minutes at 4°C. Phosphorylated serine 935 (pS935) leucine-rich repeat kinase 2 (LRRK2) analysis in the phase 1 study was performed as previously described.[s1,s2] pS935 LRRK2 analysis in the phase 1B study was performed at a bioanalytical laboratory using a fit-for-purpose assay. Briefly, a 96-well Meso Scale Discovery® (MSD®) Gold small-spot streptavidin plate (MSD L45SA; Rockville, MD) was washed once with ~300 mL of wash buffer per well and 25 mL of capture antibody (1 mg/mL of biotinylated pS935 Abcam AB172382) was added to each well. The plate was sealed and incubated at room temperature for 1 hour ± 6 minutes on a Heidolph plate shaker set at ~1000 RPM. Following incubation, the plate was washed 3 times with ~300 mL of wash buffer per well. Then, 25 mL of standards, blank, QC samples, and study samples were added to wells according to the plate layout. Samples collected from patients with Parkinson's disease treated with BIIB122 were analyzed alongside a recombinant full-length wild-type LRRK2 (Thermo Fisher 2082796) standard curve, and concentrations of pS935 LRRK2 in each sample were calculated. Otherwise, pS935 LRRK2 was quantified in raw luminescence units.

The plate was sealed and incubated overnight at 2°C to 8°C on a Heidolph plate shaker set at ~1000 RPM. On DAY 2, the plate was washed 3 times and 25 mL of detection antibody (0.25 mg/mL ruthenylated ANTI-LRRK2 BioLegend MC.028 in detection antibody dilution buffer) was added to each well. The plate was sealed and incubated at room temperature for 1 hour ± 6 minutes on a Heidolph plate shaker set at ~1000 RPM. Following incubation, the plate was washed 3 times. Residual wash buffer was removed as described above, and 150 mL of 2× read buffer T was added to each well. The plate was read immediately on an MSD Sector Imager 600 plate reader.

Phosphorylated threonine 73 (pT73) RAB10 in peripheral blood mononuclear cells was measured as previously described.[s1,s2] Briefly, Streptavidin-coated plates (MSD) were coated with biotinylated pT73 RAB10 antibody (Denali Therapeutics; South San Francisco, CA) for 1 hour at room temperature. Lysate was then pipetted onto these plates and incubated overnight at 4°C. Plates were washed and then ANTI-RAB10 antibody (Abcam; AB181367 with SULFO-TAG) diluted in 25% blocker A (MSD) 75% 1X TBST, D-R block (MSD), and D-M BLOCK (MSD) was added to each well. Following 1-hour room temperature incubation with shaking, 2X read buffer (diluted from 4X with water) was added to each well, and the plate was read on an MSD imager.

Total LRRK2 in CSF was detected using a slightly modified version of a previously reported anti-peptide immunoprecipitation–LC-MS assay measured as previously described.[s3] A total of 500 mL of human CSF was digested using 10 mg trypsin at 40°C for 1.5 hours in the presence of 100 fg of isotopically labeled heavy peptide (*KAEEGDLLVNPDQPR). Antipeptide immunoprecipitation was performed using biotinylated LRRK2 monoclonal antibody (MAB) N241A/34 (Antibodies Inc.). A WPS-3000 rapid-separation liquid chromatography (RSLC) system coupled to a Q EXACTIVE™ HF-X mass spectrometer (Thermo Fisher) operating in parallel-reaction monitoring mode was used to detect the ratio between light and heavy KAEEGDLLVNPDQPR peptide for absolute quantitation.

The quantitation of di-22:6-bis(monoacylglycerol)phosphate [BMP(22:6/22:6)] in human urine was conducted by Nextcea, Inc. (Woburn, MA) using a validated LC-MS/MS method, as previously described.[s2] The calibration standards and quality control samples were prepared using an authentic DI-22:6-BMP reference standard provided by Nextcea, INC. (Woburn, MA). A stable isotope labelled DI-22:6-BMP was employed as an internal standard and added during extraction. Di-22:6-BMP was extracted from urine by liquid-liquid extraction and the phospholipid layer was dried down and reconstituted for LC-MS/MS analysis. The chromatographic separation of the analyte from matrix components was achieved on a Nexera XR Ultra High Performance Liquid Chromatograph system (Shimadzu Scientific Instruments, Japan). The analyte was detected with SCIEX QTOF X500 and TripleQuad 7500 LC-MS/MS systems (SCIEX, Framingham, MA).

The intensities of DI-22:6-BMP and the internal standard were determined by integration of extracted ion peak areas using SCIEX OS software. Calibration curves were prepared by plotting the peak area ratios for each analyte to internal standard versus concentration. The model for the calibration curves was linear with (1/×2) weighting. Measured concentrations of DI-22:6-BMP in urine were divided by urine creatinine and reported in ng/mg creatinine.

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S2 Jennings D, Huntwork-Rodriguez S, Henry AG, et al. Safety, tolerability, and pharmacodynamics of LRRK2 inhibitor DNL201: from preclinical studies to Parkinson's clinical trials. *Sci Transl Med.* In press.

S3 Mabrouk OS, Chen S, Edwards AL, Yang M, Hirst WD, Graham DL. Quantitative measurements of LRRK2 in human cerebrospinal fluid demonstrates increased levels in G2019S patients. *Front Neurosci*. 2020;14:526. doi: 10.3389/fnins.2020.00526.

Table S1 Phase 1 study: demographic and other baseline characteristics.

Characteristic	SAD: PART A (N = 48)	Single-Dose Elderly: PART C (N = 8)	MAD 10 Days: PART B (N = 80)	Multiple-Dose 28 Days: PART D (N = 17)	MAD 14 Days: PART E (N = 31)	Total (PARTS A–E) (N = 184)
Age, Y						
Mean (SD)	26.8 (8.1)	69.5 (2.1)	28.9 (8.6)	29.0 (7.5)	31.0 (8.8)	30.5 (11.7)
Median (MIN, MAX)	25.0 (18, 50)	69.0 (67, 74)	26.5 (18, 50)	29.0 (18, 39)	30.0 (18, 50)	27.0 (18, 74)
Sex, N (%)						
Male	48 (100.0)	4 (50.0)	79 (98.8)	17 (100.0)	31 (100.0)	179 (97.3)
Female	0	4 (50.0)	1 (1.3)	0	0	5 (2.7)
Race, N (%)						
American Indian or Alaska Native	1 (2.1)	0	4 (5.0)	0	1 (3.2)	6 (3.3)
Asian	0	0	6 (7.5)	1 (5.9)	3 (9.7)	10 (5.4)
Black or African American	1 (2.1)	0	6 (7.5)	1 (5.9)	3 (9.7)	11 (6.0)
Native Hawaiian or other Pacific Islander	0	0	1 (1.3)	0	0	1 (0.5)
White	43 (89.6)	8 (100.0)	53 (66.3)	13 (76.5)	21 (67.7)	138 (75.0)
Multiple races reported	1 (2.1)	0	9 (11.3)	1 (5.9)	2 (6.5)	13 (7.1)
Other	2 (4.2)	0	1 (1.3)	1 (5.9)	1 (3.2)	5 (2.7)
Ethnicity, N (%)						
Hispanic or Latino	0	0	5 (6.3)	2 (11.8)	1 (3.2)	8 (4.3)
Not Hispanic or Latino	48 (100.0)	8 (100.0)	75 (93.8)	15 (88.2)	30 (96.8)	176 (95.7)
BMI, kg/m^2						
Mean (SD)	23.73 (2.66)	24.69 (3.72)	24.01 (2.62)	25.47 (3.42)	24.87 (2.72)	24.24 (2.80)

MAD = multiple-ascending dose/MAX = maximum/MIN = minimum/SAD = single-ascending dose.

