Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

LRRK2 Inhibitors

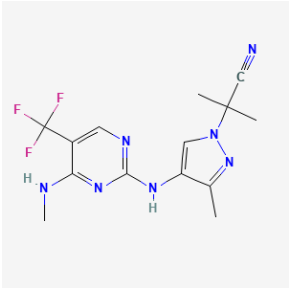
Evidence Summary

LRRK2 inhibition could have benefit for diseases with LRRK2 or lysosomal dysfunction like PD. Clinical trials have not yet tested efficacy. There are safety concerns, including long-term use and lung function.

Neuroprotective Benefit: Based on preclinical work, LRRK2 kinase inhibition could be beneficial to sporadic and familial PD patients, as well as for other diseases with lysosomal dysfunction. Trials testing efficacy are underway.

Aging and related health concerns: LRRK2 inhibitors have not been explored clinically outside of neurodegenerative diseases. There may be rationale for testing LRRK2 in other diseases such as colitis, stroke, or multiple sclerosis, but this is very preliminary.

Safety: Headache is the most common side effect of LRRK2 inhibitors based on early trial data. Orthostatic hypotension may be a drug class side effect as well. Data from long-term use, especially for lung function, is needed.

Availability: in clinical development	**Dose**: Dosing has not yet been optimized for LRRK2 inhibitors. BIIB122, the most advanced clinical compound, is an oral formulation and has been tested at a variety of doses; an ongoing study uses 225 mg daily.	There are numerous LRRK2 inhibitors. Below is the only structure available for a LRRK2 inhibitor that has been tested in patients. **DNL201** **Chemical formula:** $C_{14}H_{16}F_3N_7$ **MW**: 339.32 g/mol  Source: PubChem
Half-life: Varies. The half-life of the most advanced compound, BIIB122, is 2 to 5 days.	**BBB**: All of the LRRK2 inhibitors in clinical trials are either BBB penetrant or are administered intrathecally (BIIB094)	
Clinical trials: LRRK2 inhibitors have been tested in several trials; results have been published on trials comprising a total of 372 participants.	**Observational studies**: There are no observational studies of LRRK2 inhibitors.	

What is it?

Leucine-rich repeat kinase 2, better known as LRRK2, is a large protein with multiple domains, including a kinase domain and a GTPase domain. LRRK2 is thought to play a role in many cellular processes, ranging from signaling pathways, vesicular trafficking, lysosome function, endocytosis, cytoskeletal dynamics, immune system modulation, and mitochondrial function. LRRK2 is expressed in various tissues such as brain, heart, lungs, different components of the immune system, and kidney (Usmani et al., 2021; Azeggagh & Berwick, 2022; Müller, 2023).

Mutations in *LRRK2* such as *LRRK2*^{G2019S} are among the most common causes of familial Parkinson's disease (PD). *LRRK2* mutations are also associated with sporadic PD, and genome-wide association studies have found that certain noncoding variants of *LRRK2* are risk factors for PD. These mutations typically increase the activity of the LRRK2 kinase domain (Usmani et al., 2021; Azeggagh & Berwick, 2022; Jennings et al., 2022). Interestingly, increases in LRRK2 kinase activity have been observed in

sporadic PD cases with no known genetic mutation or variation in LRRK2 (Jennings et al., 2022). Inhibiting LRRK2 kinase has therefore been an area of active research in the community. Genetic variants of LRRK2 are also thought to be a risk factor for Crohn's disease, leprosy, and tuberculosis, and emerging evidence suggests that LRRK2 variants may contribute to other neurodegenerative diseases; for instance, genetic variation of LRRK2 is thought to be associated with progression of progressive supranuclear palsy (PSP) (Azeggagh & Berwick, 2022; Herbst et al., 2022). Successful LRRK2 inhibition thus has the potential to treat not just familial PD but also sporadic PD and other diseases.