Table S2 Phase 1 study: summary of treatment-emergent adverse events in healthy participants – single-dose cohorts.

	Placebo	BIIB122							BIIB122
	(N = 14)	10 mg (N = 6)	20 mg (N = 6)	40 mg (N = 6)	40 mg Elderly (N = 6)	60 mg (N = 6)	225 mg (N = 6)	300 mg (N = 6)	Total (N = 42)
Any TEAE[1]	9 (64.3)	4 (66.7)	6 (100.0)	2 (33.3)	2 (33.3)	5 (83.3)	5 (83.3)	6 (100.0)	30 (71.4)
Severe	0	0	1 (16.7)[2]	0	0	0	0	0	1 (2.4)
Moderate	4 (28.6)	1 (16.7)	5 (83.3)	0	0	1 (16.7)	0	0	7 (16.7)
Mild	5 (35.7)	3 (50.0)	0	2 (33.3)	2 (33.3)	4 (66.7)	5 (83.3)	6 (100.0)	22 (52.4)
Study drug–related TEAE	2 (14.3)	0	0	0	0	0	4 (66.7)	5 (83.3)	9 (21.4)
TEAE leading to study drug discontinuation	0	1 (16.7)	0	0	0	0	0	0	1 (2.4)
Most common TEAEs (reported for ≥5% healthy participants overall) by preferred term									
Headache	2 (14.3)	2 (33.3)	0	1 (16.7)	1 (16.7)	1 (16.7)	2 (33.3)	5 (83.3)	12 (28.6)
Procedural headache	5 (35.7)	0	6 (100.0)	0	0	1 (16.7)	0	3 (50.0)	10 (23.8)
Post procedural complication	0	2 (33.3)	3 (50.0)	0	0	1 (16.7)	3 (50.0)	1 (16.7)	10 (23.8)
Procedural pain	2 (14.3)	1 (16.7)	3 (50.0)	0	0	2 (33.3)	2 (33.3)	1 (16.7)	9 (21.4)
Fatigue	1 (7.1)	0	0	0	0	0	4 (66.7)	1 (16.7)	5 (11.9)
Dizziness	1 (7.1)	0	1 (16.7)	1 (16.7)	0	0	0	1 (16.7)	3 (7.1)
Nausea	3 (21.4)	0	2 (33.3)	0	0	0	0	1 (16.7)	3 (7.1)
Vomiting	1 (7.1)	0	3 (50.0)	0	0	0	0	0	3 (7.1)
Abdominal pain	2 (14.3)	1 (16.7)	0	0	0	0	0	0	1 (2.4)
Diarrhoea	2 (14.3)	1 (16.7)	0	0	0	0	0	0	1 (2.4)

TEAE = treatment-emergent adverse event. / Data are N (%) of participants. / TEAE Preferred Terms are presented in order of decreasing frequency in the Total BIIB122 group. / No deaths or serious adverse events were reported in the single-dose cohorts (PARTS A and C). / 1) Each participant is counted only once, in the highest severity category. / 2) Severe TEAE procedural headache, reported as not related to study drug.

Table S3 Phase 1 study: summary of treatment-emergent adverse events in healthy participants—multiple-dose cohorts.

	PART B (QD)								PART D (QD)			PART E (BID)			
	PBO	BIIB122							PBO	225 mg	BIIB122				
	(N = 15)	15 mg (N = 9)	30 mg (N = 8)	45 mg (N = 8)	70 mg (N = 8)	105 mg (N = 8)	150 mg (N = 8)	225 mg (N = 8)	300 mg (N = 8)	Total (N = 65)	(N = 4)	(N = 13)	PBO (N = 6)	150 mg (N = 7)	250 mg (N = 9)	400 mg (N = 9)	Total (N = 25)
Any TEAE (n [%])[1]	13 (86.7)	7 (77.8)	7 (87.5)	8 (100.0)	6 (75.0)	7 (87.5)	5 (62.5)	8 (100.0)	8 (100.0)	56 (86.2)	2 (50.0)	10 (76.9)	6 (100.0)	7 (100.0)	9 (100.0)	9 (100.0)	25 (100.0)
Severe	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (11.1)[2]	1 (11.1)[3]	2 (8.0)
Moderate	3 (20.0)	0	1 (12.5)	2 (25.0)	1 (12.5)	0	1 (12.5)	3 (37.5)	1 (12.5)	9 (13.8)	1 (25.0)	0	0	0	2 (22.2)	6 (66.7)	8 (32.0)
Mild	10 (66.7)	7 (77.8)	6 (75.0)	6 (75.0)	5 (62.5)	7 (87.5)	4 (50.0)	5 (62.5)	7 (87.5)	47 (72.3)	1 (25.0)	10 (76.9)	6 (100.0)	7 (100.0)	6 (66.7)	2 (22.2)	15 (60.0)
Study drug–related TEAE (N [%])	3 (20.0)	1 (11.1)	0	0	0	0	0	6 (75.0)	7 (87.5)	14 (21.5)	2 (50.0)	2 (15.4)	4 (66.7)	6 (85.7)	8 (88.9)	8 (88.9)	22 (88.0)
TEAE leading to study drug discontinuation (N [%])	0	0	0	0	0	0	0	0	0	0	1 (25.0)	0	0	0	1 (11.1)	3 (33.3)	4 (16.0)
Most common TEAEs (reported for ≥5% healthy participants overall) by preferred term (N [%])																	
Headache	5 (33.3)	3 (33.3)	2 (25.0)	2 (25.0)	3 (37.5)	3 (37.5)	3 (37.5)	6 (75.0)	7 (87.5)	29 (44.6)	0	3 (23.1)	4 (66.7)	6 (85.7)	7 (77.8)	8 (88.9)	21 (84.0)
Procedural pain	2 (13.3)	0	7 (87.5)	3 (37.5)	3 (37.5)	0	1 (12.5)	4 (50.0)	2 (25.0)	20 (30.8)	1 (25.0)	1 (7.7)	1 (16.7)	2 (28.6)	3 (33.3)	3 (33.3)	8 (32.0)
Procedural headache	4 (26.7)	0	4 (50.0)	4 (50.0)	5 (62.5)	0	0	1 (12.5)	0	14 (21.5)	0	0	1 (16.7)	0	1 (11.1)	3 (33.3)	4 (16.0)
Post procedural complication	4 (26.7)	1 (11.1)	1 (12.5)	1 (12.5)	2 (25.0)	3 (37.5)	1 (12.5)	1 (12.5)	0	10 (15.4)	0	2 (15.4)	1 (16.7)	2 (28.6)	1 (11.1)	0	3 (12.0)
Fatigue	2 (13.3)	1 (11.1)	0	0	0	0	1 (12.5)	4 (50.0)	6 (9.2)	1 (25.0)	1 (7.7)	2 (33.3)	3 (42.9)	0	0	3 (12.0)	
Nausea	4 (26.7)	1 (11.1)	0	1 (12.5)	2 (25.0)	0	0	1 (12.5)	1 (12.5)	6 (9.2)	0	0	0	0	1 (11.1)	3 (33.3)	4 (16.0)
Myalgia	0	1 (11.1)	1 (12.5)	1 (12.5)	0	0	0	0	0	3 (4.6)	0	0	1 (16.7)	0	4 (44.4)	5 (55.6)	9 (36.0)
Dizziness	0	1 (11.1)	0	1 (12.5)	0	0	0	0	2 (25.0)	4 (6.2)	0	0	0	1 (14.3)	2 (22.2)	1 (11.1)	4 (16.0)
Insomnia	2 (13.3)	1 (11.1)	0	1 (12.5)	0	1 (12.5)	0	0	0	3 (4.6)	0	0	0	0	2 (22.2)	0	2 (8.0)
Back pain	0	1 (11.1)	0	0	0	0	1 (12.5)	0	0	2 (3.1)	0	1 (7.7)	0	2 (28.6)	2 (22.2)	0	4 (16.0)

BID = twice daily / PBO = placebo / QD = once daily / TEAE = treatment-emergent adverse event. / Data are N (%) of participants. / TEAE Preferred Terms are presented in order of decreasing frequency overall in the multiple-dose cohorts (PARTS B, D, and E). / No deaths or serious adverse events were reported in the multiple-dose cohorts (PARTS B, D, and E). / 1) Each participant is counted only once, in the highest severity category. / 2) Severe TEAE (procedural headache) in one participant randomized to BIIB122 250 mg BID, reported as not related to study drug. / 3) Severe TEAEs (headache and malaise) in one participant randomized to BIIB122 400 mg BID, reported as related to study drug.

Table S4 Phase 1B study: summary of treatment-emergent adverse events in patients with Parkinson's disease.

	Placebo QD (N = 10)	BIIB122 QD 80 mg (N = 8)	BIIB122 QD 130 mg (N = 9)	BIIB122 QD 300 mg (N = 9)	BIIB122 Total (N = 26)
Any TEAE (N [%])[1]	5 (50.0)	8 (100.0)	8 (88.9)	7 (77.8)	23 (88.5)
Severe	0	0	1 (11.1)[2]	1 (11.1)[3]	2 (7.7)
Moderate	1 (10.0)	1 (12.5)	2 (22.2)	2 (22.2)	5 (19.2)
Mild	4 (40.0)	7 (87.5)	5 (55.6)	4 (44.4)	16 (61.5)
Study drug–related TEAE (N [%])	3 (30.0)	4 (50.0)	3 (33.3)	7 (77.8)	14 (53.8)
TEAE leading to study drug discontinuation (N [%])	0	0	1 (11.1)	1 (11.1)	2 (7.7)
Most common TEAEs (reported for ≥5% patients overall) by preferred term (N [%])					
Headache	2 (20.0)	4 (50.0)	2 (22.2)	5 (55.6)	11 (42.3)
Back pain	0	1 (12.5)	3 (33.3)	2 (22.2)	6 (23.1)
Tremor	2 (20.0)	1 (12.5)	2 (22.2)	1 (11.1)	4 (15.4)
Nasopharyngitis	0	2 (25.0)	3 (33.3)	0	5 (19.2)
Procedural pain	1 (10.0)	2 (25.0)	1 (11.1)	1 (11.1)	4 (15.4)
Nausea	0	1 (12.5)	1 (11.1)	2 (22.2)	4 (15.4)
Myalgia	1 (10.0)	1 (12.5)	1 (11.1)	1 (11.1)	3 (11.5)
Dizziness	0	0	1 (11.1)	2 (22.2)	3 (11.5)
Hypotension	0	0	1 (11.1)	2 (22.2)	3 (11.5)
Orthostatic hypotension	0	1 (12.5)	0	2 (22.2)	3 (11.5)
Hyperhidrosis	1 (10.0)	0	0	2 (22.2)	2 (7.7)
Cough	2 (20.0)	0	1 (11.1)	0	1 (3.8)
Fatigue	0	2 (25.0)	0	0	2 (7.7)
Gastrooesophageal reflux disease	0	0	1 (11.1)	1 (11.1)	2 (7.7)
Insomnia	0	1 (12.5)	0	1 (11.1)	2 (7.7)
Vomiting	0	1 (12.5)	0	1 (11.1)	2 (7.7)
Dizziness postural	1 (10.0)	1 (12.5)	0	0	1 (3.8)
Hypoacusis	1 (10.0)	0	0	1 (11.1)	1 (3.8)
Tinnitus	1 (10.0)	0	0	1 (11.1)	1 (3.8)

QD = once daily / TEAE = treatment-emergent adverse event. / Data are N (%) of patients. / TEAE Preferred Terms are shown in order of decreasing frequency overall. / No deaths or serious adverse events were reported in the study. / 1) Each patient is counted only once, in the highest severity category. / 2) Severe TEAE (asymptomatic hypotension) in one patient randomized to BIIB122 130 mg QD, reported as not related to study drug, led to early discontinuation of study drug. / 3) Severe TEAE (headache) in one patient randomized to BIIB122 300 mg QD, onset after last dose study drug, reported as not related to study drug.

Table S5 Phase 1B study: change from baseline in neurological assessments in patients with Parkinson's disease.