There are a variety of LRRK2 inhibitors available for preclinical research and in the clinical development pipeline. The inhibitors act in different ways. Some of the strategies currently in use are reviewed in Wojewska & Kortholt, 2021 and Azeggagh & Berwick, 2022 and include:

- Inhibitors that compete with ATP for a binding site in the kinase domain. The inhibitors in clinical development largely fall into this category.
- Inhibitors that modulate the GTPase domain of LRRK2, which may indirectly affect the kinase domain in addition to altering the GTPase function of LRRK2.
- Inhibitors that prevent LRRK2 dimerization, which is thought to be associated with kinase activity.
- Inhibitors that are designed to specifically modulate LRRK2 protein with a G2019S mutation while not interacting with wild-type LRRK2.
- Antisense oligonucleotides (ASO) that are designed to bind to the mRNA for LRRK2 and prevent protein translation, thus reducing the amount of protein available.
- PROteolysis-TArgeting Chimera (PROTAC) approaches to selectively degrade LRRK2.

BIIB122, also known as DNL151, is the most clinically advanced LRRK2 inhibitor and is an ATP-competitive inhibitor under development by Biogen and Denali Therapeutics. DNL201, a closely related compound that was developed by the same companies, is also an ATP-competitive inhibitor. Studies of both of these compounds in humans have been published, though these studies were early safety and tolerability studies rather than efficacy studies. Denali Therapeutics and Biogen have preferentially focused on developing BIIB122 based on its preferable pharmacokinetic profile (press release).

Neuroprotective Benefit: Based on preclinical work, LRRK2 kinase inhibition could be beneficial to sporadic and familial PD patients, as well as for other diseases with lysosomal dysfunction. Trials testing efficacy are underway.

Types of evidence:

- 2 clinical trials
- 1 observational study
- 1 commentary article
- 3 news articles or press releases
- 7 reviews
- 6 laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

No LRRK2 inhibitor has been tested in humans and assessed for dementia prevention, prevention of decline, or effect on cognitive function.

Human research to suggest benefits to patients with dementia:

BIIB122, has been tested in a randomized, placebo-controlled, double-blinded trial of 36 patients with Parkinson's disease (PD). This study focused on safety, pharmacokinetics, and pharmacodynamics in different patient populations, and is described at length in the 'Safety' section. The portion of the study with PD patients tested 3 different doses of BIIB122 for 28 days. The study assessed cognition and non-motor PD symptoms as a safety measure; changes were otherwise not expected on the scale of 28 days. There were no changes in cognition as measured by Montreal Cognitive Assessment (MoCA) or non-motor PD symptoms as measured by the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III.

Based on blood, CSF, and urine markers that are thought to be reflective of LRRK2 activity, the authors reported that LRRK2 kinase inhibition was sufficient to modulate lysosomal pathways. An ongoing Phase 2b study is investigating the effects of BIIB122 on function and disease progression; please see the 'Research Underway' section for more information.

DNL201 has also been tested in a randomized, placebo-controlled, double-blinded trial of 28 patients with PD. Like the study of BIIB122, this study focused on safety, pharmacokinetics, and pharmacodynamics in different patient populations and is described in depth in the 'Safety' section. This

trial also assessed cognition and non-motor PD symptoms by MoCA and the MDS-UPDRS Part III, respectively, as a safety measure. No change in either measure was observed.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

LRRK2 is a large, multidomain protein; besides the leucine-rich repeat domain that led to the name of LRRK2, the protein has an armadillo repeats region, an ankyrin repeat region, a kinase domain, a RAS domain, a GTPase domain, and a WD40 domain. As reviewed by many papers, including Usmani et al., 2021, Azeggagh & Berwick, 2022, and Jennings et al., 2022, familial Parkinson's disease (PD) accounts for approximately 5 to 10% of all PD cases, and mutations in *LRRK2* are among the most common of these familial mutations, though these mutations have variable penetrance. *LRRK2* mutations are also found in some cases of sporadic PD, and variations in *LRRK2* and its gene regulatory regions are also associated with risk of PD. These mutations generally result in an increase in activity of the kinase domain of LRRK2. Increased LRRK activity has also been reported in sporadic PD patients with no LRRK2 variation. Reducing LRRK2 kinase activity has therefore been an area of active research interest.