Neurological Assessment Time Point	Placebo (N = 10)	BIIB122 80 mg QD (N = 8)	BIIB122 130 mg QD (N = 9)	BIIB122 300 mg QD (N = 9)
MDS-UPDRS PART III off-state score				
Baseline	29.8 (14.9)	29.9 (12.9)	26.1 (11.6)	35.8 (14.4)
DAY 28	26.5 (14.4)	32.1 (12.4)	22.3 (11.7)	35.4 (15.0)[1]
Change from baseline at DAY 28	-3.3 (7.5)	2.3 (6.2)	0.0 (6.0)	-1.4 (6.0)[1]
NMSS				
Baseline	18.0 (8.5)	36.5 (19.8)	24.3 (17.6)	38.4 (24.9)
DAY 27	23.9 (15.8)	34.3 (27.7)	27.1 (23.0)[1]	35.8 (19.4)[1]
Change from baseline at DAY 27	5.9 (10.1)	-2.3 (23.0)	2.8 (12.3)[1]	2.8 (9.2)[1]
MOCA				
Baseline	27.6 (1.6)	27.5 (1.5)	27.1 (1.5)	27.1 (1.8)
DAY 27	28.1 (2.1)	28.8 (1.3)	27.6 (1.6)[1]	27.8 (1.5)[1]
Change from baseline at DAY 27	0.5 (2.2)	1.3 (1.9)	0.5 (1.2)[1]	0.8 (1.3)[1]

MDS-UPDRS PART III = Movement Disorders Society Unified Parkinson's Disease Rating Scale Part III / MOCA = Montreal Cognitive Assessment / NMSS = Non-Motor Symptoms Scale / QD = once daily. Data are mean (SD) / For each data point, N = 10 for placebo, N = 8 for the BIIB122 80 mg QD group, and N = 9 for the BIIB122 130 and 300 mg QD groups, unless otherwise indicated. / 1) N = 8.

Table S6 Phase 1 study: BIIB122 steady-state plasma pharmacokinetic parameters after once- or twice-daily administration in healthy nonelderly participants.

Parameter	PART B BIIB122 QD								PART D BIIB122 QD	PART E BIIB122 BID		
	15 mg (N = 9)	30 mg (N = 8)	45 mg (N = 8)	70 mg (N = 8)	105 mg (N = 8)	150 mg (N = 8)	225 mg (N = 8)	300 mg (N = 8)	225 mg (N = 13)	150 mg (N = 7)	250 mg (N = 9)	400 mg (N = 9)
	DAY 10 (Last Dose)								DAY 28 (Last Dose)	DAY 14 (Last Dose)		
$C_{max,\ ss}$ (mM)												
N	8	8	8	8	8	8	8	8	12	7	8	6
Mean (SD)	1.22 (0.270)	2.88 (0.713)	3.89 (0.894)	4.48 (1.17)	7.32 (1.61)	7.56 (1.93)	9.04 (2.80)	10.3 (0.918)	10.5 (2.53)	8.91 (2.29)	12.3 (2.96)	13.0 (1.35)
CV%	22.2	24.7	23.0	26.1	21.9	25.6	31.0	8.9	24.2	25.7	24.0	10.4
$T_{max,\ ss}$ (h)												
N	8	8	8	8	8	8	8	8	12	7	8	6
Median (MIN, MAX)	1.0 (0.50, 4.1)	1.5 (0.50, 2.0)	1.1 (1.0, 2.0)	1.5 (1.5, 4.0)	1.0 (0.50, 2.0)	1.5 (1.0, 3.0)	1.0 (1.0, 3.0)	1.5 (1.0, 3.0)	1.5 (0.52, 2.0)	1.1 (0.52, 2.0)	1.5 (1.0, 2.0)	1.5 (1.0, 2.0)
AUC_{0-24} (mM · h)[1]												
N	8	8	8	8	8	8	8	8	12	7	8	6
Mean (SD)	16.6 (6.61)	35.9 (13.5)	44.6 (16.0)	58.2 (11.9)	92.1 (25.1)	91.1 (22.3)	119 (34.3)	127 (16.4)	123 (39.8)	149 (44.4)	205 (71.6)	211 (14.1)
CV%	39.9	37.6	35.9	20.4	27.3	24.5	28.9	13.0	32.4	29.9	35.0	6.7
$T_{1/2}$ (h)												
N	7	7	6	8	8	7	8	8	12	7	8	6
Mean (SD)	77.0 (47.9)	53.4 (18.5)	92.6 (102)	82.9 (43.6)	86.9 (62.0)	89.0 (48.8)	66.6 (34.1)	47.1 (11.2)	71.7 (34.0)	62.0 (27.9)	73.8 (39.8)	60.7 (23.1)
C_{max} AR[2]												
N	8	8	8	8	8	8	8	8	12	7	8	6
Mean (SD)	1.60 (0.566)	1.66 (0.415)	1.79 (0.941)	1.50 (0.275)	1.36 (0.287)	1.60 (0.335)	1.10 (0.149)	1.32 (0.434)	1.26 (0.431)	1.97 (1.03)	1.51 (0.574)	1.26 (0.183)
AUC AR[2]												
N	8	8	8	8	8	8	8	8	12	7	8	6
Mean (SD)	3.16 (1.07)	2.79 (0.936)	2.84 (1.35)	2.84 (0.682)	2.85 (0.829)	2.48 (0.519)	1.89 (0.257)	1.77 (0.404)	2.02 (0.654)	3.22 (1.37)	2.42 (1.17)	1.74 (0.112)

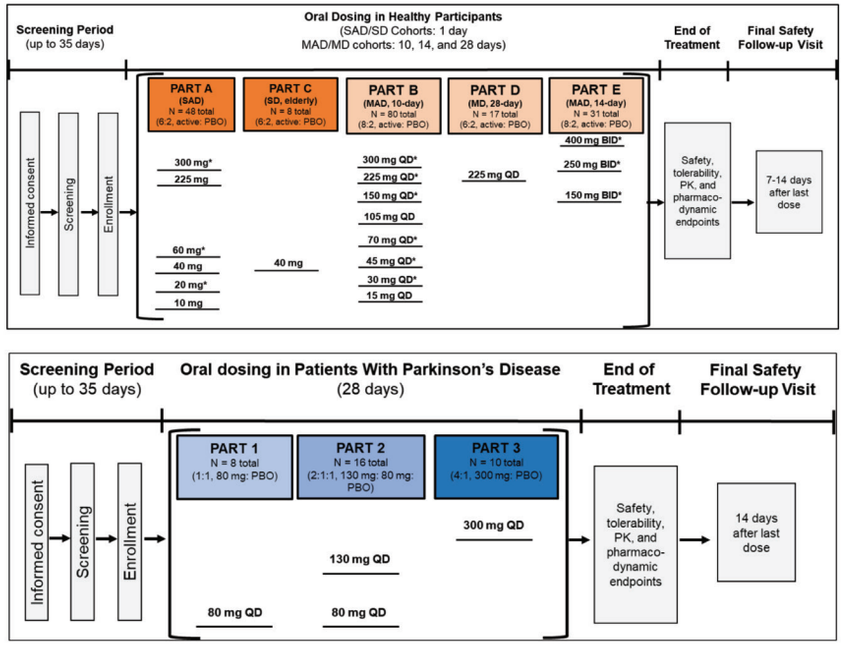
AR = accumulation ratio / AUC = area under the plasma concentration-time curve / AUC_{0-24} = area under the plasma concentration-time curve from the time of dosing to 24 hours the end of the dosing interval / AUC_{0-tau} = area under the plasma concentration-time curve from the time of dosing to the end of the dosing interval / BID = twice daily / C_{max} = maximum concentration / $C_{max,ss}$ = maximum concentration at steady state / CV = coefficient of variation / MAX = maximum / MIN = minimum / PIC = powder-in-capsule / QD = once daily / $T_{1/2}$ = elimination half-life / $T_{max,ss}$ = time of maximum concentration at steady state. / In PARTS B, D, and E, BIIB122 was administered as a PIC formulation to nonelderly participants in the fasted state. / 1) In PARTS B and D, AUC_{0-24} = AUC_{0-tau}. In PART E, AUC_{0-24} was calculated by multiplying the AUC_{0-12} (AUC_{0-tau}) value by 2. / 2) C_{max} AR = $C_{max,ss}$ [DAY 10, 14, or 28] / C_{max} [DAY 1] / AUC AR = AUC_{0-tau} [DAY 10, 14, or 28] / AUC_{0-tau} [DAY 1].