There are numerous proposed roles of LRRK2, including involvement in cytoskeletal dynamics, mitochondrial regulation, and various aspects of membrane trafficking including autophagy, endocytosis, and endolysosomal function (reviewed by Usmani et al., 2021; Jennings et al., 2022, among others). LRRK2 is often localized to the cytosol and typically is thought to have lower kinase activity, whereas dimerized LRRK2 is often associated with membranes and has higher kinase activity. LRRK2 phosphorylates a variety of substrates, such as several Rab-GTPases, which are involved in intracellular vesicular transport (Steger et al., 2016). It is worth noting that there is a lot of uncertainty about LRRK2 function as it is expressed at low levels in some cell types, including neurons. Many studies of LRRK2 therefore need to overexpress or knock out the protein, and these model systems may not reflect the physiological function of LRRK2. The interconnected nature of many of LRRK2's potential roles brings additional complexity to teasing apart the disease-relevant functions of LRRK2 and how LRRK2 inhibitors can affect those functions (Usmani et al., 2021).

LRRK2 inhibitors reduce LRRK2 kinase activity. Most of the lead compounds achieve this via competing with ATP for binding sites. Other groups are exploring modulating the GTPase domain, as there is evidence that the GTPase domain can modulate activity in the kinase domain. Two studies seek to decrease LRRK2 activity by reducing levels of LRRK2 overall. One trial is investigating a PROTAC approach that degrades a targeted protein – in this case, LRRK2 – and another is utilizing an antisense

oligonucleotide that would degrade the mRNA of LRRK2, thus reducing the amount of LRRK2 protein. The 'What is this?' and 'Research underway' sections both discuss these approaches (Wojewska & Kortholt, 2021; Azeggagh & Berwick, 2022).

As LRRK2 has many functions, reducing kinase activity or levels of LRRK2 may have a variety of downstream effects through which neuroprotection could be achieved. The current prevailing theory is that modulating the effects of LRRK2 action on endolysosomal function is a main route of benefit. Preclinical evidence suggests that LRRK2 inhibitors can mitigate or reverse lysosomal dysfunction, both in the context of LRRK2 mutation and in context of lysosomal storage disorders. The latter result supports the idea that LRRK2 inhibition may be beneficial for people without genetic variations in LRRK2, and also for diseases other than PD (Baptista et al., 2020). Bis(monoacylglycerol)phosphate (BMP), also known as lysobisphosphatidic acid, is a phospholipid that is found in the membranes of late endosomes and lysosomes. Levels of BMP are altered in lysosomal storage disorders, and LRRK2 mutation carriers have higher levels of urine BMP than noncarriers (Alcalay et al., 2020). Treatment of both preclinical models and patients with LRRK2 inhibitors have led to reductions in urinary BMP levels, which is thought to reflect changes in the endolysosome system (Jennings et al., 2022; Jennings et al., 2023). While there is still some controversy as to whether this is an appropriate biomarker of LRRK2 target engagement, these data suggest that LRRK2 inhibitors are able to reduce LRRK2 kinase activity, and that this leads to improvements in the function of the endo-lysosome system.

The hypothesis that LRRK2 kinase inhibition primarily provides benefit through improvement of endolysosomal function does not rule out the possibility that the inhibitors could also, or instead, act through different pathways, such as modulating autophagy, mitochondrial dynamics, or cytoskeletal function. As LRRK2 is also present in immune cells, LRRK2 inhibitors could also impact neuroinflammation.