Table S7 Phase 1B study: BIIB122 steady-state plasma pharmacokinetic parameters after once-daily administration in patients with Parkinson's disease.

PK parameter	BIIB122 80 mg QD (N = 8)	BIIB122 130 mg QD (N = 8)	BIIB122 300 mg QD (N = 8)
	DAY 28 (Last Dose)		
$C_{max,ss}$ (μM)			
N	8	8	8
Mean (SD)	6.23 (2.20)	8.10 (1.67)	9.95 (1.09)
CV%	35.3	20.6	10.9
$T_{max,ss}$ (h)			
N	8	8	8
Median (MIN, MAX)	1.31 (0.5, 3.1)	1.50 (0.5, 2.0)	1.55 (1.0, 4.0)
AUC_{0-tau} (μM · h)			
N	8	8	8
Mean (SD)	76.3 (25.5)	104 (34.3)	127 (32.2)
CV%	33.4	32.9	25.4
$T_{1/2}$ (h)			
N	8	8	8
Mean (SD)	87.8 (44.0)	122 (102)	69.7 (44.6)
C_{max} AR[1]			
N	8	8	8
Mean (SD)	2.25 (1.17)	1.63 (0.320)	1.03 (0.180)
AUC AR[1]			
N	8	8	8
Mean (SD)	3.85 (1.62)	2.85 (0.961)	1.63 (0.452)

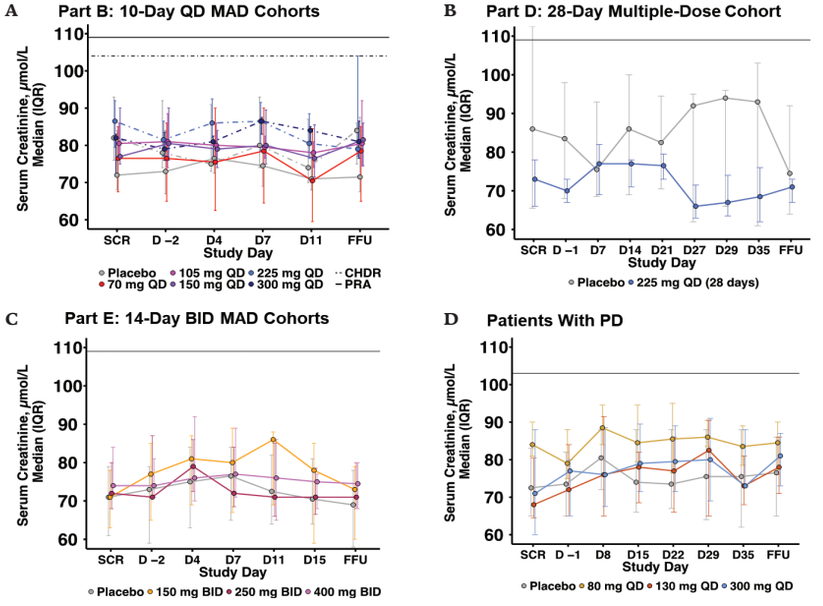
AR = accumulation ratio / AUC = area under the plasma concentration-time curve / AUC_{0-tau} = area under the plasma concentration-time curve from the time of dosing to the end of the dosing interval / C_{max} = maximum concentration / $C_{max,ss}$ = maximum concentration at steady state / CV = coefficient of variation / MAX = maximum / MIN = minimum / PIC = powder-in-capsule / PK = pharmacokinetic(s) / QD = once daily / $T_{1/2}$ = elimination half-life / $T_{max,ss}$ = time of maximum concentration at steady state. / BIIB122 was administered as a PIC formulation at the 80 and 130 mg doses and as a tablet formulation at the 300 mg dose in the fasted state. / 1) C_{max} AR = $C_{max,ss}$ [DAY 28] / C_{max} [DAY 1] / AUC AR = AUC_{0-tau} [DAY 28] / AUC_{0-tau} [DAY 1].

Figure S1 Study designs for phase 1 study and phase 1B study. A. For the phase 1 study, only cohorts designated by an asterisk (*) completed lumbar punctures for CSF collection. Sentinel dosing was used for the following cohorts: PART A 40, 60, 225, and 300 mg single-dose cohorts; PART B 30, 45 70-, 105, 150, 225, and 300 mg QD cohorts; and PART E 150, 250, and 400 mg BID cohorts. Two sentinel participants in each cohort received study drug (1 placebo and 1 BIIB122) and ≥24 hours of safety data from these participants were reviewed before the remainder of the participants in the cohort were dosed. For all cohorts, a PIC formulation was administered. B. For PART 1 of the phase 1B study, patients with PD were randomly assigned in a 1:1 ratio to receive placebo or BIIB122 80 mg QD for 28 days (PIC). In PART 2, patients were randomly assigned in a 1:1:2 ratio to receive placebo, BIIB122 80 mg, or BIIB122 130 mg, respectively, QD for 28 days (PIC). PART 2 was initiated after 8 patients were enrolled in PART 1 and after review of blinded safety data from ≥6 patients who completed ≥8 days of dosing in PART 1. In PART 3, patients were randomly assigned in a 1:4 ratio to receive placebo or BIIB122 300 mg QD for 28 days (tablet formulation). PART 3 was initiated after review of blinded safety data from PARTS 1 and 2.