Studies have shown that LRRK2 inhibitors can improve disease phenotypes in animal models, including mitigating neurodegeneration and improving motor function (Azeggagh & Berwick, 2022; Jennings et al., 2022; Chen et al., 2023). It is not yet known whether LRRK2 inhibitors will provide clinically meaningful improvements to patients.

Much of the research of LRRK2 has focused on PD. Interactions between LRRK2 and AD are relatively understudied. LRRK2 mutations generally do not appear to be associated with risk of or occurrence of AD (Fatahian et al., 2019). One study reported a single case of a LRRK2 mutation in a patient with early-

onset probable AD without parkinsonian features. It is difficult to say whether this was a coincidence or a rare event that had not been identified before, as no other report has identified a case of this specific LRRK2 mutation with dementia without a parkinsonian phenotype, and LRRK2 mutations are not always fully penetrant (Zhang et al., 2020).

Still, there is biological rationale for exploring a potential role of LRRK2 inhibitors in AD, particularly if the ongoing trials of LRRK2 inhibitors report promising results with acceptable safety and tolerability. Studies have reported tau and Aβ pathology in LRRK2 carriers with PD and genetic variations of LRRK2 have been associated with progression of progressive supranuclear palsy (PSP), raising the question of whether there could be some interconnected pathways or a utility of LRRK2 inhibitors in AD or pure tauopathies (Henderson et al, 2019; Herbst et al., 2022). It is possible that LRRK2 interacts with tau and/or Aβ. For instance, there is some evidence that LRRK2 can affect Aβ through LRRK2 phosphorylation of APP, and it has been suggested that LRRK2 could potentially increase tau phosphorylation either directly or indirectly. It has also been suggested that LRRK2 might contribute to spread of AD pathology. There is also growing appreciation for the role of LRRK2 in inflammatory processes, and a preclinical study found that LRRK2 inhibitors attenuated neuroinflammation in both PD and AD animal models (Herbst et al., 2022; Mutti et al., 2023). More research is needed to validate and expand these findings.

APOE4 interactions:

It is not known whether LRRK2 inhibitors have differential interactions with APOE2, APOE3, and APOE4.

One study of 390 Han Chinese individuals with sporadic AD and 545 unrelated age- and sex-matched controls found that a LRRK2 variant, R1628P, was found more frequently in control cases than in AD cases (OR 0.264; 95% CI, 0.088–0.792, P = 0.018). When they stratified by APOE status, the R1628P variant was found much more frequently in control cases than in AD cases (OR 0.104; 95% CI, 0.013–0.818, P = 0.031); that is, an APOE4 carrier who also had an R1628P LRRK2 variant was much more likely to not have AD than an APOE4 carrier with wild-type LRRK2. The researchers also looked at another LRRK2 variant and found no association between that variant, G2385R, and AD incidence in APOE4 carriers or non-carriers. This study hints at the possibility that at least certain LRRK2 variants may be protective in sporadic AD (Li et al., 2013). It should be noted that R1628P LRRK2 is inconsistently associated with PD, potentially due to testing in different ethnic groups. Future work is needed to clarify if and how LRRK2 and APOE interact (Zhang et al., 2017).

Aging and related health concerns: LRRK2 inhibitors have not been explored clinically outside of neurodegenerative diseases. There may be rationale for testing LRRK2 in other diseases such as colitis, stroke, or multiple sclerosis, but this is very preliminary.

Types of evidence:

- 3 laboratory studies

LRRK2 inhibitors have not been explored clinically for aging or related health concerns. While there is growing interest in the peripheral role(s) of LRRK2, the field is still developing.