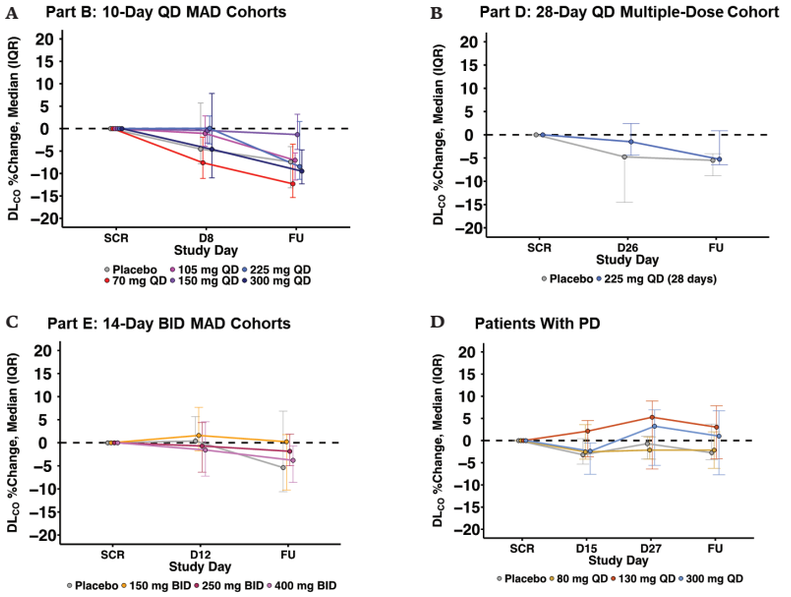
BID = twice daily / MAD = multiple ascending dose / MD = multiple dose / PBO = placebo / PD = Parkinson's disease / PIC = powder-in-capsule / PK = pharmacokinetic(s) / QD = once daily / SAD = single ascending dose / SD = single dose.

Figure S2 Phase 1 and phase 1B studies: summary of renal safety findings (serum creatinine) after multiple doses in healthy participants and patients with Parkinson's disease. Median percent change from baseline in serum creatinine in the A. PART B 10-day QD, B. PART D 28-day QD, and C. PART E 14-day BID cohorts from the phase 1 study in healthy participants and the (D) 28-day QD cohorts from the phase 1B study in patients with PD. The horizontal lines indicate the upper local laboratory limits of normal values for serum creatinine in males.



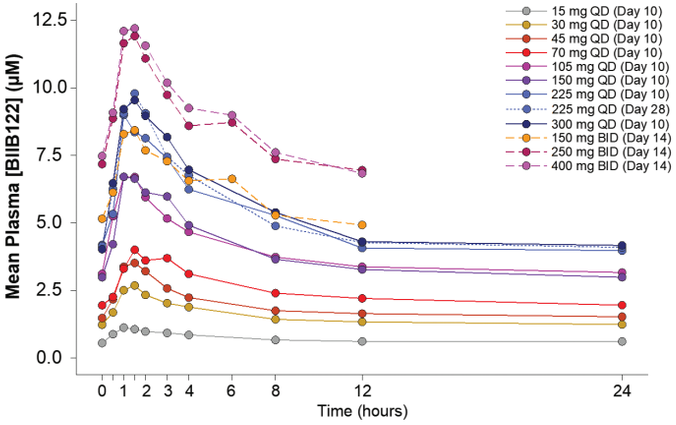
BID = twice daily / BL = baseline / CHDR = Centre for Human Drug Research / D = DAY / FFU = final follow-up / IQR = interquartile range / MAD = multiple ascending dose / PD = Parkinson's disease / PRA = PRA Health Sciences / QD = once daily / SCR = screening.

Figure S3 Phase 1 and phase 1B studies: summary of pulmonary safety findings (DLCO) after multiple doses in healthy participants and patients with Parkinson's disease. Median percent change from baseline in DLCO in the A. PART B 10-day QD, B. PART D 28 day QD, and C. PART E 14-day BID cohorts from the phase 1 study in healthy participants and the (D) 28-day QD cohorts from the phase 1B study in patients with PD. All DLCO values were adjusted for measured blood hemoglobin (closest central laboratory hemoglobin measurement to the time of DLCO measurement).



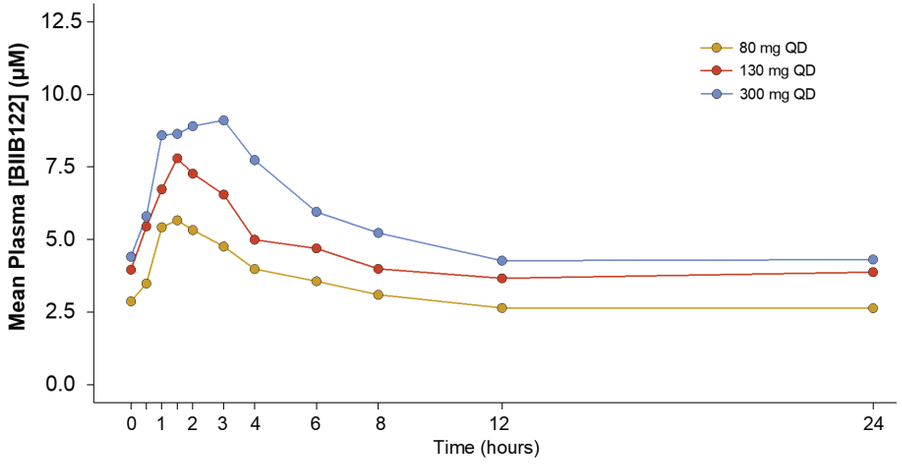
BID = twice daily / BL = baseline / D = DAY / DLCO = diffusing capacity of lungs for carbon monoxide / FU = follow-up / IQR = interquartile range / MAD = multiple ascending dose / PD = Parkinson's disease / QD = once daily / SCR = screening.

Figure S4 Phase 1 study: mean plasma concentration-time profiles of BIIB122 after multiple doses in healthy participants. Plasma pharmacokinetics of BIIB122 at steady state in healthy participants from PART B DAY 10 (15–300 mg QD), PART D DAY 28 (225 mg QD), and PART E DAY 14 (150–400 mg BID).



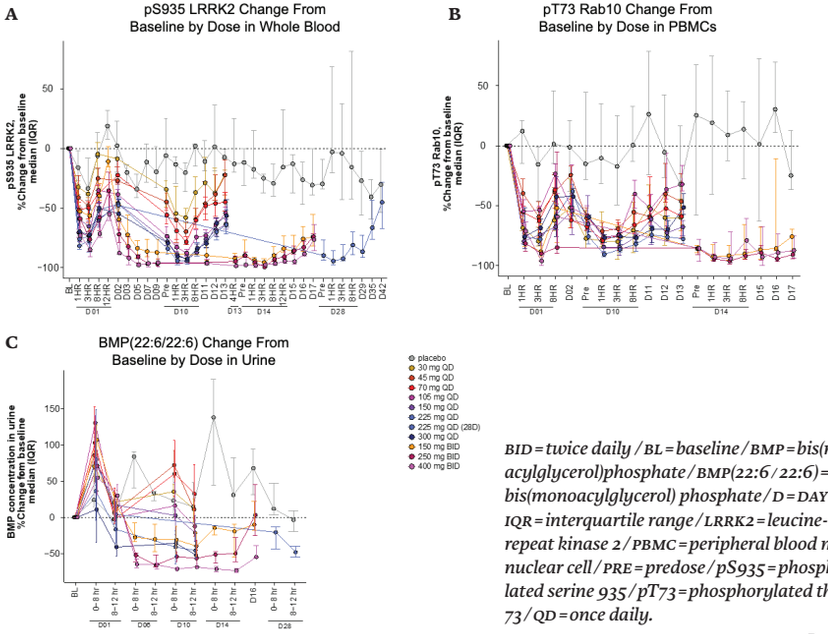
BID = twice daily / QD = once daily.

Figure S5 Phase 1B study: mean plasma concentration-time profiles of BIIB122 after multiple-doses in patients with Parkinson's disease. Plasma pharmacokinetics of BIIB122 at steady state in patients with PD from PARTS 1 through 3 (80–300 mg QD).



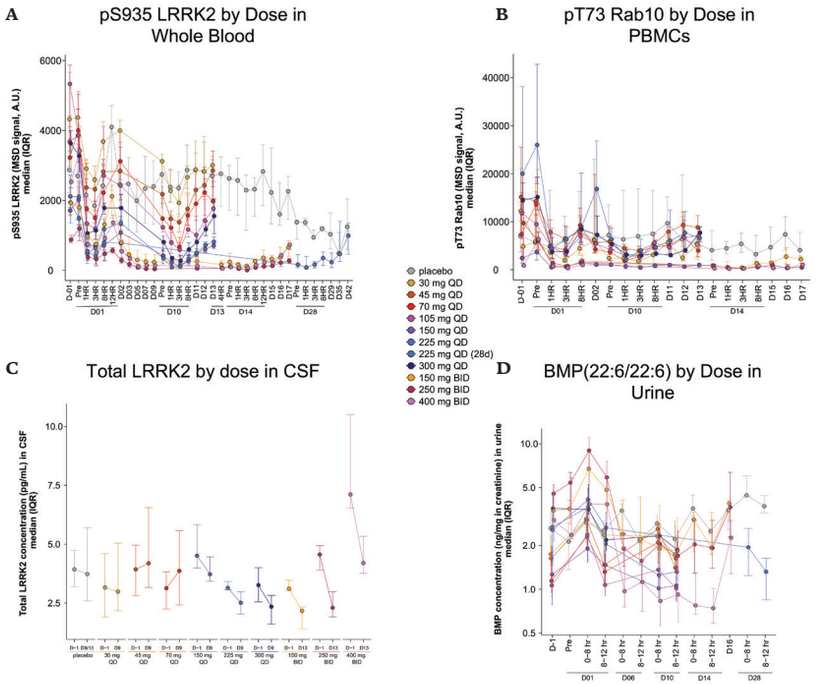
PD = Parkinson's disease / QD = once daily.

Figure S6 Phase 1 study: dose-dependent target and pathway engagement in healthy participants in multiple-dose cohorts. Pharmacodynamics of LRRK2 kinase inhibition in healthy participants from the phase 1 study (multiple-dose cohorts from PARTS B, D, and E). A. pS935 LRRK2 reduction from baseline in whole blood. B. pT73 RAB10 reduction from baseline in PBMCs. Time points of collection are denoted on the x-axis (D = day after first dose, where first dose is on D01). If no hour is specified (e.g., D02, D03), sample was collected predose or, where applicable, after the last dosing time point (e.g., D11, D12). On days on which multiple postdose time points were collected, the day of collection is indicated below the hourly time points on that day. For pS935 LRRK2 in whole blood (A), the D13 time point refers to the collection in the QD cohorts 3 days after the last dosing day, and the D13 4-hour time point refers to the collection in the BID cohorts 4 hours after the dose on D13. C. Urine BMP reduction from baseline. Time points of collection are denoted on the x-axis. On days on which multiple postdose time points were collected, the day of collection is indicated below the time periods of collection on that day (pooled sample collection over the time interval). Baseline was defined as the average of DAY −1 and DAY 1 predose measurements. A DAY 1 predose urine sample was not collected for the QD cohorts, so baseline BMP for these cohorts is defined as the DAY −1 measurement. The placebo group consists of all participants randomized to placebo across the multiple-dose cohorts in PARTS B, D, and E (variable N across time points, in particular for time points specific to PARTS D and E).



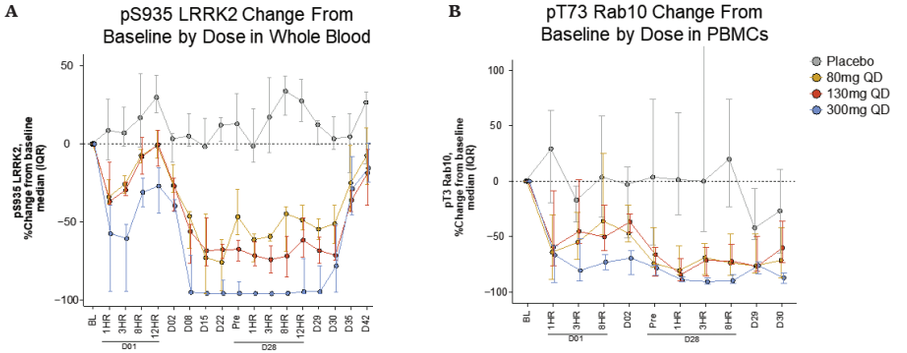
BID = twice daily / BL = baseline / BMP = bis(monoacylglycerol)phosphate / BMP(22:6/22:6) = di 22:6 bis(monoacylglycerol) phosphate / D = DAY / IQR = interquartile range / LRRK2 = leucine-rich repeat kinase 2 / PBMC = peripheral blood mononuclear cell / PRE = predose / pS935 = phosphorylated serine 935 / pT73 = phosphorylated threonine 73 / QD = once daily.

Figure S7 Phase 1 study: pharmacodynamics of LRRK2 inhibition in healthy participants in multi-dose cohorts plotted as median (IQR) value over time. A. pS935 LRRK2 in whole blood by dose group (MSD signal, A.U.) B. pT73 RAB10 (MSD signal, A.U.) in PBMCs by dose group. C. Urine BMP (ng/mg creatinine) by dose group. D. Total LRRK2 (pg/mL) in CSF by dose group. (A-D) Timepoints of collection are denoted on the x-axis (D=DAY before or after first dose where first dose is on D01 and D-01 is the day prior to the first dose). If no hour is specified (e.g. D02, D03), sample was collected predose, or where applicable, after the last dosing timepoint (e.g. D11, D12). On days where multiple postdose timepoints were collected, the day of collection is indicated below the hourly timepoints on that day. For pS935 LRRK2 in whole blood (A), the D13 timepoint refers to the collection in the QD groups three days after the last dosing day, and the D13 4 hour timepoint refers to the collection in the BID groups 4 hours after the dose on D13. For urine BMP (D), the time periods on the x-axis denote pooled sampling timepoints on the noted day of collection. The placebo group consists of all subjects randomized to placebo across PART B, D and E (variable N across timepoints, in particular for timepoints specific to PARTS D & E in the healthy volunteer study).