There is preclinical evidence that suggests a potential for use of LRRK2 inhibitors in other conditions, such as through modulation of inflammation or mitochondrial dynamics. For instance, genome-wide association studies have linked variants of LRRK2 to Crohn's disease, and there has been interest in whether LRRK2 inhibitors may be useful in treating colitis (Cabezudo et al., 2023). LRRK2 mutations in humans have been associated with a potential for increased risk of stroke, providing rationale for a preliminary preclinical study of LRRK2 inhibitors in an animal model of stroke (Hwang et al., 2024). Early studies of LRRK2 inhibitors in animal models of multiple sclerosis have also been published (Benítez-Fernández et al., 2024).

Safety: Headache is the most common side effect of LRRK2 inhibitors based on early trial data. Orthostatic hypotension may be a drug class side effect as well. Data from long-term use, especially for lung function, is needed.

Types of evidence:

- 1 meta-analysis and systematic review
- 2 clinical trials
- 2 observational studies
- 1 book chapter
- 1 commentary article
- 1 press release
- 1 review

- 2 laboratory studies

A significant concern of LRRK2 inhibitors is their effect on lung structure and function. Preclinical studies of LRRK2 inhibitors have consistently found morphological changes in certain lung cells known as type II pneumocytes. Type II pneumocytes secrete surfactant, among other roles; surfactant is required for proper lung function (NCBI StatPearls). Studies of genetic *LRRK2* knockout animal models have reported morphological abnormalities in peripheral tissues such as lung and kidney tissue (Baptista et al., 2013). Treatment with high enough doses of a variety of LRRK2 inhibitors in different animal models has also resulted in an increase of vacuolation in the cytoplasm of type II pneumocytes (Press release for MJFF LRRK2 Safety Initiative Study overview). This morphological finding has been reported to resolve in animals upon cessation of treatment. Moreover, studies have not found a functional impact of these changes in cellular structure; a study of three LRRK2 inhibitors in non-human primates for two weeks, for instance, found no difference in lung function, including lung diffusion, elasticity, forced vital capacity, forced expiratory volume or flow, mean mid-expiratory flow, or ventilator capacity. Data from this study has also suggested that there was not a decrease in surfactant release, and that there was not an inflammatory response. The morphological changes were not observed in brain tissue, and some data suggests that doses that sufficiently inhibit brain LRRK2 may be within an appropriate safety margin for lung tissue (Baptista et al., 2020; Press release for MJFF LRRK2 Safety Initiative Study results). These findings enabled in-human studies of this drug class. Lung function has been assessed in 28 day clinical trials, and no pulmonary adverse events have been reported (Jennings et al., 2022, Jennings et al., 2023). Evidence that there are sporadic loss-of-function mutations of LRRK2 that are not significantly associated with any particular phenotype or disease has also provided some reassurance to the field (Whiffin et al., 2020). It is also possible that there is some drug class element at play; all of these effects have been reported from ATP-competitive inhibitors, and a different inhibitor strategy might not lead to the same phenotype (Cao et al., 2023). Still, lung function during LRRK2 inhibitor treatment should continue to be monitored for all LRRK2 inhibitors, especially with long-term use, until this phenomenon is better understood.

Several LRRK2 inhibitors either are or have been tested in human patients; results from studies with two of the inhibitors are available.

Results of a trial of BIIB122, also known as DNL151 are described in Jennings et al., 2023. The Phase 1/1b study randomized placebo-controlled double-blinded study evaluated an oral formulation of BIIB122 for up to 28 days in 186 healthy participants, including healthy elderly volunteers, and for 28 days in 36

patients with Parkinson's disease (PD). The study included both single and multiple ascending dosing cohorts and therefore assessed a variety of doses, frequencies of doses, and duration of dosing. The dose amount ranged from 10 to 400 mg; dosing was either daily or twice daily; and duration ranged from a single dose to daily dosing for 28 days. The outcomes of the study focused on safety, tolerability, and measurements of pharmacokinetics and pharmacodynamics.

No serious adverse events that were thought to be study drug related were reported at any dose, frequency, or duration. There were five total discontinuations due to treatment-emergent adverse events; four of these events were in patients treated with BIIB122. Of these events, two were in healthy volunteers: one reported diarrhea, nausea, headache, and disturbance in attention, and another reported severe headache, malaise, and mild myalgia. Hypotension in two patients with PD receiving BIIB122 led to the other two study discontinuations. Both patients had pre-existing hypotension or orthostatic hypotension, which will be discussed in greater detail below. There were no clinically meaningful or dose-related changes in any vital signs, clinical laboratory values, measurements of pulmonary function or suicidal ideations, or physical or neurological exams in healthy participants or PD patients.

Headache was the most common treatment-emergent adverse event for both healthy participants and PD patients. The incidence and severity of headache was dose dependent. Myalgia was more frequent in patients receiving doses of 250 mg or more of BIIB122 twice daily as opposed to once daily dosing.

Orthostatic hypotension is a common non-motor symptom of PD; incidence is estimated at 30 to 50% of patients (Palma & Kaufmann, 2021). As discussed above, two patients with PD discontinued treatment due to hypotension. Both were asymptomatic; one was severe and determined to be unrelated to study drug, and one was mild and determined to be related to study drug. Two additional patients experienced hypotension as a treatment-emergent adverse event that resolved while continuing study drug. Both of these adverse events were asymptomatic.

The companies that are developing BIIB122 also had a related LRRK2 inhibitor, DNL201, in trials. BIIB122 has a better safety profile and pharmacokinetic profile suited to once daily dosing, and so the companies discontinued development of DNL201 and are focusing on BIIB122. Safety data for DNL201 will be described in this report as it is informative for potential class effects.

Jennings et al., 2022 details the results of a randomized, placebo-controlled, blinded trial that tested DNL201 in 122 healthy participants, including older adults, and 28 patients with PD. Both single and multiple ascending dose cohorts were included in the study design, and all study drugs were oral formulations. Single doses ranged from 10 mg to 225 mg of DNL201 or matching placebo in healthy adults for 10 days. In the multiple ascending dose cohorts, healthy participants took the study medication for 28 days and received a range of doses, from 40 mg once daily to 100 mg twice daily DNL201 or placebo. PD patients received 30 or 50 mg DNL201 three times daily or matching placebo for 28 days.

There were no changes in pulmonary or renal function in the DNL201 treated groups in either healthy volunteers or PD patients. There were no clinically meaningful declines in motor function, mood, or cognition in participants treated with DNL201.

No serious adverse events were reported in the study of healthy volunteers. DNL201 was generally well-tolerated at doses of 150 mg or less once a day, or 100 mg or less twice a day; individuals who received 150 mg twice on day 1 required dose reductions on day 2 due to two adverse events of mild dizziness and one instance of asymptomatic orthostatic hypotension. Most adverse events were mild. There were three treatment-emergent adverse events that lead to study drug discontinuation: two participants with headache, and one participant with atrial fibrillation that was considered unrelated to study drug. The most common treatment-emergent adverse events that were more frequent in the study drug group compared to placebo were headache, dizziness, and nausea, reported by 40%, 13%, and 15%, respectively, of healthy individuals receiving DNL201. The type and incidence of the adverse events were similar between the elderly and nonelderly healthy volunteers.

In the portion of the study with PD patients, there was one event of severe headache in the 50 mg DNL201 TID group; the patient received a dose reduction to 30 mg DNL201 TID, and the headache resolved. Another patient receiving 50 mg TID withdrew from the study due to moderate symptomatic orthostatic hypertension, moderate headache, and mild nausea, all three of which resolved after cessation of study drug. There was one serious adverse event of *Legionella* pneumonia after the end of dosing which was considered unrelated to study drug. Most adverse events were mild or moderate in severity. Headache was the most common treatment-emergent adverse event, with 33% of the DNL201 group reporting headache compared to 14% of the placebo group. Nausea was the only other event that was numerically more common in the DNL201 group compared to placebo (24% compared to 14%).