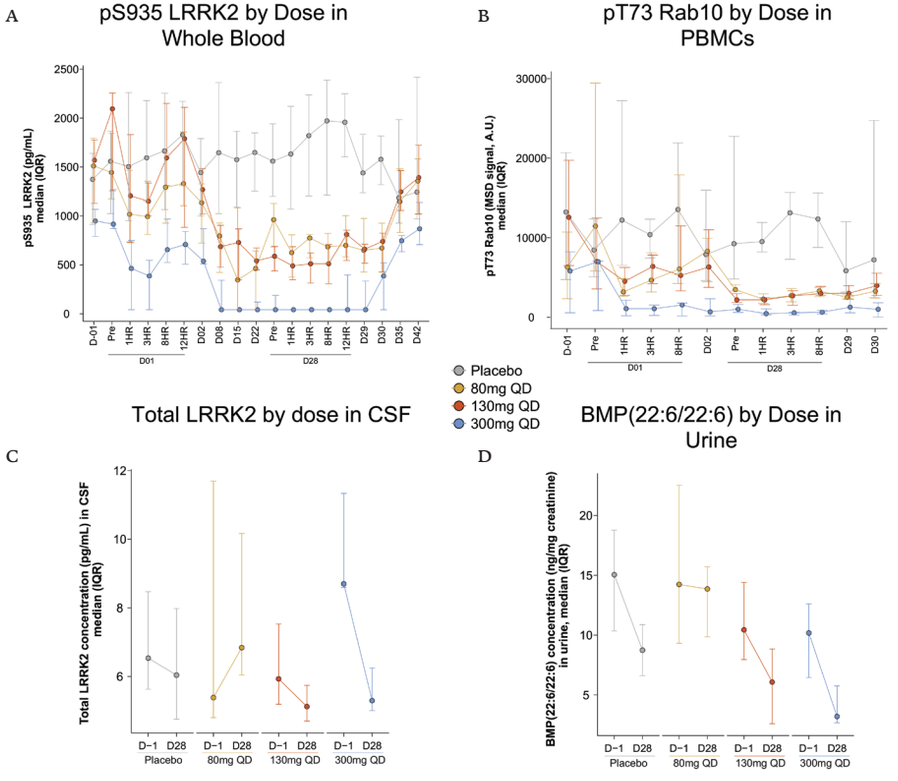
BMP=di-22:6 bis[monoacylglycerol]phosphate / IQR=interquartile range / PD=Parkinson's disease / QD=once daily / BID=twice daily.

Figure S8 Phase 1B study: dose-dependent target and pathway engagement in patients with Parkinson's disease. Pharmacodynamics of LRRK2 kinase 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. Collection time points are indicated on the x-axis (D=day after first dose, where first dose is on D01). If no hour is specified (e.g., D02, D08), sample was collected predose or, where applicable, after the last dosing time point (e.g., D30, D35). On days with multiple postdose time points, the day of collection is indicated below the hourly time points on that day. Baseline was defined as the average of DAY −1 and DAY 1 predose measurements.



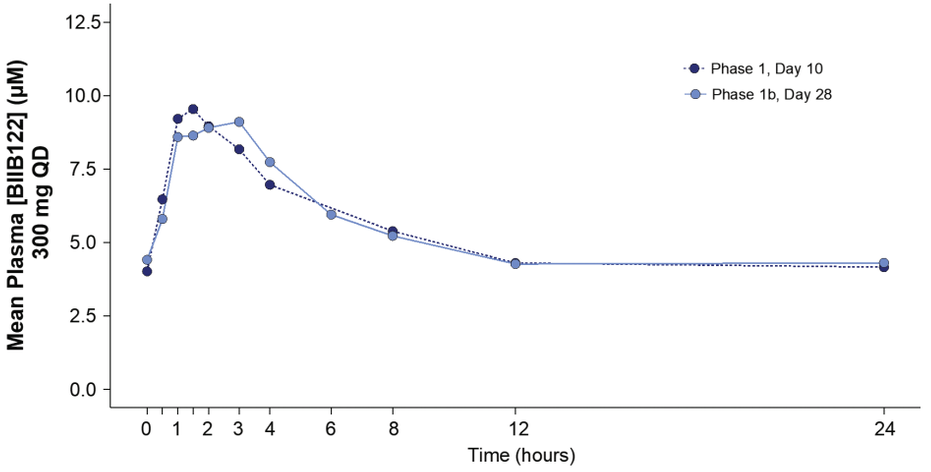
BL=baseline / D=DAY / IQR=interquartile range / LRRK2=leucine-rich repeat kinase 2 / PBMC=peripheral blood mononuclear cell / PD=Parkinson's disease / pS935=phosphorylated serine 935 / pT73=phosphorylated threonine 73 / QD=once daily.

Figure S9 Phase 1B study: pharmacodynamics of LRRK2 inhibition in PD patients, plotted as median (IQR) value over time. A. pS935 LRRK2 in whole blood by dose group. B. pT73 RAB10 (MSD signal, A.U.) in PBMCs by dose group. C. Urine BMP (ng/mg creatinine) by dose level. D. Total LRRK2 (pg/mL) in CSF by dose level. (A-D) Timepoints of collection are denoted on the x-axis (D=DAY before or after first dose where first dose is on D01 and D-01 is the day prior to the first dose). If no hour is specified (e.g. D03 and D08 for phase 1B study), sample was collected predose, or where applicable, after the last dosing timepoint (e.g. D30, D35 for phase 1B study). On days where multiple postdose timepoints were collected, the day of collection is indicated below the hourly timepoints on that day. For urine BMP in PD patients (C), the time periods on the x-axis denote pooled sampling timepoints on the noted day of collection.



BMP = di-22:6 bis[monoacylglycerol]phosphate / IQR = interquartile range / PD = Parkinson's disease / QD = once daily / BID = twice daily.

Figure S10 Phase 1 and 1B studies: mean plasma concentration-time profiles of BIIB122 300 mg once daily after multiple-doses in healthy participants and patients with Parkinson's disease. Plasma pharmacokinetics of BIIB122 300 mg QD at steady state in healthy participants from the phase 1 study and patients with PD from the phase 1B study.



PD = Parkinson's disease / QD = once daily.

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