Drug interactions:
The drug interactions of LRRK2 inhibitors are not yet known.

Research underway:

NCT05348785, known as LUMA, is a randomized, placebo-controlled, double-blinded trial of BIIB122. The study plans to enroll 640 patients with early-stage PD. Participants will take either 225 mg of BIIB122 or matching placebo by mouth daily for a minimum of 48 weeks and a maximum of 144 weeks. The primary outcome measure is time to confirmed worsening in motor and non-motor symptoms of PD as measured by the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts II and III. Other outcome measures will assess safety and change from baseline in daily function and disease progression.

This study is also offering enrollment to patients who participated in the now-terminated Phase 3 study of BIIB122 known as LIGHTHOUSE (NCT05418673). LIGHTHOUSE was a similarly designed trial of BIIB122 that planned to only enroll PD patients with LRRK2 mutations. Due to the long timeline of LIGHTHOUSE, along with the study's complexity, the trial sponsors decided to terminate LIGHTHOUSE and focus on LUMA. The study sponsors emphasized that this decision was not due to any safety or efficacy data (Press release).

NCT03976349 is an ongoing study of BIIB094 / ION859, which is an antisense oligonucleotide (ASO) targeting LRRK2 kinase. This randomized, double-blinded, placebo-controlled study aims to enroll 82 patients with PD, including some participants with LRRK2 gene mutations and some without LRRK2 gene mutations. The ASO is administered via intrathecal injection. The study will include single and multiple doses of the ASO as well as a placebo control. The primary outcome of the study is safety as assessed by number of adverse events and serious adverse events. Other outcome measures will assess the pharmacokinetics and pharmacodynamics of BIIB094.

NCT06264440 is an open-label, crossover study assessing the impact of rabeprazole, a proton pump inhibitor (PPI), on BIIB122 pharmacokinetics. The study will also collect data on safety and tolerability of BIIB122 with and without concomitant PPI in healthy participants. The researchers plan to enroll 15 healthy participants. Each participant will have three doses of BIIB122: a single oral dose of BIIB122 while fasting, one pretreatment period with once-daily PPI followed by a single oral dose of BIIB122

while fasting, and then one pretreatment period with once-daily PPI followed by a single oral dose of BIIB122 while fed. The primary outcomes are pharmacokinetic assessments of BIIB122; the secondary outcome is number of adverse events.

A Phase 1 trial of ARV-102 was announced in February 2024; this study is not yet registered or described on clinicaltrials.gov or in the European Union Clinical Trials Register as of March 2024. ARV-102 is a PROteolysis-TArgeting Chimera (PROTAC) LRRK2 degrader that is taken orally and is blood-brain barrier penetrant. This Phase 1 study plans to investigate safety, tolerability, pharmacokinetics, and pharmacodynamics of ARV-102 in healthy volunteers (Press release).

NCT05633745 is a now-terminated trial of NEU-723. This study planned to assess single ascending doses and multiple ascending doses of NEU-723 in healthy adults and assess safety, tolerability, and pharmacokinetics. The trial is listed as terminated; no information could be found as to the reason for the termination. NEU-723 is or was being developed by Neuron23; the company reports that they have other LRRK2 inhibitors in their pipeline (Press release).

Search terms:

Pubmed, Google: LRRK2 inhibitors

- Parkinson's disease, clinical trial, Alzheimer's, stroke, multiple sclerosis, colitis

Websites visited for LRRK2 inhibitors:

- Clinicaltrials.gov: BIIB122, BIIB094
- PubChem: LRRK2 Inhibitor; DNL201
- Cafepharma: BIIB122, LRRK2

***Disclaimer**: Cognitive Vitality Reports® do not provide, and should not be used for, medical advice, diagnosis, or treatment. You should consult with your healthcare providers when making decisions regarding your health. Your use of these reports constitutes your agreement to the **Terms & Conditions**.*

If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.